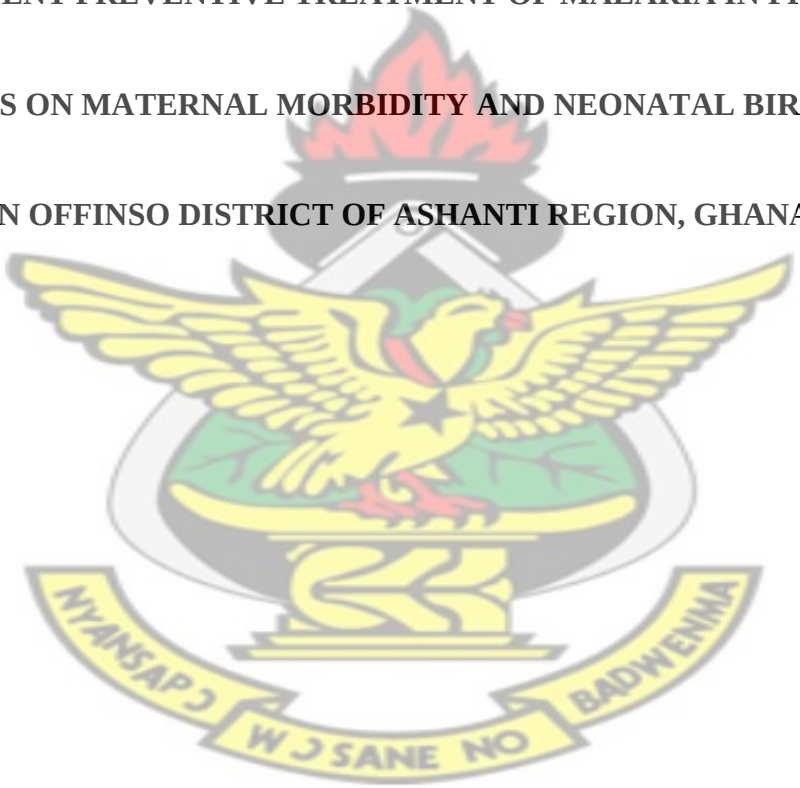
KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY KUMASI

COLLEGE OF SCIENCE

DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY

INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY: ITS EFFECTS ON MATERNAL MORBIDITY AND NEONATAL BIRTHWEIGHT IN OFFINSO DISTRICT OF ASHANTI REGION, GHANA



BY

OSEI TUTU, EMMANUEL

JUNE 2009

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A THESIS SUBMITTED TO THE DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY, COLLEGE OF SCIENCE, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI

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DOCTOR OF PHILOSOPHY (BIOLOGICAL SCIENCES)

BY

OSEI TUTU, EMMANUEL BSc. (HONS) BIOLOGICAL SCIENCES

JUNE 2009

DECLARATION

I hereby declare that this work is the report of the research I undertook towards the PhD and that to the best of my knowledge (except where due acknowledgement has been made in the text), it contains no material which has been accepted for the award of any other degree in this or any other University.

Osei Tutu Emmanuel (PG7669004)	.....…….....	…….....
PhD Candidate (ID)	Signature	Date

Certified by:

Prof. Bernard Walter Lartekwei Lawson	……..	..……....
Supervisor	Signature	Date
Rev. Dr. Edmund Nii Laryea Browne	……...	…….....
Supervisor	Signature	Date
Dr. Philip Kwaku Baidoo	…….....	…..…….....
Head of Dept. Name	Signature	Date

DEDICATION

THIS WORK IS DEDICATED TO THE LORD GOD FOR HIS BOUNDLESS MERCIES AND GUIDANCE IN ALL MY ENDEAVOURS

TO MY PARENTS FOR THEIR PRAYERFUL SUPPORT AND ENCOURAGEMENT.

ABSTRACT

The World Health Organization (WHO) has adopted the use of Sulphadoxine – Pyrimethamine (SP) to control malaria during pregnancy in the sub–Saharan Africa region. Implementation of this programme in Ghana is less than 10% nationwide probably due to lack of knowledge on its efficacy and benefits to the pregnant woman and the neonate. The present study, therefore evaluated the effect of SP use in pregnancy on malaria–associated maternal morbidity and neonatal birthweight in Offinso District of Ashanti Region, Ghana.

Two analytical cross–sectional studies were conducted on pregnant women of gestational age of 16 weeks to term, in Offinso District of Ashanti Region between November 2005–July 2007 of which haemoglobin level (Hb) determination, parasitaemia level, anthropometric and other quantitative determinants were assessed. Qualitative study using in-depth interviews (IDIs) and focus group discussions (FGDs) were used to assess the malaria burden and the effect of SP–IPTp in the district. Routine deliveries during pre–IPTp period (January 2000–July 2004) and onset of the IPTp programme (January 2005- October 2007) were reviewed to assess the trend and effect of SP on birthweights of neonates in these periods, respectively. Diversity of the parasite, *Plasmodium falciparum*, was also studied in the women in the district.

In the first analytical study, where the effect of SP in the IPTp programme in control of malaria was assessed; 444 pregnant women were involved of which 190 (43%) took SP. Of these, 82 (43%) took first dose only, 57 (30%) and 51(27%) respectively took second and third doses of SP. One hundred and twenty three (28%) of the 444 pregnant women had parasitaemia. Of the parasitaemic group, 65 (53%) took no dose of SP, 29 (24%), 18 (15%) and 11 (9%) respectively took 1, 2 and 3 doses of SP. The influence of SP intake on malaria infection was insignificant (Pearson correlation: r = 0.0008, p = 0.986). However, there was a tendency towards reduced prevalence of parasitaemia as number of SP doses taken increased: one dose: 29/82 (35%), two doses: 18/57 (32%) and three doses: 11/51(22%). Anaemia (Hb<11g/dl) was found in 266 /444(60%) of the study subjects. The mean Hb level (10.4±1.69g/dl) for the SP group (all doses combined) was significantly higher than that (9.9±1.64g/dl) in the no SP group (p < 0.002). Furthermore, there was a significant positive association between IPTp using SP and haemoglobin level (p < 0.01) with a dose-response relationship.

In the second analytical study, where the effect of SP in IPTp programme, knowledge on malaria and antenatal clinic (ANC) attendance during pregnancy were assessed; 306 pregnant women were studied, of which 92 (30%) took 1 dose of SP, 100 (33%) 2 doses and 114 (37%) 3 doses of SP. Of 115 (38%) of these 306 pregnant women who were followed up to delivery in the health centres, 104(90%) delivered babies of normal birthweight (birthweight ≥ 2.5 kg) and 11 (10%) had low birthweight babies (birthweight < 2.5 kg). There was significant association between gravida and the doses

of SP taken (Pearson χ^2 =18.9, $p < 0.001$). One hundred and thirteen (37%) of these pregnant women reported adverse effects such as nausea, dizziness, anorexia, general malaise, fatigue and others. However, these effects had no significant association between the use of SP and the number of doses of SP taken (Pearson's $\chi^2 = 2.3$, $p \geq 0.32$). Forty seven (15%) of the pregnant women who took SP had peripheral parasitaemia. Regression analysis did show that a unit increase in dose of SP decreased peripheral parasitaemia levels by 19% ($p \geq 0.25$). However, generally, there was poor negative relationship of doses of SP taken with peripheral, placental and cord blood parasitaemia ($r = -0.06$, $r = -0.05$, $r = -0.07$) respectively, ($p \geq 1$). Mean haemoglobin (Hb) level was 11.3±1.6 g/dl (95% CI: 11.1 to 11.4), with 118 (39%) of the pregnant women being anaemic (Hb < 11.0 g/dl) whilst 187 (61%) had normal Hb levels (Hb ≥11.0 /dl). There was a significant positive correlation of SP use with Hb level ($r = 0.15$, $p < 0.008$). Haemoglobin levels among those who took various doses of SP did show significant difference ($p < 0.007$).

Over 70% of respondents in both the 307 questionnaires administered and the qualitative studies were knowledgeable on the malaria menace in their communities and how it could be prevented. FGDs (four held) with pregnant women showed that SP was good for their health, produced mild side effects and had reduced malaria and anaemia prevalence among them. Fifty five IDIs conducted with health staff, chiefs and opinion leaders in the district showed that SP is effective in the IPTp programme, had helped reduce maternal morbidity and mortality, had also improved birthweight of neonates and reduced mortality in them.

The delivery data in the two periods (pre–IPTp and onset of IPTp) showed that male neonates have significantly higher birthweights as compared to the female neonates and thus, sex of neonates, age of pregnant women, gravida of women and terms of pregnancy have great influence on birthweight of babies ($p < 0.0001$). Increased dose of SP significantly reduced the proportion of low birthweights in the neonates ($p < 0.001$). However, in the IPTp period, seasonal variation had no significant impact on birthweight of neonates ($p \geq 1.8$).

On diversity of the parasite, MSP2 gene was found to be more diverse in the women, with GLURP genes being most common in them.

Results of the present study, thus, suggest that effective implementation of the IPTp using SP is an evidence-based measure for control of malaria-related anaemia in pregnancy. Reduction in maternal anaemia impacts positively on both maternal and neonatal health. Strategies should therefore, be designed and implemented by the Ghana Health Service to increase the proportion of pregnant women (especially primigravid women) who take three doses of SP during pregnancy. Nevertheless, stringent measures should be put in place to guide against abusing the drug hence, rendering it ineffective. Attitudinal change and discipline would go a long way to curb the malaria menace and its effects on pregnancy in Ghana.

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ACRONYMS AND ABBREVIATIONS

AT	Adenine and Thymine
Bp	base pair
DHMT	District Health Management Team
DNA	Deoxyribonucleic acid
dNTP	deoxynucleoside triphosphate
DOT	Direct Observed Therapy
GC	Guanine and Cytosine
GDP	Gross Domestic Product
GHS	Ghana Health Service
GLURP	Glutamate Rich Protein
IEC	Information, Education and Communication
IPT	Intermittent Preventive Treatment
IPTp	Intermittent Preventive Treatment in pregnancy
ITN	Insecticide Treated Net
IV	Intravenous
IUGR	Intrauterine growth retardation
LBW	Low Birthweight
MOH	Ministry of Health
MSP	Merozoite Surface Protein
NMCP	National Malaria Control Programme
PCR	Polymerase Chain Reaction
PE	Pre-erythrocyte
RBM	Roll Back Malaria
SP	Sulphadoxine-Pyrimethamine
UNICEF	United Nations Children's Fund
UV	Ultra violet light
WHO	World Health Organization

DEFINITIONS

Antenatal	Period of pregnancy from conception to the onset of labour
Genome	The entire complement of the genetic information carried by an organism.
Gestational age	The duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed weeks.
IPTp	Administration of a curative antimalarial treatment dose at predefined intervals during the 16-36 weeks of gestation to asymptomatic pregnant women who are at special risk of malaria, regardless of whether or not they are parasitaemic.
Low birthweight	Birthweight less than 2.5kg
Maternal death	Death of woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not accidental or incidental cause.
Maternal mortality ratio	Number of pregnancy related deaths per 100,000 live births.
Miscarriage	Delivery at less than 24 weeks of gestational age.
Neonatal mortality rate	The number of deaths of babies within the first 28 days of life per 1000 live born babies.
Neonatal Period	A period from birth to the 28th day of life of a baby.
Newborn weight	Weight of newborn baby measured before the age of seven days.
Parasitaemia	The presence of asexual stage parasites in thick blood films.
Perinatal mortality rate	The number of stillbirths after 22 weeks of gestation, or deaths of newborns during the first seven days of extrauterine life per 1000 births.
Perinatal period	A period from 22 completed gestation weeks to seven completed days of life of a foetus baby.

Preterm	Gestational age of less than 37 completed weeks.
Sub-Saharan Africa	39 mainland countries of the continent south of the Sahara (thus excluding Western Sahara, Morocco, Algeria, Tunisia, Libya and Egypt). This term is used interchangeably with the term “Africa”

CHAPTER ONE − INTRODUCTION

1.1 BACKGROUND INFORMATION

Malaria is recognized as a serious health problem in tropical and subtropical regions of the world. It has far-reaching medical, social and economic consequences for the countries in which it is endemic due to its high and alarming morbidity and mortality rates. Each year approximately 2.5 million people die of malaria, many of whom are children. According to WHO estimates, 40% of the population of the world live in areas where malaria is endemic with the direct and indirect costs of management being very high (WHO/UNICEF, 2005). It is estimated that the annual economic burden of malaria in Africa is about 1% (US$1.9 billion) of the continent's Gross Domestic Product (GDP) (WHO/UNICEF, 2005). Around 300 million people are infected with malaria at any one time and a third of them develop clinical disease, 90% of which occur in Africa. It has been estimated that one person in Africa dies of malaria every ten seconds and the groups of people most at risk are pregnant women and young children (WHO/UNICEF, 2003). Malaria affects five times as many people as AIDS, leprosy, measles and tuberculosis combined (WHO/UNICEF, 2003). WHO (2008) put malaria cases in the Africa region at 86% of the world malaria menace with 80% of the cases occurring in 13 countries in Africa.

Malaria poses a serious threat to the health of pregnant women and young children in sub–Saharan Africa and other tropical regions of the world. More than 45 million women (30 million of them in Africa) become pregnant in malaria endemic areas each year (Shulman *et al.*, 1999; Steketee *et al*., 2001). Women, infected with *Plasmodium*

falciparum, a type of malaria parasite that is most prevalent in Africa experience maternal anaemia and impaired foetal growth, both of which contribute to low birthweight in newborns (Shulman *et al.*, 1999; Steketee *et al*., 2001). Malaria can also cause miscarriage, stillbirth, premature birth and intrauterine growth restriction (Menendez *et al.*, 2000). In high or moderate transmission areas including Ghana, malaria infections in pregnant women are mostly asymptomatic and infected women do not present for treatment. In such areas, the WHO recommends a combination of interventions to prevent malaria in pregnancy; these include insecticide-treated bednets (ITNs), intermittent preventive treatment in pregnancy (IPTp) and effective case management and treatment (Nahlen, 2000; WHO, 2004, 2006; Gamble, Ekwaru and ter Kuile, 2006; Garner and Gülmezoglu, 2006).

The complexity of *P. falciparum* in adapting to changing environments, drug pressure, and host immune response has been an area of several recent biomedical studies (Tongren *et al*., 2004; Kumkhaek *et al*., 2005; Chenet *et al*., 2008) to ascertain the success of malaria control programs. Knowledge of the nature and extent of genetic diversity within the species becomes increasingly relevant as control measures become more sophisticated and more selectively targeted towards the molecular components of the parasite. Populations of *P. falciparum* are known to be genetically diverse, even at low levels of endemicity (Paul *et al.*, 1999; Bendixen *et al.*, 2001). This shows that there is a remarkably high genetic diversity in endemic transmission settings such as Ghana. Jordan *et al*. (2001) found that parasites of major epidemics associated with abnormal weather and the extensions of malaria transmission to other non–malarious areas are also genetically diverse. The present study, also assessed the genetic diverse of *P. falciparum* in the district of study.

1.2 MALARIA SITUATION IN GHANA

The single and most important cause of morbidity in Ghana since 1985 is malaria, contributing to 45% of all outpatients' visits to government health facilities; it is also the leading cause of in–patients admissions and accounts for 15% of all deaths every year (GHS, 2004a). GHS (2007) put mortality due to malaria at 18% of all deaths annually. Moreover, malaria is more than a health issue as the activities of other sectors may be negatively affected and this in the long run impacts adversely on the productivity of all sectors of the economy. As a cause of mortality, it is surpassed only by anaemia to which malaria makes a major contribution mostly in young children (about 25% of all deaths in children under five) and primigravidae (GHS, 2004a). The incidence of clinical malaria is about 3 attacks per year. Most of the cases are caused by *P. falciparum*, which is transmitted through the bite of the *Anopheles* mosquito. Malaria has accounted for about 36% of patients admitted to hospitals for the past ten years (GHS, 2004a).There is, however, no evidence that the prevalence of severe malaria has gone up over time. In general, case fatality ratios in most hospitals have remained the same. Severe malaria is still a major cause of morbidity in the country and case fatality rate in selected sentinel hospitals is about 1.5%.

Malaria infection during pregnancy causes maternal anaemia and placental parasitaemia both of which pose substantial risks to the mother, the foetus and the newborn. In pregnant women, 13.8% are affected and 10.6% go on admission with the disease and as much as 9.4% of pregnant women die from malaria (GHS, 2004a). The Ashanti Region, between January 2002−November 2004, recorded 476 maternal deaths of which malaria was among one of the major causes. In a report (GHS, 2005), malaria contributed 24.5%

of all causes of admissions and was the highest cause of death in health institutions with a proportional mortality rate of 16.4%. Malaria cases in Ashanti region were 48.1% in 2005, an increase of 3.1% from the year 2004. Reports by GHS/Ashanti Region (2004) put malaria and anaemia as the leading cause of mortality in the hospitals (17.5% and 12.1%) respectively. GHS (2007) reported that maternal and neonatal mortalities increased unprecedentedly as compared to the previous years.

In studies by Browne *et al.* (1996; 2001), it was found that primigravidae have a prevalence of both *P. falciparum* infection and anaemia above 80% in Northern Ghana. In 1975, malaria accounted for 26% of admissions and 30% of total deaths in the paediatric ward in Komfo Anokye Hospital in Kumasi (Asafo-Agyei, 1978). Binka *et al.* (1994) have estimated that malaria may account for over 25% of under-five mortality in Northern Ghana whilst WHO/UNICEF (2003) estimated that malaria may account for 25% of early childhood deaths in Africa.

The malaria situation in Ghana is hyperendemic with crude parasite rates ranging from 10-70%. *Plasmodium falciparum* is the predominant malaria parasite in Ghana accounting for about 90% of all cases while *P. malariae* accounts for 9% and *P. ovale* is responsible for the remaining 1% (Appawu *et al.*, 2001; Tutu, 2003; Ghana RBM, 2004; Yawson *et al.*, 2004). Mixed infections of *P. falciparum* and *P. malariae* are not common. The principal vectors are the *Anopheles gambiae* complex and *An. funestus* accounting for 95% of catches (Appawu *et al.*, 2001; Tutu, 2003; Ghana RBM, 2004; Yawson *et al.*, 2004). *Anopheles gambiae* subspecies of the complex predominates and transcends across the country. *Anopheles arabiensis* and *An. melas* also exist but in small proportions. *Anopheles melas* is predominantly in the swampy south-west and *An.*

arabiensis is found in the northern part of the country (Appawu *et al*., 2001; Tutu, 2003; Ghana RBM, 2004).

The burden of malaria is heaviest in the forest belt of rural Ghana (Ahmed, 1989). Definitive studies on malaria carried out in Bomfa, the present-day Ejisu-Juaben district (Colbourne and Wright, 1955) showed that the known vectors of malaria in that area were *An. gambiae, An. funestus, An. hargreavesi* Evans and *An. nili* Theobald. *Anopheles gambiae* and *An. funestus* accounted for 95% of total "knock down" catches. The probable number of infective bites per person per year was 24. The parasite species were predominantly *P. falciparum* (90%). Slide positivity for *P. malariae* and *P. ovale* alone or mixed infections were 12.6% and 3.5% respectively. There was little seasonal variation in malaria transmission though parasite rates were slightly higher after the rains. Also in year 2000, parasitological survey of classes 1-3 school children in Juaben gave a parasite rate of 62% with *P. falciparum* accounting for 90% of infections (Browne *et al.,* 2000). Recent data from the forest region of Ghana shows that the malaria situation is no different from that of the past half century (Browne *et al.,* 2000). Data on malaria deaths estimate malaria-related childhood mortality between 10-15% (GHS/NMCP, 2003).

1.3 HISTORY OF ANTIMALARIAL DRUG POLICY AND PRACTICES IN GHANA

The main strategy for control of malaria in Ghana is case management. Malaria is diagnosed on clinical grounds based on the presence of fever; thus, treatment is presumptive whilst parasitological diagnosis of malaria is reserved for diagnosis of

treatment failure and severe malaria. In uncomplicated malaria, combination therapy instead of monotherapy (chloroquine or sulphadoxine–pyrimethamine) is used for treatment since it is evident there are high parasitological failures of these monotherapies (Adjuik *et al*., 2004). To date, Artemisinin Combination Therapy (ACT) is used as treatment for uncomplicated malaria. The GHS/NMCP has adapted artesunate - amodiaquine as the first line combination therapy for treatment of uncomplicated malaria. The dosage combination for the treatment is artesunate 4mg/kg body weight and amodiaquine 10mg/kg body weight which is administered concurrently for three (3) consecutive days. Quinine is administered as a second line drug and is also used for treating severe malaria.

A study conducted in six district hospitals in Ghana showed malaria treatment failure using chloroquine between 6% and 25% among the different demographic cohorts (GHS, 2004b). Some sources quote as high as 30% treatment failures though chloroquine tablets and syrup on the market are generally of good quality (GHS, 2004b). Based on WHO Global Response to Antimalarial Drug Resistance, there is a four–tier action framework for antimalarial drug resistance:

i.) Grace Period -Treatment failure less than 5%

ii.) Alert Period - Treatment failure of 6% to 15%

iii.) Action Period - Treatment failure of 16% to 24%

iv.) Change Period - Treatment failure of more than 25%

Ghana's state of affairs at best was in the 'Alert Period' and at worst, in the 'Change Period'. The level of treatment failure, therefore, did call for a review of the policy to displace chloroquine as first line drug for malaria treatment, introduce alternatives and review the treatment guidelines.

In 2003, the Ghana Health Service reviewed the guidelines for malaria chemoprophylaxis to bring it in line with the evidence associated with rising resistance and poor compliance with chloroquine. A survey showed that only 11.6% of pregnant women complied with the recommended regimen for chloroquine chemoprophylaxis (GHS, 2004b). This was attributed to poor knowledge of health staff on correct dosage, unfounded fear on the part of pregnant women that chloroquine causes abortion, the unpleasant itching due to chloroquine and the fact that they had to swallow too many tablets.

Another contributing factor to the poor compliance was that, the average antenatal clinic attendance was 2 or 3 visits and therefore many pregnant women were not at the clinic regularly to receive the chloroquine tablets that would protect them and their babies. Coupled with this is the fact that resistance to chloroquine was quite high, there was, therefore, the need to look for an alternative drug that would be easier to administer, effective and involved swallowing of fewer tablets.

At the same time, growing evidence in the country and internationally pointed to the efficacy of Intermittent Preventive Treatment (IPT) in preventing malaria in pregnancy (Parise *et al*., 1998; Shulman *et al*., 1999; WHO, 2002). The evidence showed that:

i.) Compliance with IPT using sulphadoxine–pyrimethamine (SP) was high.

ii.) SP had greater protective effect against low birthweight and anaemia than chloroquine.

iii.) Generally, birthweights improved with compliance with SP.

As a result, the guidelines for malaria chemoprophylaxis in pregnancy were changed from chloroquine to IPT using SP.

1.4 PROBLEM STATEMENT

Malaria and pregnancy are mutually aggravating conditions. The physiological changes due to pregnancy and the pathological changes due to malaria have a synergistic effect on the course of each other, thus making life difficult for the mother, the child and the treating physician. Falciparum malaria can run a turbulent and dramatic course in pregnant women. The primigravidae are usually the most affected (Alnwick, 2000; Kakkilaya, 2002). In Africa, perinatal mortality due to malaria is about 1500 per day. In areas where malaria is endemic, 20-40% of all babies born may have a low birthweight (Kakkilaya, 2002).

Pregnant compared to non-pregnant women are at an increased risk for malaria, and the severity of the clinical manifestations in the woman and her foetus depend on the level of pre-pregnancy immunity (Menendez, 1995). While in areas of low malaria endemicity all pregnant women are equally susceptible to the consequences of malaria infection; in areas of high endemicity women appear to be most susceptible during their first pregnancy (Garner and Gülmezoglu, 2001). However, a study by Shulman *et al.* (2001) points to significant susceptibility in primigravidae as well as in multigravidae. Pregnancies in women living in malaria endemic regions are associated with a high frequency and density of *P. falciparum* parasitaemia, with high rates of maternal morbidity including fever and severe anaemia, with abortion and stillbirth. This is also associated with high rates of placental malaria and consequently low birthweight in newborns caused by both prematurity and intrauterine growth retardation (WHO, 2002).

Malaria is a great problem in Ghana, hampering individual and national prosperity due to its influence on social and economic decisions. The risk of contracting malaria can

deter investment, both internal and external and affect individual and household decision making in many ways that have a negative impact on economic productivity and growth. There have been high maternal and neonatal death rates reported mostly due to malaria and its complications. Just recently the Ministry of Health, Ghana, reported higher maternal mortality in some of the regions. Ashanti region was not left out, with Offinso District recording the highest mortality rate in the region (GHS, 2005).

The vulnerable (pregnant women and children) are susceptible to malaria infection leading to chronic anaemia, acute severe anaemia, miscarriage/forced abortion and pre-term delivery in the mother; stillbirth, low birthweight, congenital malaria, peri-natal death and neonatal death in the newborns (Shulman *et al.*, 1999; Menendez, Fleming and Alonso, 2000). Maternal morbidity and neonatal mortality are increasing in Ghanaian communities despite the introduction of the IPT programme in antenatal clinics. There is, therefore, the need to evaluate IPT performance and its effectiveness so as to update and review the policy on malarial control.

1.5 RATIONALE OF STUDY

Malaria is the most common infection in pregnant women that results in maternal morbidity, anaemia, low birthweight and infant mortality. Sulphadoxine–pyrimethamine has been the drug of choice based on WHO recommendation of IPT programme. The use of SP has proved to be effective, highly complied with, and rarely has side effects based on WHO report (WHO, 2004). However, its implementation in Ghana is less than 10% (WHO/UNICEF, 2005). Thus, the present study is of importance since it would provide data on IPT performance and effectiveness so that problems arising from this programme could be recognised early and measures taken to resolve them appropriately

and in good time. The present study also assesses the genetic diversity of *P. falciparum* in pregnant women in a routine IPT setting in the Offinso District of Ghana.

1.6 SIGNIFICANCE OF STUDY

This study was meant to evaluate the performance and consequences of SP as a tool in controlling and preventing malaria morbidity in the pregnant mother and the effect on birthweights of neonates which would inform the need to adopt new strategies for effective implementation of SP- IPTp programme and/or search for alternative drug. The study was also meant to determine the genetic diversity of *P. falciparum* in pregnant women to inform us of the genotyping of the parasite in the district with respect to the use of SP in control of malaria in pregnancy.

1.7 RESEARCH QUESTIONS

Malaria in pregnancy has been a topic of great discussion among the public. Recently, the Ministry of Health in the Ashanti Region reported a record 476 maternal deaths between 2002 - 2004 most of which were as a result of malaria; Offinso and Asante–Akyem districts recorded the highest maternal deaths (GHS, 2005). The question is, do these deaths occur because of negligence on the part of the mother attending antenatal clinic or, is drug compliance the problem or, the health systems are not effective in addressing this malaria problem by use of IPT? Have there been side effects occurring in the use of the drug that the safety of it is worth looking at seriously?

1.8 OBJECTIVES

MAIN OBJECTIVE

The main aim of the present study, therefore, was to assess the effect of IPT use in pregnancy on malaria-associated maternal morbidity and neonatal birthweight in the Offinso District.

SPECIFIC OBJECTIVES

Specific Primary Objectives

1. To determine the effects of IPT using SP on maternal morbidity and malaria-associated anaemia in pregnancy.
2. To determine the effects of IPT using SP on birthweight of neonates.

Specific Secondary Objectives

3. To assess transplacental transmission of malaria
4. To evaluate the knowledge of IPT of health care personnel at the health facilities and assess the understanding of community members of IPT in general

Specific Tertiary Objective

5. To determine the genetic diversity of *P. falciparum* in the District.

CHAPTER TWO − LITERATURE REVIEW

2.1 OVERVIEW OF MALARIA

2.1.1 MALARIA AND PREGNANCY

Pregnant women are vulnerable to the effects of malaria. They are more likely than non-pregnant women to become infected with *P. falciparum* malaria and, once infected, there is a tendency toward increased severity of disease (Parise *et al.*, 1998; WHO, 2004) caused in part by the transient depression of cell-mediated immunity that occurs during pregnancy (Griffith *et al.*, 2007). The effects of malaria on pregnant women differ with various factors, such as the woman's level of immunity, her gravidity, the trimester of pregnancy, and the presence or absence of co–morbidity (Bouyou-Akotet *et al.*, 2003; Coll *et al.*, 2008).

The effects of malaria in pregnancy also are affected by the status of malaria in the community.

The main factors, which influence the epidemiology of falciparum malaria and malaria of other *Plasmodium* species, are the intensity of transmission and immune response of the infected person (Cheesbrough, 1987; Tutu 2003). Malaria transmission in an area may be stable or unstable. Immunity is maintained through continued exposure to malarial parasite(s). In stable transmission areas, most malaria infections are asymptomatic (Sirima *et al.*, 2003; Desai *et al.*, 2007). In areas of unstable, non-endemic transmission, adult women who have no significant level of immunity are more likely to be symptomatic when parasitaemic, and are at greater risk of developing severe disease and of death (WHO, 2004). Lower parity, especially first and second

pregnancies, and younger age increase the susceptibility to malaria (Mutabingwa *et al*., 2005).

2.1.2 MALARIA AND MATERNAL HEALTH

Morbidness in the pregnant women in the sub–Saharan region of Africa is most common, for in pregnancy, there is a synergistic change in both the physiological and humoral immunity level which render these women vulnerable to diseases of any kind (especially malaria which is endemic) [Kakkilaya, 2000].

Ghana is a malaria hyperendemic country, and pregnant women are especially vulnerable to malaria, which can adversely affect the outcome of pregnancy. The placenta may be heavily infected with malaria parasites in pregnancy, and this may result in adverse effects on the foetus (Menendez *et al*., 2000; Adebami *et al*., 2007). Malaria endemicity and parity are two of the factors that can influence the effects of malaria on a mother and her baby (Brabin, 1983). Primigravidae are more susceptible than multigravidae and have higher incidence of placental malaria (Brabin, 1983; Adebami *et al*., 2007). In malaria-endemic regions, even the babies of asymptomatic pregnant women may show intrauterine foetal growth retardation and low birthweight (Adebami *et al*., 2007). The evidence for malaria infection in pregnancy can be obtained from either the density of peripheral parasitaemia during pregnancy or placental infection at the time of delivery (Brabin, 1983). Parasite densities in placental infections are sometimes difficult to assess with accuracy because there seems to be no correlation between parasite density in peripheral blood and in the placenta in pregnant women with well-developed immunity in malaria-holoendemic regions (Brabin, 1983). Thus, the

placenta may contain large numbers of infected red blood cells (as many as 65%), whereas the peripheral blood is free from parasites (Brabin, 1983).

2.1.3 PATHOPHYSIOLOGY OF MALARIA

When an *Anopheles* mosquito penetrates human skin with its proboscis to obtain blood, it injects saliva mixed with an anticoagulant. If the mosquito is infected with *Plasmodium* cells known as sporozoites (a stage in its life cycle) it injects these into the bloodstream of its victim, the parasite makes its way to the liver where it rapidly grows, develops and multiplies mitotically into schizonts (pre-erythrocytic, PE, schizonts) in the liver (Figure 1). In *Plasmodium falciparum* the PE schizonts take 5½ - 7 days to develop. When mature each measures about 60μm in diameter and contains up to 30,000 merozoites. Merozoites (Figure 2), which are the next stage of division phase of the life cycle, either invade other liver cells (hepatocytes) or enter the host's bloodstream. In the bloodstream the merozoites invade the red cells through the sinusoids of the liver. These merozoites become attached to the red cells by special organelles, which bind to specific glycophorin protein receptors on the red cell membranes. The membranes become indented and the parasites enter the red cells. Thus, the merozoites in the bloodstream develop into trophozoites within a vacuole formed by the internal membrane of the host cell (Figure 1).

The trophozoites feed on haemoglobin by ingesting small amounts of red cell cytoplasm. Malaria pigment, haemozoin, is formed as an end product of haemoglobin breakdown. The trophozoite is fully developed through nuclear and cytoplasmic division in the process of schizogony to form schizonts. Mature schizonts rupture from the cells releasing merozoites, haemozoin, and toxins into the host's plasma (Figure 1). The entry

of toxic metabolites into the blood circulation brings about the well–known fever and chills that is characteristic of malaria (Cheesbrough, 1987; Tutu, 2003).

In *P. falciparum*, the incubation time from infection to an attack is 9-14 days. Those merozoites which are not destroyed by the host's immune system invade new red cells and develop into trophozoites and schizonts thereby causing further red cells to be destroyed. After several erythrocytic cycles, some merozoites enter red cells and instead of developing into schizonts they follow a sexual development and become gametocytes (these are thought to form in response to a developing immunity, lack of nutrients, or an accumulation of metabolites or parasite debris) [Cheesbrough, 1987; Tutu, 2003].

These gametocytes (gamete producing) are ingested by a female *Anopheles* mosquito in a blood meal or they die if not taken by a mosquito vector (Figure 1).

In the stomach of the mosquito, the male gametocyte rapidly divides into a number of male gametes each with a flagellum, which becomes free and highly motile, that on contact and entry into female gamete fertilization occurs to result in a zygote (Figure 1). The zygote develops into a motile oökinete, which penetrates the stomach wall of the mosquito, forming oöcyst (which contains large number of sporozoites) as shown in Figure 3. The sporozoites when mature leave the oöcyst and spread to all parts of the mosquito, particularly to the salivary glands and can then be injected into a subsequent victim, starting the cycle again (Figure 1).

In *P. vivax*, *P. ovale* and probably *P. malariae*, all stages of development subsequent to the liver cycle can be observed in the peripheral blood. However, in the case of *P. falciparum* only ring forms and gametocytes are usually present in the peripheral blood; developing forms appear to stick to the blood vessels of the large organs such as the

brain and restrict blood flow with serious consequences (Chessbrough, 2000, Miller *et al.*, 2002; Wiser, 2004).

While all four species have a haemolytic component i.e. when a new brood of parasites break out of the red blood cell, this is usually of little consequence. The exception is falciparum malaria where the parasites multiply very rapidly and may occupy 30% or more of the red blood cells causing a very significant level of haemolysis. One reason for this is that *P. falciparum* invades red cells of all ages whereas *P. vivax* and *P. ovale* prefer younger red cells (reticulocytes), while *P. malariae* seeks mature red cells (Chessbrough, 2000; Miller *et al*., 2002; Wiser, 2004).

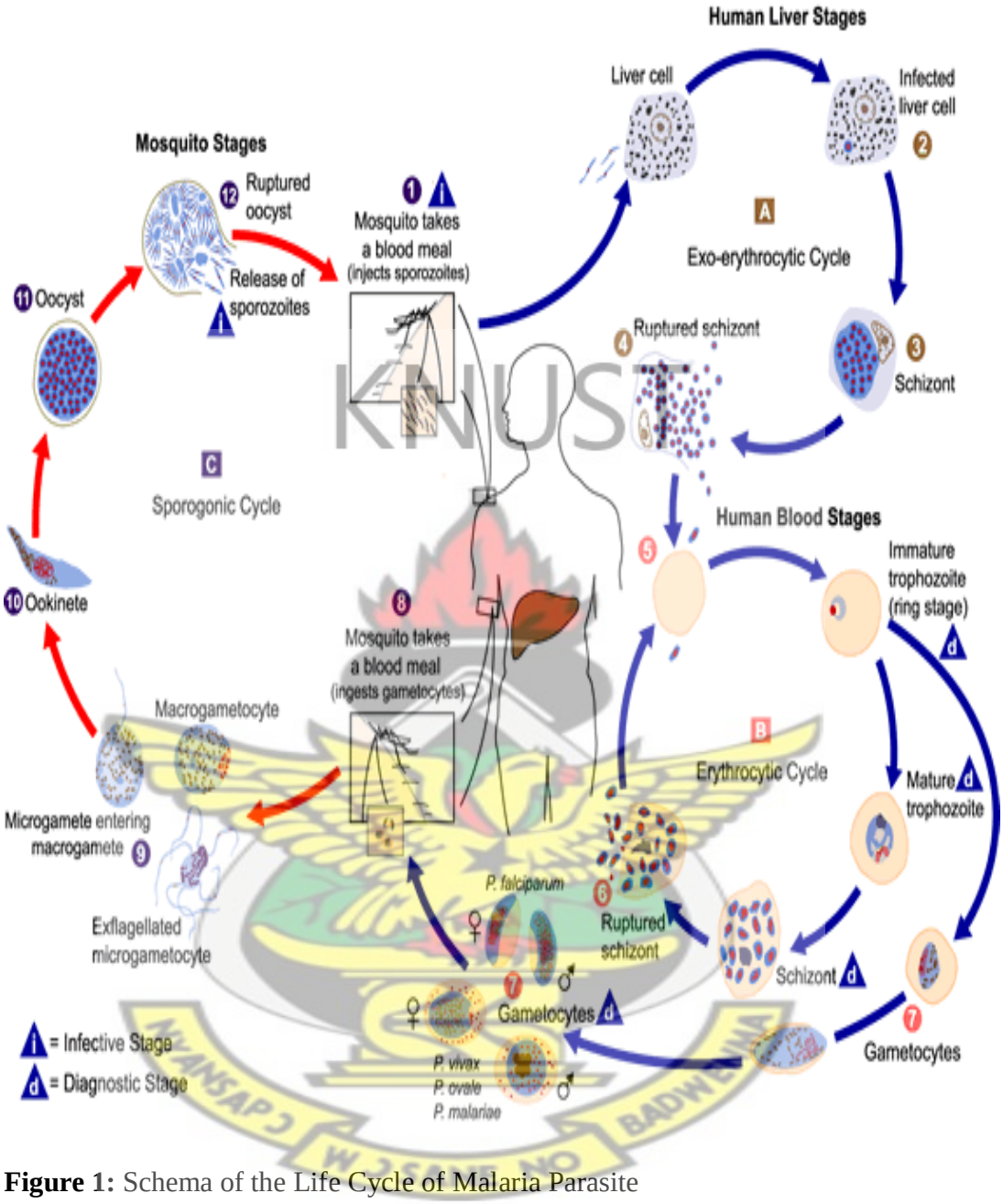

Figure 1: Schema of the Life Cycle of Malaria Parasite
(*Source: USA National Centre for Infectious Diseases, Division of Parasitic Diseases April 23, 2004***)**

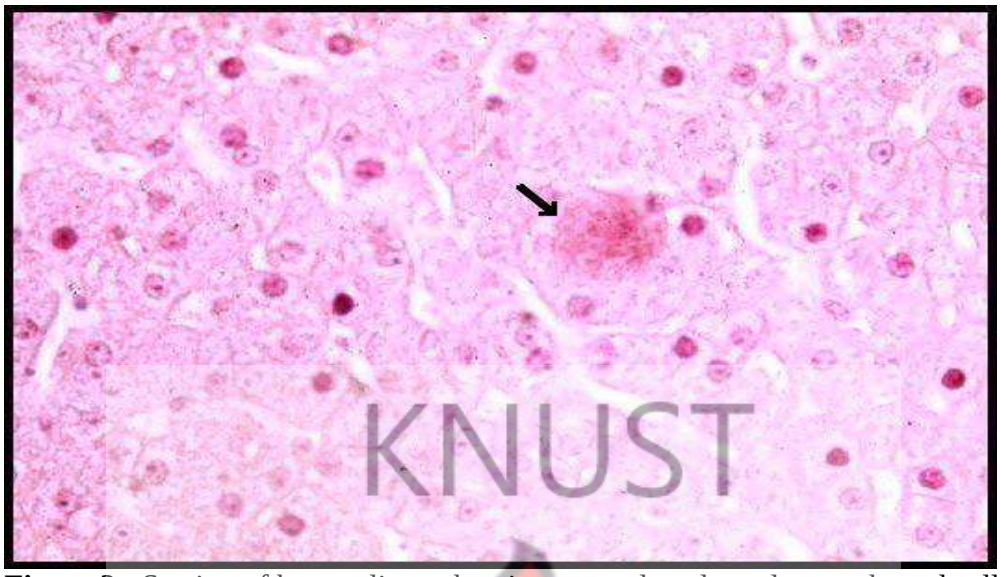

Figure 2: Section of human liver, showing a greatly enlarged parenchymal cell full of merozoites (see arrow). *(Source: www.rph.wa.gov.au/labs/haem/malaria)*

Figure 3: Section of mosquito stomach showing oöcysts (1) and sporozoites (2) *(Source: www.rph.wa.gov.au/labs/haem/malaria)*

2.1.4 THE *PLASMODIUM* SPECIES CAUSING MALARIA

***Plasmodium falciparum*.** This species causes falciparum malaria (formerly called malignant tertian malaria), kills through cerebral malaria or renal failure. Fever occurs about every 48 hours but this periodicity is often masked because the stages are not always synchronous. This periodicity is termed tertian because of fever on the first day, no fever on the second and then a return of fever on the third day. *Plasmodium falciparum* needs an average ambient temperature of at least 20ºC so is found mainly in the hotter and humid regions of the world. Its main species are found in tropical and subtropical Africa and parts of Central America and South America, Bangladesh, Pakistan, Afghanistan, Nepal, Sri Lanka, East Asia, Indonesia, Philippines, Haiti, Solomon Islands, Papua New Guinea and many islands in Melanesia. It is also found in parts of India, the Mediterranean and countries of North Africa (Cheesbrough, 1987, 2000; Wiser, 2004).

Again, malaria caused by *P. falciparum* (falciparum malaria) is the most serious form of the malarial disease and the most widespread, accounting for up to 80 of malaria cases worldwide (Alnwick, 2000).

Plasmodium vivax. This species causes vivax malaria (formerly called benign tertian malaria) which rarely kills. This species is not found in tropical Africa mainly because black Africans lack the red cell surface Duffy antigen that *P. vivax* requires for cell invasion (Chessbrough, 2000; Miller *et al.*, 2002; Wiser, 2004). It can exist in places with an average summer temperature of only 16ºC. *Plasmodium vivax* is mainly found in South America (occurring as far south as northern Argentina), Mexico, Sri Lanka, Papua New Guinea, and the Solomon Islands. It is also found in parts of South East Asia

Indonesia, Philippines, Madagascar, tropical and subtropical Africa, Korea and China (Chessbrough, 2000). Together with *P. ovale*, *P. vivax* is considered as causing relapsing malaria, so named because it can remain in a dormant hypnozoite stage for very long periods (years) in the liver. The adaptive value of this ability is that the parasite can persist in areas that experience long winters with no opportunities for transmission (Chessbrough, 2000; Wiser, 2004).

Plasmodium ovale. This species causes rare ovale malaria (formerly called tertian malaria) with a long incubation period and relapses at three-month intervals. It is found mainly in West Africa where it accounts for up to 10% of malaria infections (Chessbrough, 2000). There have been sporadic reports of infections from other parts of Africa and from the Philippines, Indonesia, China, and parts of the Far East, South East Asia and South America (Chessbrough, 2000). Like *P. vivax*, it is recurrent with a dormant liver stage.

Plasmodium malariae. This species causes quartan malaria with fever returning every 72 hours. It is remarkable in that it can persist in the blood of a host for decades at very low densities, but it does not have a dormant stage in the liver. Relapses can sometimes occur half a century after being infected (Chessbrough, 1987; Wiser, 2004). *Plasmodium malariae* accounts for up to 25% of malaria infections in tropical Africa and it is also found in Guyana, India, Sri Lanka and Malaysia of which it accounts for less than 10% of malaria infections (Chessbrough, 2000).

2.1.5 DISTRIBUTION OF MALARIA

All four species, except *P. vivax* which is not found in tropical Africa are found in regions all round the world but they are thought to have been introduced to the New World from Europe and Africa during the sixteenth century (Chessbrough, 1987). The distributions of *P. vivax* and *P. ovale* rarely overlap. Figure 4 below shows the world distribution of malaria of which the most affected continent is Africa. In the African Region where most cases and deaths due to malaria do occur, 74% of the population live in areas that are endemic and 19% in epidemic prone areas. Only 7% of the region's population live in low risk or malaria–free areas as shown in the Figure 5 below.

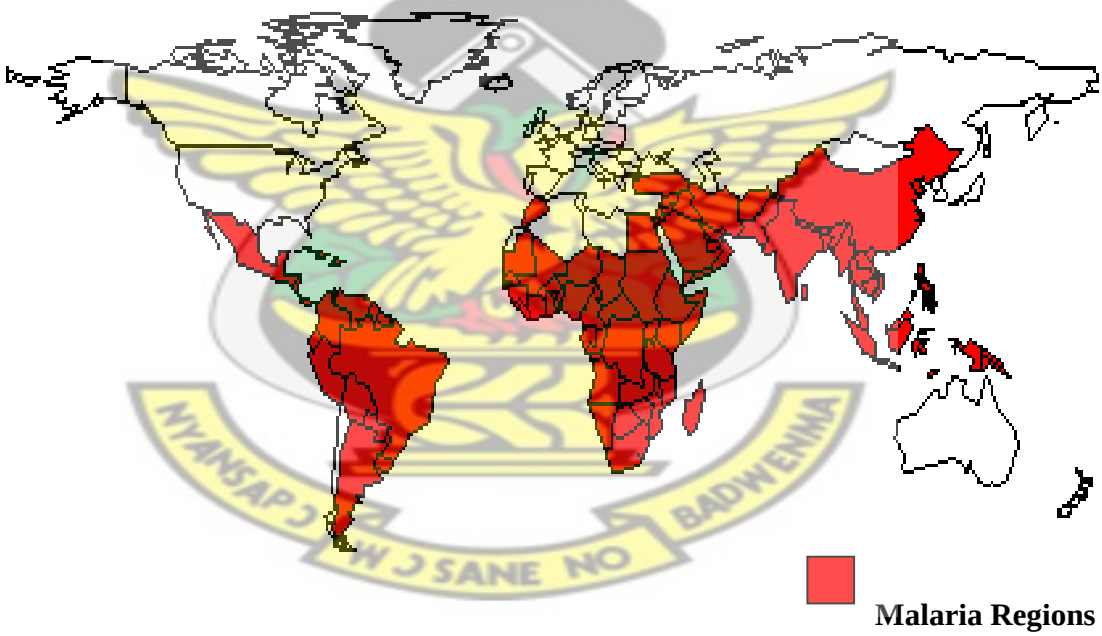

Figure 4: World Distribution of Malaria *(Source: U.S.A. Centres for Disease Control and Prevention, Atlanta, GA; 2004)*

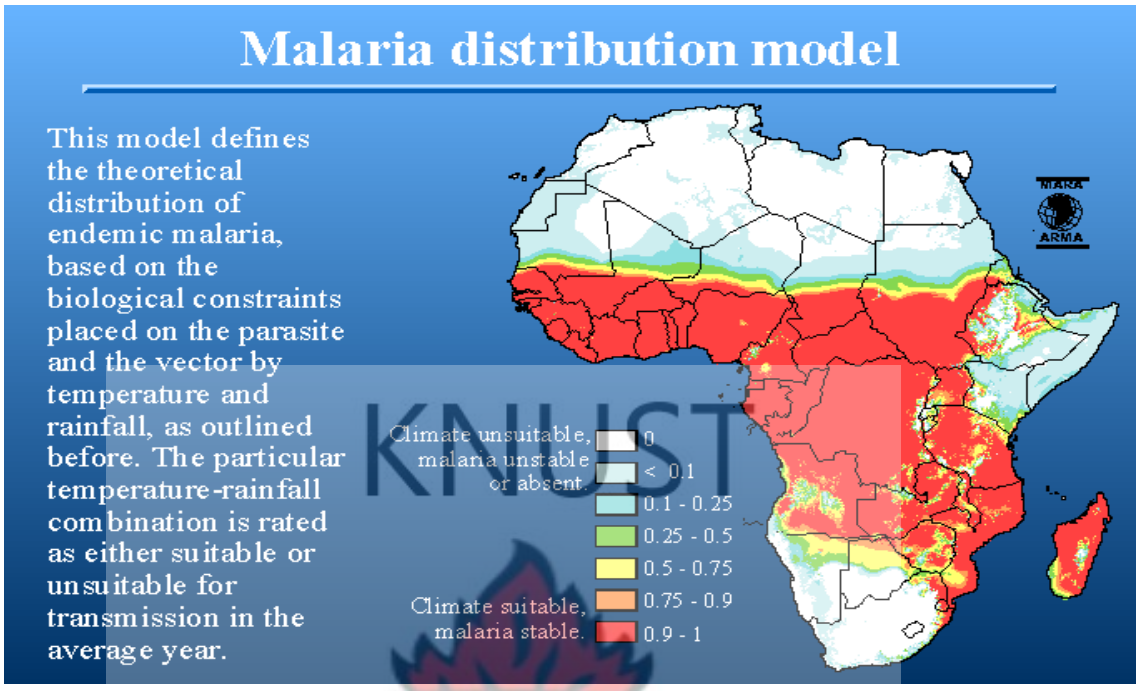

Figure 5: Malaria Distribution in Africa on climatological survey *(Source: www.mara.co.za)*

2.1.6 MOSQUITO VECTORS

Mosquitoes belong to the Order Diptera of the Class Insecta in the Phylum Arthropoda. Their life span is generally 3-4 weeks. They go through complete metamorphosis stages in their development i.e. from the egg, larval and pupal stages to a mature adult. Anopheline mosquitoes are the exclusive vectors of human malaria:

The *Anopheles* vectors

There are about 422 species of *Anopheles* worldwide, many of them, sibling species that can only be identified using genetic techniques. Of these, about 70 are malaria vectors but only about 40 are important (Kettle, 1995). The ability to transmit *Plasmodium* parasites depends on the mosquito living long enough for the parasite to complete its development, the mosquito's propensity to feed on humans; and whether or not the

mosquito is physiologically suitable for the parasite. However, most *Anopheles* are thought to be able to support normal development of at least one of the *Plasmodium* species.

They feed at night although few also feed at daytime. Anopheline mosquitoes rest with the body sloping forwards. Their breeding sites vary and include permanent or temporary pools, swamps, seepages, rice fields, tree holes, ditches and reservoirs with some requiring sunlight and others shade for breeding (Cheesbrough, 1987).

In Africa members of the *An. gambiae* and *An. funestus* species complexes are important vectors.

2.1.7 PATHOGENESIS, TREATMENT, PREVENTION AND COMPLICATIONS

Malaria is an acute febrile illness with incubation period of 7 days or longer. Thus, a febrile illness developing less than one week after the first possible exposure is not malaria (Vanderberg, 1980).

The different malarial parasites produce fevers of different frequency, depending on how long it takes to complete schizogony in erythrocytes. With the first attack of *P. falciparum*, fever is usually irregular rather than occurring with a regular, repeating pattern as seen with a tertian fever in subsequent attacks, and there are usually no relapses unlike with *P. ovale* and *P. vivax* where hypnozoites are formed (Vanderberg, 1980). For *P. falciparum* the temperature may rise at 48 hour intervals. Again, *P. falciparum* has the ability to cause infected red blood cells (RBCs) to adhere to the linings of small blood vessels (Figure 6). Such sequestrations of the parasites cause

considerable obstruction to tissue perfusion which may lead to the severity of malaria (Miller *et al*., 2002).

Malaria is especially dangerous to pregnant women and small children. Severe and complicated malaria is usually caused by delay in treating an uncomplicated attack of *P. falciparum*. The patient complains of headache, fever and aches and pains all over the body, diarrhoea and abdominal pain are sometimes present. Spleen and liver are often palpable on clinical examination. This may be misdiagnosed as influenza in non-endemic areas, and unless treated promptly, the clinical picture can deteriorate rapidly (Schulman, Oppenheim and Vanderberg, 1980). A patient with severe and complicated malaria will often present with impaired consciousness, weakness, and jaundice. Other complications are cerebral malaria (non-rousable coma), generalized convulsions, normocytic anaemia, renal failure, hypoglycaemia, fluid, electrolyte and acid-base disturbances, pulmonary oedema, circulatory collapse, shock, disseminated intravascular coagulation, hyperpyrexia, hyperparasitaemia, and malarial haemoglobulinurea. These features may occur singly or in combinations (Cheesbrough, 1987).

As to whether the *Plasmodium* parasites cause their mosquito hosts such discomfort and morbidity is a matter of debate, with several contrasting opinions stressed. It does seem that mosquitoes that are carrying the malaria parasite do experience decreased life expectancy and higher mortality rates than their non-infected counterparts (Kettle, 1995).

Cell-mediated and humoral immunity play active roles in immune-competent individuals living in malaria endemic areas. More immunoglobins especially IgG is raised when the immune cells are activated by specific antigens, for instance, circumsporozoite proteins found on sporozoites. Vaccines are currently being developed

against three stages of the parasite: gametocytes, sporozoites, and intra-erythrocytic merozoites (Vanderberg, 1980, Rogerson *et al*., 2007). The most important part of host defence seems to be antibody production; hence non-immune individuals visiting endemic areas are very vulnerable.

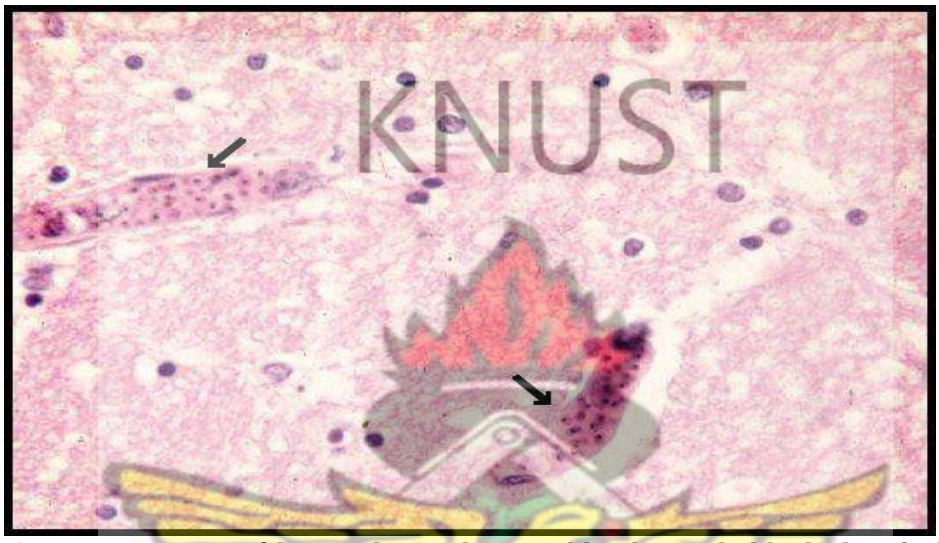

Figure 6: Section of human brain showing blood vessels blocked with developing *P. falciparum* parasites (arrows). *(Source: www.rph.wa.gov.au/labs/haem/malaria)*

Prevention of Malaria Infection

Prevention may be carried out either by interrupting transmission in vector control, or by giving the patient prophylactic drugs. As yet, there is no widespread effective vaccination scheme. Vector control effectiveness has declined in recent years; due to lack of personnel, inefficient insecticide usage, and mass population movements (Peters, Gilles and Mosby-Wolfe, 1995) and other factors alluded. However, simple means such as insecticide impregnated mosquito nets remain effective.

The use of prophylactic drugs has been generally effective, for both travellers and people living in endemic areas. There are several considerations when prescribing chemoprophylactic drugs, such as duration of travel, species of parasite, and parasite

transmission intensity in the specific area. It is very hard to recommend prophylactic drugs for South East Asia due to the high degree of resistance there (Bradley, 2001). In Africa, chloroquine resistance is widespread, so chloroquine does not offer effective prophylaxis. For prophylaxis against chloroquine sensitive malaria, a course of 300mg chloroquine per week could be prescribed before travel and followed through the whole time the person is at risk in an endemic area. For resistant malaria, more expensive drugs such as mefloquine could be used at a dosage of 250mg weekly. It is important to know the degree of malarial drug resistance in the particular area of destination. A recommended combination for areas with resistant *P. falciparum* consists of 300mg chloroquine weekly, with 200mg proguanil daily (Bradley, 2001).

Treatment and Diagnosis

For treatment, chloroquine sensitive malaria is controlled by intravenous chloroquine. For drug resistant forms, quinine dihydrochloride combined with a dose of tetracycline antibiotics should be used (tetracycline in pregnant women and children under one year old is not recommended). Quinine may also be infused. The most important element in the diagnosis of malaria is a high level of suspicion (Schulman, Oppenheim and Vanderberg, 1980), since most of the physicians (particularly in sub-Saharan Africa) base diagnosis of diseases on their clinical judgements (Polage *et al.,* 2006). As malarial distribution is patchy, a geographical and travel history indicating exposure is important, though the possibility of induced malaria (through contaminated needles or transfusions) cannot be overlooked. The clinical symptoms may be confused with a number of other diseases. In the majority of cases, microscopic examination of thick and thin films of the peripheral blood will reveal malaria parasites, though thick films are more useful (Figure

7). Most patients with severe malaria have significant hyperparasitaemia, unless they have already taken antimalarial drugs. The presence of malaria pigment in monocytes is also a useful diagnostic indicator in malaria, especially in anaemic children and in suspected severe malaria with absent parasitaemia due to the synchronous nature of infection (Schulman, Oppenheim and Vanderberg, 1980). It is important to treat promptly on diagnosis to avoid complications.

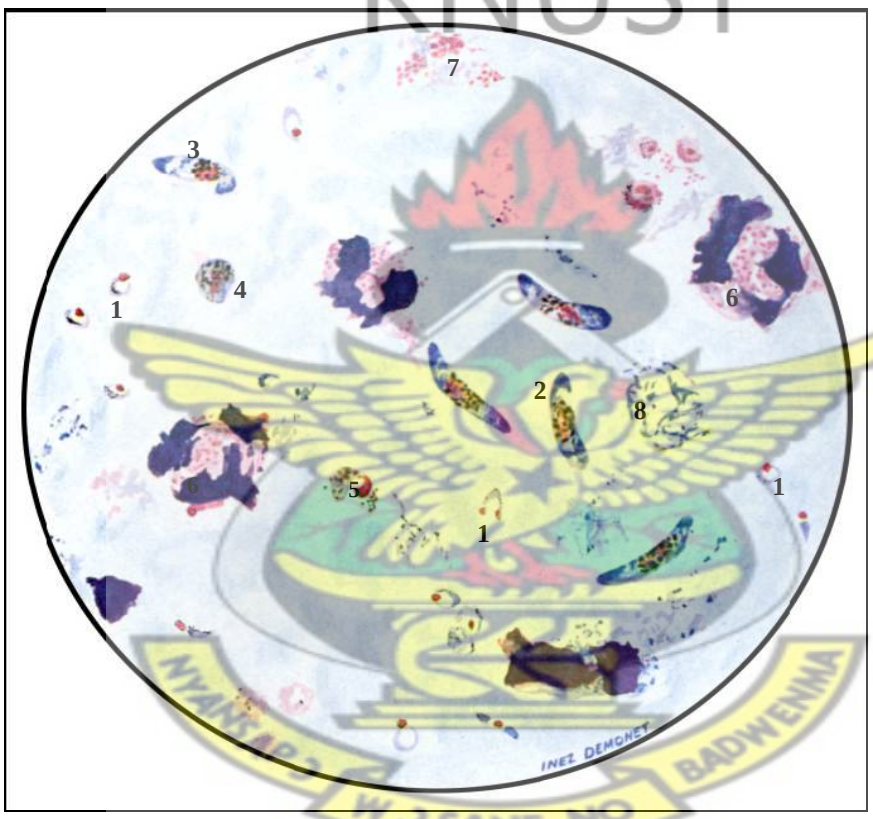

Figure 7: Stages of *P. falciparum* appearance in thick blood smears **(**Source: Wilcox A. Manual for Microscopical Diagnosis in Man. U.S. Department of Health, Education and Welfare, Washington 1960)

1: Small trophozoites
2: Gametocytes–normal.
3: Slightly distorted gametocyte.
4: "Rounded-up" gametocyte.
5: Disintegrated gametocyte.
6: Nucleus of leukocyte.
7: Blood platelets.
8: Cellular remains of young erythrocyte

Differential Diagnosis and Management of Malaria

Failure of physicians to consider the diagnosis of malaria in a person returning from an endemic area is a frequent cause of morbidity and mortality (WHO, 1991). Errors in diagnosis can result from failure to do a malarial blood film, failure to take a travel history, misjudgement of severity, faulty parasitological diagnosis and laboratory management, missed hypoglycaemia, failure to carry out ophthalmoscopic examination for retinal haemorrhages, or misdiagnosis.

Malaria may be misdiagnosed as a number of other conditions, most importantly meningitis, typhoid fever and septicaemia. Other differential diagnoses include influenza, hepatitis, and scrub typhus, all types of viral encephalitis, gastro-enteritis, and haemorrhagic fevers. It is easy to see why so many conditions may be confused with malaria, given the wide range of symptoms and complications (WHO, 1991).

A number of measures should be applied to all patients with clinically diagnosed or suspected severe malaria. Antimalarial chemotherapy must be given parenterally (intravenously or intramuscularly). Oral treatment should be substituted as soon as possible. It is necessary to eliminate other possible causes of coma in the unconscious patient, so lumbar puncture should be carried out. The patient should be monitored for hypoglycaemia and glucose given if necessary (Schulman, Oppenheim and Vanderberg, 1980). The rate of infusion of intravenous (IV) fluids should be carefully monitored, as should the urine production. High body temperatures should be reduced by antipyretics or sponging.

The administration of a prophylactic anticonvulsant such as Phenobarbital sodium (10-15 mg/kg body weight, intramuscularly) is advised in severe malaria. Regular monitoring is essential, and the patient should be nursed on his/her side to avoid the risk

of aspiration of fluid. The patient must not be allowed to lie in a wet bed, and should be turned every couple of hours. The airways must be kept open, and if rectal temperature (monitored every 4 hours for at least the first 48 hours after infection) rises above 39°C then paracetamol may be given, and sponging initiated. Drugs which increase the risk of gastrointestinal bleeding such as Aspirin or corticosteroids must be avoided (Schulman, Oppenheim and Vanderberg, 1980).

The drugs currently appropriate for the treatment of malaria vary according to the type of malaria. For chloroquine sensitive malaria quinine, is administered 10 mg base/kg of body weight in isotonic fluid by constant rate IV infusion over 8 hours followed by 15 mg base/kg body weight given over the next 24 hours. Alternatively, chloroquine 5mg base/kg body weight in isotonic fluid by constant rate IV infusion over 6 hours may be given, repeated every 6 hours for a total of 5 doses. If IV infusion is not possible, chloroquine 3.5 mg base/kg every 6 hours intramuscularly may be given until the total dose is 25 mg base/kg. Oral therapy should be initiated as soon as the patient can swallow (Schulman, Oppenheim and Vanderberg, 1980).

For chloroquine resistant malaria (largely diagnosed by the geographical area in which the malaria was contracted), a loading dose of 20 mg quinine dihydrochloride salt/kg body weight should be infused over 4 hours, in 5% dextrose saline. An infusion pump may be used to introduce 7 mg salt/kg over 30 minutes, if available. Next a maintenance dose of quinine 10 mg salt/kg in dextrose saline should be administered 12 hours after the loading dose (no delay is needed if an infusion pump was used). The maintenance dose must be repeated every 8-12 hours until the patient can take oral therapy.

Alternatively, quinidine gluconate (only used if parenteral quinine is unavailable) may be infused as a loading dose of 15 mg base/kg body weight over 4 hours. The

maintenance dose is 7.5 mg base/kg repeated every 8 hours until oral medication can be taken. In all cases, loading doses are not required if the patient has taken quinine, quinidine or mefloquine in the preceding 7 days. If patients require more than 48 hours parenteral therapy, then the maintenance doses of quinine and quinidine must be reduced by one third to one half (Schulman, Oppenheim and Vanderberg, 1980).

Oral therapy depends on parasite sensitivity and drug availability. Quinine tablets, 10mg/kg, every 8 hours to complete 7 days treatment is a common treatment. Alternatively, 15 mg/kg mefloquine may be given in 2 doses 12 hours apart (but not to pregnant women). A study (WHO, 1995) suggests that higher than normal (i.e. 25 mg/kg as opposed to 15 mg/kg) doses of mefloquine are considerably more effective, although unpleasant side effects such as dizziness, anorexia over the 7 days after treatment, and vomiting which may necessitate re-treatment, may be observed. Another useful oral antimalarial drug is halofantrine, 8 mg base/kg every 6 hours for three doses, although this must not be given to pregnant women. Where there is significant quinine resistance (as in malaria contracted in Thailand, Cambodia and Vietnam) an oral dose of tetracyclines, 250 mg four times a day, for seven days of treatment should be given. It is dangerous to give IV tetracyclines, and they should not be given to pregnant women or children under 8 years of age.

All of the drugs mentioned above have certain problems associated with them. Quinine, the drug of choice for severe malaria, may cause serious hypoglycaemia, and quinine poisoning is treated with oral activated charcoal. Chloroquine, until recently, was the most widely prescribed antimalarial in the tropics, and, though providing symptomatic relief does cause nausea, blurred vision, hypotension and chloroquine poisoning, coma and dysrhythmias (WHO, 1995). Mefloquine resembles quinine in structure and remains

generally effective. It may, however, cause nausea and diarrhoea. Halofantrine is effective against resistant falciparum, but has poor bioavailability and may not be used in pregnant women. Sulfadoxine-pyrimethamine is used only if chloroquine and quinine are not available, as there is widespread resistance to it (SP). Quinghaosu, an artemisinin compound currently used is effective, with rapid action and few side effects. Even the newest drugs are not flawless; the side effects of Larium caused uproar (WHO, 1995).

The use of drugs such as mefloquine and chloroquine in the prophylactic role appears somewhat questionable, given the deteriorating global resistance situation; these drugs are no longer prescribed as prophylactic antimalarials. Perhaps insecticide impregnated mosquito nets and insect repellent creams are the best prophylaxis for a traveller, especially due to the problems of unpleasant side effects and non-compliance. Indeed, it seems that the initial widespread prophylactic use of the now outdated antimalarials was responsible for the rise of resistance in the first place (Zucker and Campbell, 1992). This is a cautionary indicator for how we use our new drugs such as artemisinins in the field. It seems that many travellers still take antimalarials in the prophylactic role, however. Paucity of information on the safety and efficacy of most antimalarials in pregnancy, particularly for exposure in the first trimester has led to different treatment recommendations in pregnant women. Organogenesis occurs mainly in the first trimester and this is therefore the time of greatest concern for potential teratogenicity, although nervous system development continues throughout pregnancy. The antimalarials considered safe in the first trimester of pregnancy are quinine, chloroquine, proguanil, pyrimethamine and sulfadoxine–pyrimethamine. Of these, quinine remains the most effective and can be used in all trimesters of pregnancy including the first trimester (WHO, 2006). In reality women often do not declare their pregnancies in the first

trimester and so, early pregnancies will often be exposed inadvertently to the available first line treatment. Inadvertent exposure to antimalarials is not an indication for termination of the pregnancy.

2.2 MALARIA AND SOCIOECONOMIC FACTORS

The low social status of women in developing countries limits their access to economic resources and basic education and thus their ability to make decisions related to their health and nutrition. Some women are denied access to care when it is needed either because of cultural practices of seclusion or because decision-making is the responsibility of other family members. Lack of access to, and use of essential obstetric services including malaria prophylaxis, are crucial factors that contribute to high maternal mortality (Adam *et al*., 2005; Evans *et al*., 2005; Sanders, Todd and Chopra, 2005; Vallely *et al*., 2007). Lack of decision-making power and of alternative opportunities consigns many women to a life of repeated childbearing. Excessive physical work coupled with poor diet also contributes to poor maternal outcomes.

Worldwide, nearly 600 000 women between the ages of 15 and 49 die every year as a result of complications arising from pregnancy and childbirth (WHO,1996a; Kulmala, 2000). The tragedy is that these women die not from disease but during the normal, life-enhancing process of procreation. Most of these deaths could be avoided if preventive measures were taken and adequate care was available. For every woman who dies, many more suffer from serious conditions that can affect them for the rest of their lives. Maternal mortality is an indicator of disparity and inequity between men and women and

its extent is a sign of women's place in society and their access to social, health, nutrition services and to economic opportunities.

Poverty, ignorance and malnutrition do contribute to the enormous burden of malaria in pregnancy. Maternal and perinatal morbidity and mortality are high, especially in neglected situations. The main burden results from infection with *P. falciparum* (Sanders, Todd and Chopra, 2005; Valley *et al*., 2007). The poor health and nutrition of women and the lack of care that contribute to their death in pregnancy and childbirth also compromise the health and survival of the infants and children they leave behind. It is estimated that nearly two-thirds of the 8 million infant deaths that occur each year result largely from poor maternal health and hygiene, inadequate care, inefficient management of delivery, and lack of essential care of the newborn (WHO, 1996b; Kulmala, 2000).

Again, malaria as a quintessential disease of poverty has long been seen as a consequence of poverty, but today there is strong evidence that malaria actually helps to create poverty and sustains underdevelopment. Reducing the burden of malaria is, therefore, an extremely cost–effective way of promoting development and reducing poverty. Around half a billion cases of malaria each year result in well over one million deaths, and over ninety percent of all these deaths occur in sub–Saharan Africa (Alnwick, 2000).

WHO (2000) reported that many African countries lacked the infrastructures and resources necessary to mount sustainable campaigns against malaria and as a result few benefited from historical effort to eradicate malaria. In Africa, not only does malaria result in lost life and lost productivity due to the disease and premature death, but

malaria hampers children's schooling and social development through both absenteeism and permanent neurological and other damage associated with severe episodes of the disease.

Although we have moderately effective ways to prevent and treat malaria, stemming the disease is very challenging, for biological as well as other sociological reasons. Not only does *Plasmodium* continue to develop drug resistance, but nations (those in Africa) with political unrest do strive to distribute drugs to prevent or treat malaria. Figure 8 below shows the estimated burden of malaria and poverty in the world.

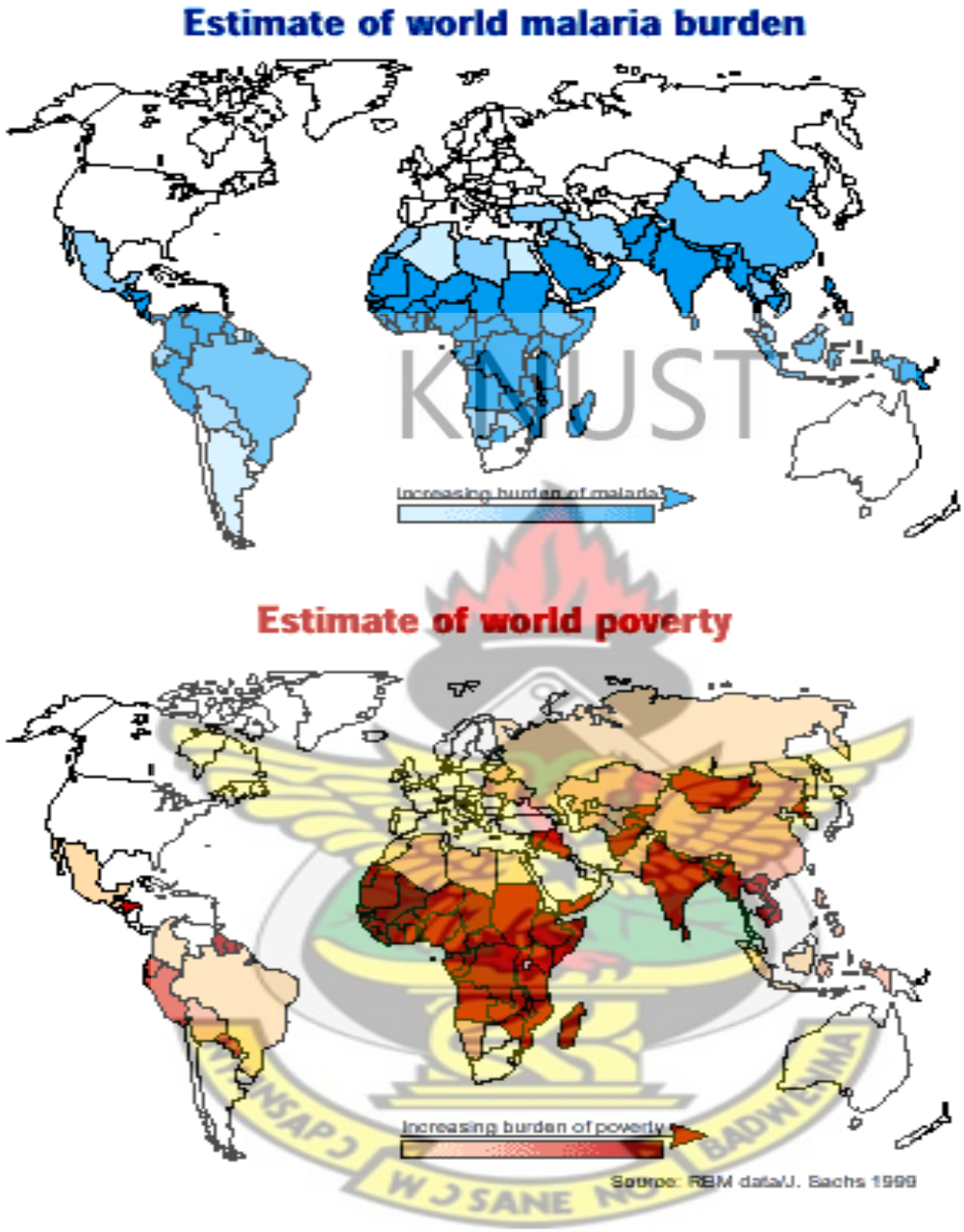

Figure 8: Global effect of malaria on humanity (*Directions of arrows are indicative of increasing burdens of malaria and poverty)* (*Source. RBM data, Sachs 1990)*

2.3 EPIDEMIOLOGY/PUBLIC IMPACT OF MALARIA IN PREGNANCY

Malaria in pregnancy is a major public health problem in tropical and subtropical regions of the world. In Africa, millions of women living in malaria-endemic areas become pregnant each year and most live in areas of relatively stable malaria transmission (WHO 2004; Tagbor *et al*., 2008). Each year more than 500 000 women die during pregnancy or childbirth (WHO, 2004) and more than 4 million babies die in the first 28 days of life, accounting for 38% of mortality in children aged less than five worldwide (Lawn, Cousens and Zupan, 2005; Adam *et al*., 2005). Of every 1000 children born in Africa and South East Asia, 44 and 38 respectively, die in the neonatal period, compared with four in high income countries.

In sub-Saharan Africa, the rate of maternal mortality is 2.5 times more than those in Asia, which are in turn more than 20 times those in developed countries (WHO/UNICEF, 2004). Effective interventions to reduce maternal and neonatal deaths exist (Darmstadt *et al*., 2005), but they are not available to people living in the poorest parts of the world (WHO, 2005).

In stable transmission areas, few malaria infections in healthy adults result in fever, and the same is true for semi-immune pregnant women. Although it is commonly assumed that most parasitaemic pregnant women are asymptomatic. Tagbor (2005) in his studies on treatment of malaria in pregnancy suggested that pregnant women were more likely to complain of symptoms compatible with malaria if they were parasitaemic than if they were not, despite the absence of a recent history of fever.

In Africa, 5–10% of pregnant women may develop severe anaemia (defined as haemoglobin <70 g/L or <80 g/L) (Verhoeff *et al*., 1999; Menendez, Fleming and Alonso, 2000; Shulman, Dorman and Bulmer, 2002). Desai *et al*. (2007) estimated that 26% of severe anaemia among pregnant women of all gravidities in both Africa and Asia is attributed to malaria. Thus, depending on the relative contribution of other possible causes of anaemia and local epidemiological profiles, approximately one in four cases of severe anaemia may be prevented with adequate prevention of malaria in pregnancy. There is scarcity of information on maternal mortality rates in Africa despite the many studies in malaria in pregnancy. The percentage of direct and indirect malaria-related maternal deaths range from 0.5% to 23% in hospital studies; and from 2.9% to 17.6% in community-based studies (Brabin and Verhoeff, 2002; Desai *et al*., 2007). A study by Brabin, Hakimi and Pelletier, (2001) estimated that in holoendemic malarious areas with a 5% prevalence of severe anaemia (haemoglobin <70 g/L), there would be nine maternal deaths related to severe malarial anaemia per 100 000 live births to primigravidae.

Malaria in pregnancy has an unequivocally devastating effect on the newborn infant and low birthweight (LBW) is associated with a marked increase in infant mortality (Steketee *et al*., 2001; Guyatt and Snow, 2001; Murphy and Breman 2001). In areas of high malaria transmission in Africa, the risk of LBW approximately doubles if women have placental malaria (Guyatt and Snow, 2004), with the greatest effect in primigravidae (Brabin *et al*., 1999). The odds ratio of LBW associated with malaria is two to seven times higher in primigravid than multigravid women (Brabin *et al*., 1999).

In sub-Saharan Africa, nearly 20% of LBW deliveries are attributable to malaria in pregnancy, and this is 35% of preventable LBW in women of all pregnancy levels

(Steketee *et al*., 2001; Guyatt and Snow, 2004). Among paucigravidae (women at first and second pregnancies), chloroquine prophylaxis or IPT have proven to be effective in prevention of malaria with reduction of the risk of LBW by as much as 43% (Garner and Gülmezoglu, 2006). Malaria-induced LBW is estimated to be responsible for between 62 000 and 363 000 infant deaths every year in Africa, which translates to three to 17 deaths per 1000 live births (Murphy and Breman, 2001). Another estimate suggests that 11.4% of neonatal deaths and 5.7% of all infant deaths in malaria endemic areas of Africa may be caused by malaria in pregnancy-associated LBW (Guyatt and Snow, 2001), which translates to around 100 000 infant deaths (Guyatt and Snow, 2004). Not surprisingly, this effect is greatest in infants born to primigravidae at 17.6% of neonatal deaths and 9.8% of infant deaths (Guyatt and Snow, 2001). The relative contribution of IUGR or preterm delivery in causing LBW varies by the level of malaria endemicity as well as other factors, such as access to prompt treatment and spread of HIV. In areas of high malaria transmission where women are exposed to a greater frequency of antenatal infections and may have acquired immunity to prevent most febrile episodes that cause preterm delivery, IUGR is likely to be the predominant cause of malaria -associated LBW (Brabin and Rogerson, 2001). Malaria in pregnancy in these settings may be responsible for up to 70% of IUGR, whereas its contribution to preterm delivery, although still substantial, is relatively lower at up to 36% (Steketee *et al*., 2001).

2.4 MALARIA IN PREGNANCY, IMPLICATION FOR BIRTHWEIGHT

2.4.1 EFFECTS OF MALARIA DURING PREGNANCY IN RELATION TO INTENSITY OF TRANSMISSION

Malaria in pregnancy causes considerable morbidity and mortality in pregnant women and newborns in sub-Saharan Africa (Guyatt and Snow, 2001; Ramharter *et al.,* 2007). The symptoms and complications of malaria during pregnancy differ by the intensity of malaria transmission of the setting (stable/unstable) and thus the level of immunity the pregnant woman has obtained.

Stable transmission predominates in Africa, south of the Sahara and consequently this region bears the greatest burden of malaria infections during pregnancy. In these areas of high or moderate (stable) malaria transmission, the ill health effects are particularly apparent in the first and second malaria-exposed pregnancies (WHO, 2002). Despite the higher prevalence of parasitaemia and higher parasite density compared to non-pregnant women, falciparum malaria infection in pregnant women in these areas is usually asymptomatic. Maternal immunity reduces the risk for severe illness. Thus, clinical malaria is not a prominent feature of the infection during pregnancy and in settings of stable transmission, maternal mortality due solely to malaria is uncommon. In these settings, the major detrimental effect of infection is low birthweight (LBW) and maternal anaemia (WHO, 2002; Guyatt and Snow, 2004). In areas with stable malaria transmission (where prevalence during pregnancy ranges from 10%-65%) malaria during pregnancy contributes to approximately 2%-15% of maternal anaemia and 8%-14% of LBW. Malaria contributes to an estimated 8%-36% of prematurity and to

additional 13%-70% of intrauterine growth retardation (IUGR) depending on level of malaria risk (Shulman *et al*., 1999; Steketee *et al.*, 2001; Gilles *et al*., 2007). Maternal malaria infection accounts for almost 30% of all causes of LBW that can be prevented during pregnancy (Steketee *et al*., 1996; Steketee *et al.*, 2001). Maternal malaria infection is estimated to account for 3%-8% of all infant deaths (Shulman *et al*., 1999; Steketee *et al.*, 2001).

Plasmodium falciparum malaria can run a very turbulent course in pregnancy, particularly in the first and second pregnancies. These complications are more common and severe in hyper-endemic areas for falciparum malaria. Physiological changes of pregnancy contribute to the aggravation of malaria infection. There is a generalized immunosuppression in pregnancy with reduction in gamma globulin synthesis and inhibition of the recticulo-endothelial system, resulting in decrease in the levels of antimalarial antibodies and loss of acquired immunity to malaria (Kakkilaya, 2002). This makes the pregnant woman more prone to malaria infection, and, parasitaemia tends to be much higher (Kakkilaya, 2002). Changes in the hormonal milieu, increase in the body fluid volume, decrease in haemoglobin level and other changes add to the severity of infection. Also, placenta is the preferred site of sequestration and development of malaria parasites. Intervillous spaces are filled with parasites and macrophages, interfering with oxygen and nutrient transport to the foetus leading to LBW and other complications of the new born (Kakkilaya, 2002). Malaria in pregnancy puts the foetus into great danger. High grades of fever, placental insufficiency, hypoglycaemia, anaemia and other complications can adversely affect the foetus. Also transplacental spread of the infection can result in congenital malaria in the foetus (Kakkilaya, 2002). Pregnant women in sub–Saharan Africa are at risk of severe

sequelae and delivering LBW babies (approximately 95% of all LBW newborns in the world occur in low-income countries) as a result of malaria infection (Steketee *et al*., 2001, Challis *et al*., 2004). However, in areas with high *P. falciparum* malaria transmission, women may have acquired substantial immunity against the malaria parasites and that, in their first and second pregnancies they are most at risk of malaria associated anaemia and LBW (McCormick, 1998; WHO, 2002; Guyatt and Snow, 2004).

Severe falciparum malaria in full term pregnancy carries very high mortality. Maternal distress may go unrecognised in these patients and, therefore, careful monitoring of maternal and foetal parameters is of great importance. Falciparum malaria induces uterine contractions, resulting in premature labour. Thus, the frequency and intensity of contractions appear to be related to the height of the fever. There is, therefore, the need to monitor the uterine contractions and foetal heart rate which may reveal asymptomatic labour, foetal tachycardia and bradycardia indicating foetal distress (Kakkilaya, 2002).

Malaria-related Anaemia in pregnancy

In malaria endemic communities, pregnant women and children are more vulnerable to malaria infection. Its effects in pregnancy include chronic anaemia, acute severe anaemia, miscarriage/forced abortion and pre-term delivery in the mother, and in the foetus and newborn; low birthweight, congenital malaria, stillbirth, perinatal and neonatal deaths (Shulman *et al*., 1999; Menendez *et al*., 2000). In Sub-Saharan Africa, the major detrimental effect of malaria infection is low birthweight (LBW) and maternal anaemia (Shulman *et al*., 1999; Steketee *et al.*, 2001; Kayentao *et al.*, 2005). In Africa, anaemia remains a major health problem. It is highly prevalent in Ghana and the fourth leading reason for admissions in many hospitals (Agyei, 2005). It has been described as

the second leading cause of death. The main causes of anaemia can be attributed to poor diet that has low iron bio-availability (extent to which a nutrient is absorbed into the blood stream), low absorption enhancers, inhibitors, excessive blood loss, breakdown of the red blood cells and increase in the requirements of essential elements during the growth of the foetus. Malaria, other fever cases, parasitic worm infestations and genetic disorders have also been identified as other causes of anaemia (van den Broek, 1996; Agyei, 2005; Glover-Amenyor, Owusu and Akanmori, 2005).

Studies on *P. falciparum*–related anaemia in pregnant women (Guyatt and Snow, 2001) suggest that about 400,000 pregnant women develop moderate or severe anaemia each year in Sub-Saharan Africa as a result of malaria infection. In Ghana, it has been estimated that 64.5% of pregnant women are anaemic whilst 59% lactating women are anaemic (Agyei, 2005).

2.4.2 PATHOPHYSIOLOGICAL PROCESSES AND RISKS FOR LOW BIRTH WEIGHT BABIES

Pregnancy–associated malaria is characterized by placental malaria and the sequestration of malaria parasites. Placental malaria is defined as the accumulation of *Plasmodium*–infected erythrocytes in the intervillous spaces in the placenta, causing histological changes including leukocyte-induced damage to the trophoblastic basement membrane. (Uneke, 2007a). The *P. falciparum* parasites in pregnant women have substantial adverse effects on pregnancy outcome (causing both prematurity and IUGR) and, are thus, the pathogenesis of LBW and infant mortality (Ismail *et al.*, 2000; Adegnika *et al.*, 2006).

Pregnancy itself is immunosuppressive, and the developing placenta provides a niche for new parasite strains to sequester and avoid elimination (Rogerson and Beeson, 1999; Duffy and Fried, 2003). Examination of placental blood films for infected erythrocytes is often much more difficult and error prone than examination of peripheral blood because of tissue debris, large numbers of white blood cells, and multiple stages of the parasites found in placental tissues (Singer *et al*., 2004; Malhotra *et al.*, 2005).

When a pregnant woman is infected with the malaria parasite, the infected erythrocytes bind to specific receptors in the placenta, especially chondroitin sulphate A, and interfere with oxygen and nutrient transport across the placenta. Anti-adhesion immunoglobulin G antibodies against chondroitin sulphate A–binding parasites are associated with protection from maternal malaria that develops only over successive pregnancies (Dorman, 2000). These infected erythrocytes congregate in the maternal placental vascular space, where the parasites replicate. Malaria-infected placentas are frequently observed to carry antibodies, cytokines, and macrophages, which are indicative of an active immune response (Ismail *et al.*, 2000). This immune response may stimulate early labour, though the precise effect of malaria-parasitized placentas on prematurity is not clear. The IUGR effect appears to relate to nutrient transport to the foetus. First, a high density of parasites and chronic parasite infection in the placental blood and the associated cellular immune response may result in consumption of glucose and oxygen that would have gone to the foetus. Second, histopathological studies of infected placentas have found thickening of the cytotrophoblastic membranes, which may interfere with nutrient transport (Ismail *et al.*, 2000). However, the details of these biological processes remain uncertain given that they can be studied only after the placenta has been delivered. Malaria-associated maternal anaemia may also contribute

independently to IUGR (Ismail *et al*., 2000; Verhoeff *et al*., 2001), most likely through a reduction in oxygen transport to the foetus.

Low birthweight is the single greatest risk factor for neonatal and infant mortality (McCormick, 1985). In Africa, malaria is responsible for a significant number of the cases of preventable LBW (Parise *et al*., 1998; Adegnika *et al*., 2006). The effects on neonatal mortality are even more marked, with a LBW baby being nine times more likely to die in the first month of life than a normal-weight baby (Aitken, 1999; Guyatt and Snow, 2004). The risks for mortality increase steadily as the birthweight decreases to below the LBW threshold. Low birthweight can be due to prematurity or IUGR. Identifying LBW cases caused by prematurity can be difficult, as many African women are not certain of their gestational age; as a result, very few studies report separately data on LBWs for preterm infants and those for infants with IUGR (Guyatt and Snow, 2004). Low birthweight is also a well-documented risk factor for poor neurosensory, cognitive, and behavioural development, as well as for limited school performance and academic achievement (Taylor *et al*., 2000). However, the most vulnerable group appears to be those infants born prematurely, who will be two to four times more likely to experience failure in school than infants of normal birthweight and will need specialist support or educational services (Hack, Klein and Taylor, 1995; Guyatt and Snow, 2004).

2.5 MALARIA TRANSMISSION AND MATERNAL IMMUNITY IN HIGH TRANSMISSION AREAS

In areas, where transmission of malaria is stable (high), such as in many parts of sub-Saharan Africa; many adults have developed immunity to malaria. They do not develop

symptoms when they become infected. However, when a pregnant woman has been infected with malaria, even if she has no clinical symptoms, she may develop placental parasitaemia, which can contribute to maternal anaemia and impaired foetal growth, two of the leading causes of LBW and poor survival of newborns and infants in Africa (Guyatt and Snow, 2004). Malaria infection during pregnancy has been estimated to cause 75 000- 200 000 infant deaths each year in stable transmission areas (Steketee *et al*., 2001; Newman *et al*., 2003). Women in stable transmission areas have greatest risks of developing these complications during their first and second pregnancies (Jelliffe, 1968; Brabin, 1983; McGregor, Wilson and Billewicz, 1983; Steketee *et al.*, 2001).

The level of immunity to malaria infection depends on the intensity of transmission, the number of previous pregnancies and the presence of other conditions not excepting HIV which increasingly impair the efficacy of immune response during pregnancy (Steketee *et al.*, 1996; Verhoeff *et al.*, 1999). The prevalence and intensity of malarial infection during pregnancy is higher among HIV-positive women and the risk to the woman and her newborn exists regardless of the number of times the woman has given birth (Verhoeff *et al*., 1999).

Women in areas of unstable transmission and whose immunity has been diminished by HIV or other factors are more likely to experience severe illness as a result of malaria infection than non–pregnant women and may also experience poor pregnancy outcomes. These women are at risk of developing malaria–related problems during every pregnancy. Hence, there is the need to find effective ways to reduce the impact of malaria during pregnancy, thus preventing illness in asymptomatic pregnant women and managing disease in women with clinical illness.

2.6 ANTIMALARIALS AND PREGNANCY; SAFETY AND APPARENT ADAPTATIONS SEEN IN RESISTANCE

2.6.1 ANTIMALARIALS AND ITS SAFETY IN PREGNANCY

The emergence of *P. falciparum* resistance to widely used antimalarial drugs such as chloroquine (CQ) has made malaria control and treatment much more difficult. This is particularly dramatic for Africa, as few affordable alternatives are available. The contribution of the extensive use and misuse of antimalarial drugs to the selection of resistant parasites became particularly evident during the Global Malaria Eradication campaign, launched by WHO in 1955.

Primaquine (8-Aminoquinolone): This drug has primarily been used against gametocytes and hypnozoites. It has been suggested that the drug works by inhibiting the electron transport chain of the parasite, though, as is so often the case with questions concerning the precise metabolic interactions; this is uncertain. Neither is it certain as to whether it is the drug itself nor derived metabolites which have the desired effects (Yamanda and Sherman, 1979). There is no evidence that gametocyte resistance exists, but if the drug is used against schizonts, then resistance is rapidly attained (Yamanda and Sherman, 1979). The surviving resistant parasites have increased numbers of mitochondria suggesting that the resistance mechanism involves the production of extra organelles to compensate for the damage caused by the drug (Collins and Paskewitz, 1995). Administration of Primaquine to people who have deficiency of glucose-6-phosphate dehydrogenase (G6PD) are at increased risk of acute haemolytic events

(Newman *et al*., 2003). Primaquine should not be used in pregnancy (Newman *et al*., 2003; WHO, 2006).

Antibiotics: Tetracyclines are often used in conjunction with other drugs to combat chloroquine resistant falciparum malaria. *Plasmodium* protein synthesis appears to be eukaryotic, and is insensitive to chloramphenicol, but affected by cycloheximide (Collins and Paskewitz, 1995). It has been suggested that antibiotics such as tetracycline act on the mitochondrial ribosomes of the parasite, inhibiting protein synthesis. Macrolides such as erythromycin seem to inhibit autophagic vacuole formation, thus potentiating the action of chloroquine (Collins and Paskewitz, 1995). Resistance to these compounds is not a current problem. However, tetracycline and doxycycline are contraindicated in pregnancy because of their effects on the foetus. Tetracycline easily crosses the placenta and can cause disturbances of skeletal growth, permanent discoloration of teeth, corneas and lenses (Newman *et al*., 2003). Doxycycline can cause similar discoloration of teeth as tetracycline does (Newman *et al*., 2003). In pregnancy, antibiotics can provide an important adjunct when treatment options are limited. Clindamycin had been shown to enhance the efficacy of quinine in multidrug–resistant *P. falciparum* infections in pregnancy (McGready *et al*., 2001; WHO, 2006; Ward *et al*., 2007), thus this drug given to full-term pregnant women before caesarean section could show concentrations in the normal range as compared with decreased concentrations for normal gentamycin (Ward *et al.*, 2007).

Sulphonamides: Parasites which become resistant to sulphonamides must bypass the metabolic step at which para-aminobenzoic acid (pABA) is incorporated into dihydropterate. Sulphonamide drugs work by inhibiting pABA, which is needed to

synthesize the dihydropterate which is an intermediate compound in the synthesis of tetrahydrofolate. Tetrahydrofolate derivatives serve as donors of one carbon compounds in a variety of essential biosynthetic pathways. Little is known about this side of parasite metabolism or the exact mechanisms of resistance; though resistance is clearly stable, transmissible, and prolific (Collins and Paskewitz, 1995). Collins and Paskewitz (1995) reported that resistance seems to be present in all stages of the parasite metabolism. It is possible that gene amplification is the mechanism by which the metabolic block of a pABA inhibitor is overcome. Sulphonamides are generally considered safe in the second and third trimesters of pregnancy (Newman *et al*., 2003).

Proguanil and Pyrimethamine (antifolates): Both of these compounds inhibit the action of dihydrofolate reductase. As with sulphonamides, resistance occurs in all stages of the life cycle. The dihydrofolate reductase enzymes of resistant strains bind to pyrimethamine 400-800 times less readily than the enzymes of drug sensitive strains (Collins and Paskewitz, 1995). Interestingly, high levels of resistance to sulphonamides are associated with hypersensitivity to antifols, and vice versa, so combination treatments have had good effects. Unfortunately, resistance to these drug cocktails is now becoming apparent (Collins and Paskewitz, 1995).

Preclinical data suggest that atovaquone –proguanil does not cause selective toxic effects on the developing foetus, although materno –foetal toxic effects were reported in rabbits (Nosten *et al.*, 2006). Clinical data on this drug is limited in human pregnancy. Sulphadoxine –pyrimethamine has been used extensively in pregnancy in intermittent preventive therapy programmes, but formal safety studies in pregnancy are limited. Preclinical studies indicate embryotoxic effects including cleft palate in rat pups exposed

to suprapharmacological doses of pyrimethamine and other toxic effects associated with antifolate action (Chung, Han and Roh, 1993; Tsuda *et al*., 1998; Ward *et al*., 2007). However, recent studies by Nosten *et al.* (2006) have shown that in over 2000 pregnant women treated with sulphadoxine –pyrimethamine in the second and third trimesters, the drug did not increase the risk of malformations or other adverse events in the foetus. The main concerns associated with the use of the drug were clinical failures because of parasites resistant to antifolate combinations.

Chloroquine and related compounds (4-Aminoquinolines): It is known that chloroquine mediates its effects on the haemoglobin metabolism of malaria parasites, perhaps preventing the neutralization of the toxic ferriprotoporphyrin IX (Zhang, Krugliak and Ginsburg, 1999; Becker *et al*., 2004; Koncarevic, Bogumil and Becker, 2007; Radfar, Diez and Bautista, 2008). Resistant parasites seem unable to produce haemozoin, but they are still able to digest haemoglobin. In non-resistant forms, most of the ferriprotoporphyrin IX is sequestered in haemozoin, but in the resistant forms, this toxic metabolite seems to become available to the host cell haemoxygenase system for elimination (Koncarevic, Bogumil and Becker, 2007; Radfar, Diez and Bautista, 2008). In chloroquine –sensitive malaria, the drug is taken up into food vacuoles, and it is proposed that here it competes with the haembinder for the ferriprotoporphyrin IX, to form a destructive compound (Zhang, Krugliak and Ginsburg, 1999; Becker *et al*., 2004; Koncarevic, Bogumil and Becker, 2007; Radfar, Diez and Bautista, 2008). Figure 9 presents the action of chloroquine on malaria parasite.

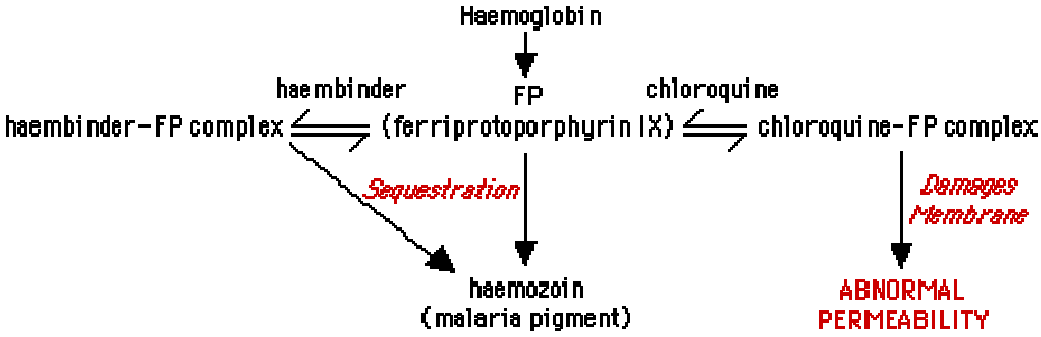

Figure 9: Diagrammatic representation of Chloroquine action (Zhang, Krugliak and Ginsburg, 1999)

Chloroquine, extensively used in pregnancy, is generally thought to be safe for mother and foetus at the therapeutically recommended dose (Okoyeh *et al*., 1993; Ward *et al*., 2007). However, the problem of treatment failure as a result of parasite resistance and poor drug compliance among others have resulted in a drastic reduction in its use especially in most African and Asian countries (Figure 10).

The other clinically available drug data in this class is amodiaquine, which is generally thought to be safe for use in pregnancy, although there are limited data to support this view (Newman *et al*., 2003; Nosten *et al*., 2006). However, in a recent clinical controlled trial study by Tagbor *et al*. (2006), it was reported that amodiaquine is safe when used in the second and third trimester of pregnancy. The use of chloroquine and amodiaquine in pregnancy may be acceptable, but widespread resistance in *P. falciparum* severely limits its use in most areas of the world (Ward *et al*., 2007).

Figure 10: Malaria–Endemic Areas in African and Asian continents with Chloroquine Resistance (*Source: U.S.A. National Centre for Infectious Diseases, Travellers' Health June 30, 2003*)

Quinoline methanols and related drugs: Quinine and mefloquine cause blebbing of the parasite membranes, and causes aggregations of haemozoin to form. Parasite resistance occurs by uncertain mechanisms, but is stable and transmissible (Collins and Paskewitz, 1995).

Studies on the preclinical toxicity of quinine, including reproductive toxicity, have been undertaken in various species of animals with some evidence of genotoxicity reported in mice (Munzner and Renner, 1983). Although quinine has been used historically as an abortifacient, use of the drug in pregnancy is generally safe. A recent review of clinical data on use of quinine in pregnancy concluded that there was no evidence of poor birth

outcome in several hundred women treated with quinine in pregnancy, including almost 400 treated in the first trimester (Nosten *et al.*, 2006).

Clinical data on use of mefloquine in pregnancy support the view that it is safe, does not induce malformations. However, in one retrospective study in Thailand, mefloquine was associated with an increased incidence of stillbirth compared with women given quinine, other antimalarials, or women without malaria (Nosten *et al.*, 1999). Hence, the use of mefloquine in pregnancy should be avoided unless there is clear benefit to the mother or foetus or until this problem is resolved; there are no alternatives.

Data on the use of halofantrine in pregnant women is hardly known, but preclinical data in rabbits indicate embryotoxic effects and identified skeletal abnormalities at doses of 60- 120 mg/kg per day at gestational days of 7-19. The related drug, lumefantrine, is in clinical use in combination with the drug, arthemeter, but there is no reported safety data on the use of this drug in pregnant women (Ward *et al*, 2007).

Artemisinins: These are among the newest and most effective of all antimalarial drugs, and seem to affect protein synthesis. These drugs must be protected, and used rationally, to prevent the emergence of inevitably resistant *P. falciparum* for as long as possible. In the laboratory, artemisinin resistant forms have already been demonstrated (Collins and Paskewitz, 1995). Although clinical experience to date indicates artemisinins to be safe, the area of reproductive toxicology demands special consideration. The teratogenic potential of artemisinin in human beings is unknown. In total, less than 1000 cases of monitored artemisinin exposure during pregnancy have been reported. These data had showed no differences in birth outcomes compared with community controls, and no evidence of teratogenic or embryotoxic events (Nosten *et al.*, 2006, WHO, 2006).

Malaria during pregnancy is itself associated with substantial mortality and morbidity to the mother and the unborn child, so there is the need to balance the risk-benefit ratio of artemisinin use (Ward *et al*., 2007).

2.6.2 MALARIA PARASITE AND DRUG RESISTANCE

The problem of drug resistance can be attributed primarily to increased selection pressures on *P. falciparum* in particular, due to indiscriminate and incomplete drug use for self treatment (Peters, Gilles and Mosby-Wolfe, 1995; D'Alessandro and Buttiëns, 2001). In countries such as Thailand and Vietnam, mosquitoes of the *An. dirus* and *An. minimus* species spread the drug resistant parasites.

Drug resistant *P. falciparum* was first reported in Thailand in 1961 (Zucker and Campbell, 1992). Various *P. falciparum* 'strains' have now attained resistance to all commonly used and generally available antimalarial drugs (WHO, 1995). In man, the problem of resistance to the common antimalarial drugs such as chloroquine and pyrimethamine, and the decreasing effectiveness of quinine are mainly limited to *P. falciparum* infection (Zucker and Campbell, 1992).

Artemisinins, a Chinese derived herbal remedy is widely used in South East Asia and some countries in Africa. The two most widely used are artesunate and arthemether. Though very effective drugs, high rate of treatment failures have been reported and it is now being combined with mefloquine and other antimalarial drugs (known as Artesunate combination therapy, ACT) for the treatment of falciparum malaria (McConnell, 1998). ACT is currently the drug of choice in treating malaria in most sub-Saharan African countries including Ghana.

Several mechanisms can account for changes in drug sensitivity in the malaria parasites, for example, physiological adaptations due to non-genetic changes, selection of previously existing drug resistant cells from a mixed population under drug pressure, spontaneous mutation, mutation of extra nuclear genes, or the existence of plasmid-like factors.

Selection of mutants by the drugs themselves appears an important mechanism (Collins and Paskewitz, 1995). In an environment where sub-therapeutic levels of the antimalarial drugs are present, those parasites which have resistance through their natural variation or through mutations clearly have an important biological advantage. This means that even though the resistant forms were initially in the minority, the continued drug mediated elimination of intraspecific competition from the non–resistant forms has allowed the resistant forms to attain numerical superiority, to the point that drugs such as chloroquine are officially considered useless (Zucker and Campbell, 1992). The majority of studies indicate that drug pressure selection is to blame for the emergence of resistant malaria (Collins and Paskewitz, 1995). The subcurative plasma levels of drugs found in many areas where there is uncontrolled and irresponsible prophylaxis and treatment will kill the most drug sensitive forms of the parasite, but the less sensitive ones and spontaneous mutations in these forms tend to further reduce the sensitivity of the parasites to the drug (WHO, 1996c). Fortunately, the problem of irresponsible prophylaxis has been recognised, and precautions are being taken; for instance, in Zimbabwe it is now illegal to sell chloroquine other than in full courses (WHO, 1996c). As drug resistance seems to be genetically determined, gametocytes produced by resistant populations will produce more resistant parasites, promoting spread of the resistant forms.

Plasmodium parasites have extremely complex genomes, coupled with the ease with which they can switch between the microenvironments in different hosts and the metabolic changes required illustrate the difficulty in studying the exact modes of action of the antimalarial drugs on parasite metabolism (Collins and Paskewitz, 1995). Resistance develops more quickly where large populations of parasites are exposed to drug pressure. The increasingly rapid spread of resistant malaria may be due to an increasingly efficient mosquito vector. This phenomenon may be explained by the increased oöcyst formation efficiency that has been observed with resistant species which, at any rate, gives the resistant forms a biological advantage with transmission (Collins and Paskewitz, 1995).

2.7 PREVENTION OF MALARIA DURING PREGNANCY

Malaria is an important health problem and pregnant women recognise its serious consequences (Agyepong *et al.*, 2002; Mbonye *et al.*, 2006, 2007). Effective malaria prevention and treatment interventions exist that have beneficial effects on the diesease in pregnancy (Schultz *et al.*, 1994; Parise *et al.*, 1998; Shulman *et al.*, 1999; WHO, 2002, 2003, 2004). However, use of these interventions largely depends on local beliefs on malaria, access, costs, attitudes towards health care providers and the level of acceptability of the health system (Menendez 1999; Shulman, 1999; Mbonye, Bygbjerg and Magnussen, 2007). These affect care seeking with regard to malaria prevention at health units and also reveal issues related to affordability and acceptance of these services in most parts of sub-Saharan Africa.

Controlling the effects of malaria infection in the pregnant woman and her foetus requires a balanced programme of effective case management of malaria illness and prevention of the consequences of asymptomatic infection. One of the main problems that did appear during the chemoprophylaxis trials was the growing resistance of the parasites to antimalarial treatments. No sooner had the first trial in Nigeria (Morley, Woodland and Cuthbertson, 1964) begun than it became evident that pyrimethamine alone could no longer be used for prophylaxis, as it had lost a great deal of its usefulness. This is why subsequent intervention studies in Africa used dapsone–pyrimethamine or sulphadoxine–pyrimethamine (SP) combinations (Greenwood *et al.*, 1989; Shulman *et al.*, 1999). In areas of multiresistant malaria such as South East Asia, neither chloroquine nor SP combinations could be used, and mefloquine was administered to pregnant women initially (Nosten *et al.*, 1994). Additionally, none of these drugs has been proven to be perfectly safe in pregnancy, except for chloroquine. Questions remain about the teratogenic effects of folic acid antagonists (such as in the SP combinations), even if such risk appears to be significant only when treatment is given during the first trimester of pregnancy (Hernandez–Diaz *et al.*, 2000). There is also a possible association between the use of mefloquine and an increased risk of stillbirth (Nosten *et al.*, 1994; Nosten *et al.*, 1999; Newman *et al.*, 2003; Nosten *et al.*, 2006; WHO 2006). Other drugs, such as tetracycline, doxycycline, primaquine, tafenoquine and halofantrine are strictly forbidden during pregnancy. Quinine or artemisinin compounds cannot be used as prophylaxis because of their short half-life.

Another concern is the poor compliance generally observed with weekly or bi-monthly chemoprophylaxis, and ineffective blood levels induced from missing out one or several doses of anti-malarial drugs.

Albeit, attendance at antenatal clinics (ANC) is generally good, and an important change in prevention strategies has occurred with the introduction of intermittent treatment with SP combinations. This regimen is given as a single curative dose of three tablets taken two or three times at monthly intervals after quickening (16 weeks gestation period) to the third trimester of pregnancy (36 weeks gestation period) at ANC visits.

Pregnant women in areas of high transmission of malaria require highly effective prevention interventions as well as prompt access to diagnosis and effective treatment for anaemia and clinical malaria. This preventive package consists of:

1. The use of Insecticide Treated Nets (ITNs) and
2. Intermittent Preventive Treatment (IPT) which is the administration of drug therapy in full treatment doses at predetermined intervals during pregnancy.

2.7.1 INSECTICIDE TREATED NETS

Insecticide Treated Nets (ITNs) kill the mosquitoes when they land on them or repel the mosquitoes, thus providing protection for both mothers and newborns. In areas of stable malaria transmission, use of ITNs has provided great protection against the infection, resulting in less anaemia, prematurity and low birthweight, and risk of maternal and newborn death (D'Alessandro *et al*., 1996; ter Kuile *et al*., 2003). ITNs prevent the nuisance of the biting mosquitoes thereby helping people to sleep better. They also enhance growth and development of the foetus and the newborn and costs less than treating malaria. The great impact ITNs make on a country's economy in reducing number of sick children and adults (helping children grow to be healthy and helping working adults remain productive) cannot be overemphasized. For pregnant women who are unable to take SP, use of ITNs is better and more appropriate intervention for

avoiding malarial infection. It is, therefore, required for women in stable and unstable areas of transmission to consistently sleep under an ITN, starting as early in pregnancy as possible, and continuing to do so with their newborns and young children.

2.7.2 INTERMITTENT PREVENTIVE TREATMENT

Intermittent Preventive Treatment (IPT) is the most promising strategy in the control of malaria in pregnancy (WHO/UNICEF, 2003). The use of antimalarial drugs for pregnant women based on giving treatment in doses at predefined intervals after quickening (16 weeks of pregnancy) have a beneficial impact on maternal and infant health. It is the preferred approach because compliance with the IPT approach is greater than compliance with weekly chemoprophylaxis (WHO/UNICEF, 2003). Whereas chemoprophylaxis requires that a woman takes the antimalarial drug (usually chloroquine) at home over the course of several days each week, the IPT approach allows her to take an entire treatment of an antimalarial drug during an antenatal care visit, under the care and supervision of a healthcare provider. This programme on malaria control in pregnancy is well documented and has been shown to reduce malaria episodes, maternal parasitaemia, anaemia and incidence of LBW (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al*., 1999; WHO, 2004; Newman *et al*., 2006; Mbonye, Bygbjerg and Magnussen, 2008; Gies *et al*., 2009).

2.7.3 INTERMITTENT PREVENTIVE TREATMENT WITH SULPHADOXINE –PYRIMETHAMINE

Sulphadoxine–pyrimethamine (SP) is the most effective antimalarial drug of choice for IPT due to its safety profile in pregnancy, relative efficacy in reproductive–age women,

and good programme feasibility, with the opportunity to deliver it as single dose treatment under observation by the health worker. SP is preferred over chloroquine, the antimalarial drug traditionally used during pregnancy, because resistance to chloroquine is prevalent and increasing in many malaria-endemic areas including Ghana. Studies in Kenya and Malawi have shown that IPT with SP has a beneficial impact on maternal and infant health (Parise *et al*., 1998; Shulman *et al*., 1999; WHO, 2004). IPT with SP when delivered as part of antenatal care significantly reduces the prevalence of maternal anaemia and placental parasitaemia and the incidence of low birthweight. No significant adverse reactions to SP in either the mother or infant have been detected (WHO, 2002, 2004).

Both sulphonamides and pyrimethamine are generally considered safe in the second and third trimesters of pregnancy. Although there are concerns that sulphur drugs may be associated with kernicterus when given to premature neonates, this problem has not been noted in studies of IPT where SP has been administered to the mother (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al*., 1999). Studies examining the risk to the foetus from *in utero* exposure to SP combinations have generally not found any increased risk in spontaneous abortions or congenital defects (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.,* 1999). A retrospective study of antifolate drugs given before and during pregnancy did find that there was an increased risk of birth defects when such drugs were taken during the first trimester, but not during the second or third trimester (Hernandez –Diaz *et al.,* 2000). WHO (2002) reported that when SP is given weekly as a prophylaxis; it is associated with rare severe cutaneous reactions such as toxic epidermal necrolysis and Stevens–Johnson syndrome. However, there is no evidence that the risk of severe cutaneous reactions is any greater in pregnant women or when SP has been

used for treatment. Although sulphonamides are excreted in breast milk, the risk to healthy full–term neonates is believed to be minimal. Pyrimethamine is usually given in combination with sulphadoxine. However, studies in which pyrimethamine has been given alone have also found no increase in adverse pregnancy outcomes and it is considered to be compatible with breast feeding (WHO, 2002; Newman *et al*., 2003).

Several studies have been conducted to determine whether or not adverse reactions to SP, including cutaneous reactions and other potentially serious conditions that would either pose risks to the pregnant woman or infant or limit programme effectiveness do occur. There had been no evidence of increased risk for serious cutaneous side effects or for increased jaundice in the newborn when SP has been given in the second and third trimesters (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al*., 1999). Although the data on safety of SP is promising, there is the need for monitoring of safety of all antimalarials used for treatment and prevention in pregnancy, including SP.

2.7.4 INTERMITTENT PREVENTIVE TREATMENT DOSING SCHEDULE

Although a single dose of SP has been shown to be effective in reducing malaria infection and parasite load, repeated doses during the second and third trimesters are recommended, especially in areas of high HIV prevalence (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al*., 1999). All pregnant women in areas of stable transmission (and , where recommended , in areas of unstable transmission) should take a single dose of SP (three tablets, each containing 500 mg of sulphadoxine and 25 mg pyrimethamine) at each scheduled antenatal care visit after foetal movement begins (quickening), but not more frequently than monthly (WHO, 2004). For women experiencing normal pregnancies, four scheduled antenatal care visits are recommended, including three after

the first trimester, which allows for up to three doses of SP after quickening. The delivery of IPT with each scheduled visit will likely assure that a high proportion of women receive at least two doses. There is no evidence that delivery of more than three doses of IPT–SP will confer additional benefit. However, there is no evidence that receiving three or more doses of IPT with SP will result in an increased risk of adverse drug reactions. For pregnant women who have four or more antenatal visits after quickening, it is advisable to deliver no more than three doses of SP to minimize unnecessary drug exposure and thereby further decrease the potential for drug–related toxicity.

2.8 GENETIC DIVERSITY OF *PLASMODIUM FALCIPARUM*

Molecular techniques now offer new possibilities to get a deeper understanding of host-parasite interactions and the biology of the parasite population.

In general, the *P. falciparum* infections include a complex mixture of biologically and genetically different populations, as has been demonstrated by different techniques, including the restriction fragment length polymorphism (RFLP) [Babiker *et al*., 1994; Cano *et al*., 2007] and the polymerase chain reaction (PCR) [Haddad *et al*., 1999; Cano *et al*., 2007]. PCR has been used to study the existing polymorphisms in various markers, such as the Merozoite Surface Proteins 1(MSP1) and 2 (MSP2), the circumsporozoite protein (CSP) and the glutamate-rich protein (GLURP) [Konate *et al*., 1999; Cano *et al*., 2007]. It is the most widely used technique for *P. falciparum* genotyping and is based on two –step PCR amplification (nested PCR). The entire gene segment of interest is amplified in a primary amplification followed by a nested amplification targeting the allelic type specific regions. Nested PCR is used to increase the specificity and sensitivity of DNA amplification and is therefore suitable for parasite genotypes detection present at low concentration in a sample (Contamin *et al*., 1995; Zwetyenga *et al*., 1998; Snounou *et al*., 1999).

The usefulness of the PCR technique together with the minimal requirement of infected samples have led to a multitude of typing studies combining various *P. falciparum* polymorphic markers such as MSP1 and MSP2 and the GLURP (Walliker, 1994; Snounou and Beck, 1998). Typing of *P. falciparum* in human hosts has been used in work on the diversity of parasite populations (Babiker, Satti and Walliker, 1995), the search for markers of parasite virulence (Engelbrecht *et al*., 1995), in researching the

importance of multiplicity of infection (Contamin *et al.,* 1995; Beck *et al.,* 1997) and the geographical distribution of the various alleles of these polymorphic genes of the parasite (Babiker *et al.,* 1997; Zwetyenga *et al.,* 1998; Felger *et al.,* 1999). Studies undertaken by Peyerl-Hoffmann *et al*. (2001) in Uganda showed that genetic diversity plays a major role in the natural acquisition of immunity to malaria infections that age has influence on the complexity of *P. falciparum* infection.

Various studies also show that genetic diversity in a specific area is related to the level of transmission (Konate *et al*., 1999; Paganotti *et al*., 2004; Cano *et al*., 2007), that high prevalence of infection multiplicity has been detected in hyper- and holoendemic zones (Raj *et al*., 2004) as compared to low transmission zones (Babiker *et al*, 1998). The basis of the genetic diversity is the recombination that occurs in the sexual phase of the parasite within the mosquito, thus, the higher the transmission, the greater the recombination frequency (Conway *et al*., 1999; Cano *et al*., 2007). However, some authors indicate that the transmission level would not be the only cause for genotype variability (Sakihama *et al*., 1999).

The genome of *Plasmodium* species is estimated to be about 30 Mb and is distributed among 14 chromosomes, which range in size from 650 kb to 3.5 Mb with estimated 5000–7000 genes (Greenwood, 2002). *Plasmodium falciparum* and several other *Plasmodium* species are unusual in that their genomes have an extraordinary bias towards two nucleotides: adenine (A) and thymine (T). In regions that code for proteins, the A-T bias is greater than 76%, whereas in intergenic regions (regions between genes) and in introns (regions within genes that are removed before final transcription), the A-T content can approach 100% (Greenwood, 2002).

2.8.1 MEROZOITE SURFACE PROTEIN I (MSP1)

The MSP1 locus of *P. falciparum* codes for a major asexual blood-stage antigen currently proposed as a major malaria vaccine candidate. The protein, however, shows extensive polymorphism, which may compromise its use in sub-unit vaccines (Holder and Riley, 1996). Comparisons of nucleotide sequences led to the identification of seven variable blocks in the gene, which are interspersed with five conserved and five semi-conserved blocks. There are essentially two versions of each block, named after the representative isolates MAD20 and K1 (Snounou *et al.*, 1999). There is, however, a third version originally described in the isolate RO33 (Snounou *et al.*, 1999). Most allelic diversity is generated by intragenic recombination between these representative sequences at the 5´ end of the gene, within blocks 3, 4 and 5. Minor differences also exist between homologous versions of the same variable block, and substitutions occur in the conserved and the semi-conserved blocks (Basco, Tahar and Escalante, 2004).

2.8.2 MEROZOITE SURFACE PROTEIN 2 (MSP2)

MSP2, also known as merozoite surface antigen 2 (MSA2) is a glycoprotein expressed on the merozoites surfaces, the stages of the parasite that infect the red blood cells. It is one of the most polymorphic genes of *P. falciparum* and is charactized by a conserved 5´ and 3´ regions (blocks 1 and 5), two non-repetitive variable regions (blocks 2 and 4) and a polymorphic central region (block 3) containing tandem repeats of varying sequence, copy number and length (Symthe *et al*., 1991). The non-repetitive variable blocks could be grouped into two allelic families, FC27 and IC/3D7. The dimorphic family –specific domains are totally conserved over extended sequence but shows in parts a remarkable length and sequence variation (Felger *et al*., 1999). The central

repetitive region differs considerably between and within allelic families given rise to considerable length polymorphism. The FC27 allelic-type central region consists of two relatively conserved repetitive sequences; one to four copies of a 32 -mer motif followed by a conserved non-repetitive 7–mer fragment and none to five copies of a12–mer motif. The 3D7 allelic block 3 repeats are highly variable in length (six to 30bp), sequence and number of copies. MSP2, is thus, highly polymorphic with more than 150 different alleles already described (Felger *et al*., 1999).

2.8.3 GLUTAMATE –RICH PROTEIN (GLURP)

The GLURP parasite gene, another polymorphic marker for genotyping of *P. falciparum* has two repeated regions; the relatively conserved N-terminal non -repetitive region (RI) and the immunodominant repetitive region (RII) in which the RII is most diverse, thus being the target for genotyping (Borre *et al*., 1991; Zwetyenga *et al*., 1998 Farnert *et al*., 2001). The 220 kDa glutamate-rich protein (GLURP) is found in all the developmental stages of the parasite in humans, including the surface of newly released merozoites (Borre *et al*., 1991). It is highly antigenic and geographically shows little polymorphism in different *P. falciparum* isolates (Thiensen *et al*., 1995; Stricker *et al*., 2000).

CHAPTER THREE – GENERAL METHODOLOGY

3.1 STUDY AREA AND POPULATION

3.1.1 STUDY AREA

This study was carried out in Offinso District (Figure 11), one of the administrative districts in the Ashanti Region of Ghana.

Offinso District stretches along the Kumasi-Techiman trunk road beginning from Old Offinso (South) and ending at Afrancho (North) a distance of 70 km. New Offinso, the district capital, is 27 km from Kumasi. It shares boundaries with Techiman District on the north and Afigya Sekyere and Atwima Districts on the south. On the east side it shares boundaries with Tano, Ahafo Ano South and Atwima Districts and on the west with Nkoranza, Ejura Sekyeredumase and Afigya Sekyere Districts. The district has an area of 1254 km^2, with 161 communities, most of them being small ones. The projected district population for 2007 was 175, 245 and with a growth rate of 3.4% (Offinso DHMT, 2008). There are two political constituencies, Offinso North and Offinso South. Like most districts, Offinso District has a high dependency ratio (Offinso DHMT, 2008). Majority of the adult population are farmers growing cocoa, plantain, cocoyam, maize and tomato. The northern part of the district is noted for tomato cultivation. Apart from the main road passing through the district which is currently under construction, roads are generally bad especially during the rainy season.

The district is divided into five sub-districts: Offinso Central, Bonsua, Abofour, Nkenkaasu and Akomadan/Afrancho.

The health delivery system in the district is based on decentralized Primary Health Care and is organized at three levels:

1. The district - led by the District Health Management Team (DHMT) with the District Director of Health Services (DDHS) as its leader.
2. The sub-district - led by the sub-District Health Team (SDHT) based at a specified health facility and responsible for a defined geographical area and catchment's population, led by a Medical Officer or Medical Assistant.
3. The community level - led by the Village Health Committee (VHC), where this has been formed and remains functional. The VHC coordinates the activities of community level health agents, community clinic attendants, community surveillance volunteers, community agents etc.

Malaria is the leading cause of morbidity in Offinso district and accounts for nearly 50% of outpatients' visits to health facilities, 30% of all health facility admissions and 10.4% of all officially reported deaths (Offinso DHMT, 2003). Two cross sectional studies and review of routine data on deliveries were carried out in six health facilities in the district that provided antenatal and delivery services and communities where these health centres were situated. The health facilities were St. Patrick's Hospital (Offinso), District Assembly Maternity (Offinso), Nkenkaasu Hospital, Abofour Health Centre, Akomadan Health Centre and A.M.E. Zion Health Centre (Afrancho).

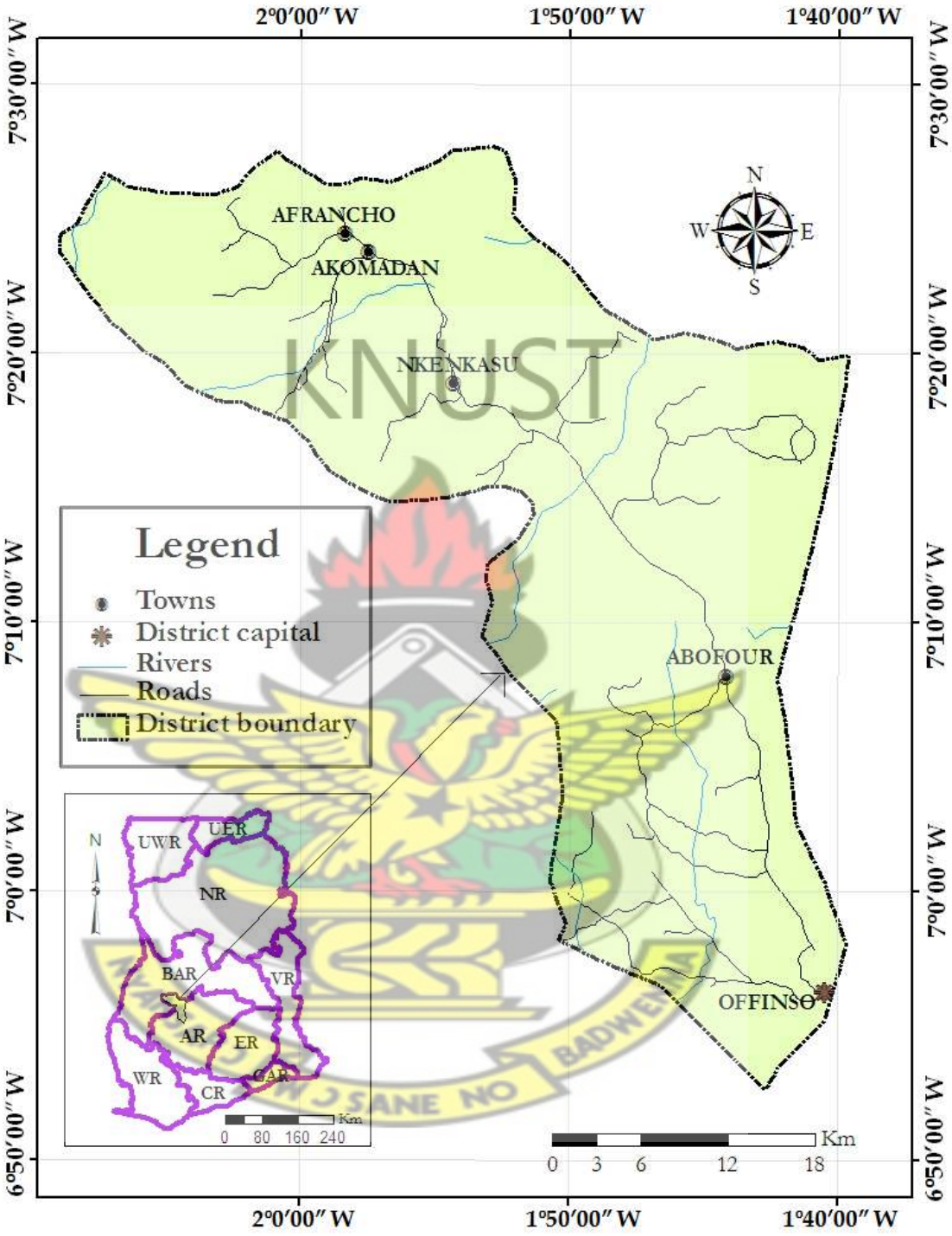

Figure 11: Map of Offinso District showing the study towns (*Source: Prepared using ArcGIS software, 2008)*

3.1.2 STUDY POPULATION

The study population were pregnant women attending antenatal clinic in the various health facilities aforementioned. Pregnant women who were 16 to 36 weeks of gestation irrespective of their SP status were studied in cross sectional study I. In cross sectional study II, pregnant women who were 32 weeks to term (third trimester) and had taken SP were used. All pregnant women irrespective of the study type were examined and interviewed in the study areas.

Routine delivery data from the six health facilities in the Offinso District, Ghana, from January 2000 to May 2004 (the pre SP-IPT period) were reviewed to assess the trend of birthweights of neonates before the implementation of the IPTp programme.

Another routine delivery data from January 2005 to October 2007 were reviewed also to assess the birthweight trends in those years and the effects of SP- IPT on the birthweight of the neonates born in those years.

3.2 STUDY DESIGN AND SAMPLING METHODS

The studies were analytical type with cross sectional designs and review of routine data on deliveries.

3.2.1 SAMPLE SIZE

A sample size of 296 was estimated for both cross sectional studies. The prevalence of anaemia in pregnant women was 50% (Offinso DHMT, 2003) and in reducing anaemia by 5% through the use of SP at the power of 80% and 5% significance, a sample size of 296 was required for the two cross sectional studies (using Statcalc, Epi info software 2002, version 6).

3.2.2 SAMPLING METHODS

Stratified sampling method was used in selecting the health facilities while convenience (purposeful) sampling method was used to sample the respondents. The total number of pregnant women seen yearly in each health facility was made as a fraction of the total number of pregnant women seen in all these health facilities annually. The proportion for each health facility was used to determine the number of pregnant women to be sampled from that health facility. Table 1 shows the proportional allocation of the study population.

Table 1: Proportional allocation of study population

Health centre *I*	**Clients' attendance** N_i	**Proportion of attendance** $w_i = N_i / N$	**Sample size** $n_i = w_i * n$
St. Patrick's Hospital	10000	0.43	127
Abofour Health Centre	5000	0.22	65
Akomadan Health Centre	1000	0.04	12
A.M.E. Zion Health Centre	600	0.03	9
Nkenkaasu Government Hospital	6000	0.26	77
District Assembly Maternity	400	0.02	6
Total	N **= 23000**	**1**	n **= 296**

N = total clients (pregnant women) attendance at ANC in the district; N_i = total clients' attendance at each health centre; w_i = proportion of clients' attendance; n_i = number of clients sampled at each health centre; n = total number of clients sampled for the study.

3.2.3 SURVEYS

Studies were carried out monthly within a one and half year period at designated health facilities and communities in the district. At each survey the following were determined for each subject:

i.) axillary temperature

ii.) height

iii.) weight

iv.) haemoglobin concentration using HemoCue®

v.) parasitaemia, using thick and thin blood films from peripheral and placental blood

vi.) filter paper (peripheral, placental and cord blood) blotted samples for PCR analysis.

3.3 DATA COLLECTION TECHNIQUES AND TOOLS

The tools for the data collections based on the study objectives are shown in Table 2

Table 2: Data collection tools

Specific Objectives	Data Tools
To determine the effects of IPT, using SP, on maternal morbidity and malaria-associated anaemia in pregnancy.	Clinic Visit Form, Side effects form, data compilation forms, In-depth interview, Structured questionnaire, Focus group discussion (FGD)
To determine the effects of IPT, using SP, on birthweight of neonates	Delivery Form, data compilation forms, Structured questionnaire, In-depth interview
To assess transplacental transmission of malaria	Laboratory Form, PCR Form for Placental and Cord blood.
To evaluate the knowledge of IPT of health care personnel at the health facilities and assess the understanding of community members of IPT in general.	In-depth interview, Structured questionnaire
To determine the genetic diversity of *P. falciparum*.	PCR Form for Peripheral and Placental blood

3.3.1 ANTHROPOMETRIC MEASUREMENTS

A standardized weighing scale was used to measure the weight of the pregnant women. Their heights were measured with a measuring rule. The Body Mass Index (BMI) were then evaluated by the ratio [weight (kg)/ height^2 (m^2)] of study participants and hence determined overweight, obese and underweight women among them. Measurement of blood pressure was done to determine hypertension in the pregnant women.

3.3.2 GENERAL LABORATORY INVESTIGATIONS

3.3.2.1 HAEMOGLOBIN MEASUREMENT

Peripheral blood was drawn from a prick of the left ring finger and a little is placed in a cuvette of hemocue machine for haemoglobin level determination. A HemoCue®

haemoglobin detection system (HemoCue AB, Angelholm, Sweden) was used to measure haemoglobin levels.

3.3.2.2 PARASITE DETECTION

Peripheral blood was drawn from a prick of the left ring finger onto clean microscopic slides for thick and thin blood films preparations. From the fresh placenta, multiple aspirations were made on the maternal half of the placenta, just below halfway between the maternal and foetal surfaces using a 19-gauge needle attached to a 2-ml syringe. From the aspirates, thick and thin films were made on clean microscopic slides. Incisions were made in the cord ~15 cm from the placenta using a fresh blade, and thick and thin blood films were also prepared from the cord blood for microscopic examinations.

The dried thick and thin blood films were stained with Giemsa for microscopic analysis of parasitaemia (peripheral, placental and cord blood), and parasite density was calculated by counting the number of asexual parasites against 200 leukocytes in the thick blood film, using a hand tally counter and multiplying by the average WBCs count of the maternal population (for peripheral or placental counts) or neonatal population (for cord counts). An assumption of 8000 leukocytes per microlitre of blood was used to determine the parasite density (per microlitre of blood) since the average WBCs count of the maternal population (for peripheral and placental counts) or neonatal population (for cord counts) were not available. This was done by dividing the number of asexual parasites by the number of leukocytes counted and then multiplying by the average WBCs count. A minimum of 100 fields were examined for each negative thick and thin film. A second reading was done independently by an expert microscopist to confirm results.

3.3.2.3 DNA EXTRACTION AND PCR AMPLIFICATION

Sample Collection and Selection DNA extraction

Filter papers (Whatman No.1, Whatman International Ltd, Maidstone, England), were used to collect blood samples for DNA extraction and polymerase chain reaction (PCR). Blood samples, peripheral, placental and cord of study subjects were blotted on the filter papers air dried, placed singly in sealed envelopes and labelled. The filter papers were stored with silica gels in a cool dry place.

The blotted filter samples for the PCR were selected based on whether the samples were positive for parasitaemia or not through microscopic examination.

Method of DNA Extraction and PCR amplification

DNA extraction from the filter paper dried blood spots was carried out using the Tris-EDTA (TE) buffer-based method (Bereczky *et al.*, 2005).

TE buffer (10 mM Tris, pH 8, 0.1 mM EDTA) was prepared and kept at room temperature (25°C). Two to three punches of the same dimension (3mm in diameter) were made from each filter paper and placed in Eppendorf tubes. The punches were soaked in 65 µl of TE buffer and incubated at 50°C for 15 minutes. They were then pressed gently at the bottom of the tubes several times, using a new pipette tip for each tube and heated at 97°C for 15 minutes on a heating block or in a water bath. The tubes were centrifuged shortly for 2-10 seconds. The punches were removed from the tubes using new pipette tips for each tube and the eluate (DNA extract) kept at 4°C in a refrigerator for use within a few hours or stored at −20°C.

PCR amplifications were performed using a PTC-100^{TM} thermal cycler (MJ Research Inc., Watertown, USA). Separate primary PCR reactions were performed for each of the

three polymorphic markers MSP1, MSP2 AND GLURP (Sambrook, Fritsch and Maniatis, 1989; Ransford-Cartwright, Carter and Walliker 1993; Arez *et al*., 2000; Snounou, 2002; Snounou and Farnet, 2004). In the primary reactions, the primers used were: MSP1, MSP2, GLURP (Table 3). The nested reactions included amplifications of DNA fragments corresponding to MSP1 gene MAD20, K1 and R033 alleles, MSP2 gene FC27 and IC alleles, and the repeat region of GLURP gene (Table 3).

Table 3: Primers for the Primary and Nested Reactions

PRIMERS	SEQUENCES
MSP1	
FORWARD	5' - CTA GAA GCT TTA GAA GAT GCA GTA TTG- 3'
REVERSE	5' - CTT AAA TAG TAT TCT AAT TCA AGT GGA TCA- 3'
MSP2	
FORWARD	5' - ATG AAG GTA ATT AAA ACA TTG TCT ATT ATA- 3'
REVERSE	5' - CTT TGT TAC CAT CGG TAC ATT CTT- 3'
GLURP	
FORWARD	5' - TGA ATT TGA AGA TGT TCA CAC TGA AC- 3'
REVERSE	5' - GTG GAA TTG CTT TTT CTT CAA CAC TAA- 3'
Allelic genes of MSP1	
M1-2M (MAD20 fragment)	
FORWARD	5'- AAA TGA AGG AAC AAG TGG AAC AGC TGT TAC -3'
REVERSE	5'- ATC TGA AGG ATT TGT ACG TCT TGA ATT ACC -3'
M1-2K (K1 fragment)	
FORWARD	5'- AAA TGA AGA AGA AAT TAC TAC AAA AGG TGC-3'
REVERSE	5'- GCT TGC ATC AGC TGG AGG GCT TGC ACC AGA -3'
M1-2R (RO33 fragment)	
FORWARD	5' - TAA AGG ATG GAG CAA ATA CTC AAG TTG TTG- 3'
REVERSE	5' - CAT CTG AAG GAT TTG CAG CAC CTG GAG ATC - 3'
Allelic genes of MSP2	
M2- FC (FC27 fragment)	
FORWARD	5' - AAT ACT AAG AGT GTA GGT GCA (AG)AT GCT CCA- 3'
REVERSE	5' - TTT TAT TTG GTG CAT TGC CAG AAC TTG AAC- 3'
M2-IC (IC fragment)	
FORWARD	5' - AGA AGT ATG GCA GAA AGT AA(GT) CCT (CT) CT ACT- 3'
REVERSE	5' - GAT TGT AAT TCG GGG GAT TCA GTT TGT TCG- 3'
GLURP genes	
FORWARD	5' - TGA ATT TGA AGA TGT TCA CAC TGA AC- 3'
REVERSE	5' - GTG GAA TTG CTT TTT CTT CAA CAC TAA- 3'

The primary and nested PCR reactions were carried out in 25 µl reaction volumes using 5 µl of template DNA and 1 µl of primary PCR product respectively in the two reactions. Each PCR reaction mix contained 1x PCR buffer, 10 mM of each dNTP, Taq DNA polymerase (1 U) and 10 µM of each of the forward and the reverse primers. For controls, genomic DNA from 3D7 laboratory strains and SDH_20 (sterilized distilled water) were used for positive and negative control respectively. One to two drops of mineral oil was added to the PCR mixtures to prevent evaporation during the thermal cycling reactions.

The PCR temperature profiles were as follows:

For MSP1 primary reaction, the initial denaturation was at 94 °C for 3 minutes followed by 30 cycles of denaturation at 94 °C for 25 seconds, annealing at 50 °C for 35 seconds and extension at 68 °C for 2 minutes and 30 seconds, then a final extension cycle at 72 °C for 3 minutes. The nested reaction was done at initial denaturation temperature of 94 °C for 2 minutes followed by 35 cycles of denaturation at 95 °C for 1 minute, annealing at 50 °C for 15 seconds and extension at 72 °C for 30 seconds. There was final cycle of denaturation at 95 °C for 1 minute, annealing at 50 °C for 15 seconds and extension at 72 °C for 3 minutes.

For MSP2 for the primary reaction, the initial denaturation was at 94 °C for 3 minutes followed by 30 cycles of denaturation at 94 °C for 25 seconds, annealing at 42 °C for 1 minute and extension at 65 °C for 2 minutes. The final extension cycle was at 72 °C for 3 minutes. The nested reaction was done at initial denaturation of 94 °C for 3 minutes followed by 30 cycles of denaturation at 94 °C for 25 seconds, annealing at 50 °C for 1 minute and extension at 70 °C for 2 minutes. The final extension cycle was at 72 °C for 3 minutes.

For GLURP primary reaction, initial denaturation was at 94 °C for 3 minutes followed by 30 cycles of denaturation at 94 °C for 25 seconds, annealing at 45 °C for 1 minute and extension at 68 °C for 2 minutes. The final extension cycle was at 72 °C for 3 minutes and cooled at 15 °C. The nested reaction was done at initial denaturation of 94 °C for 3 minutes followed by 30 cycles of denaturation at 94 °C for 1 minute, annealing at 55°C for 2 minutes, extension at 70 °C for 2 minutes. The final extension cycle was at 72 °C for 3 minutes.

Genetic Analysis

The DNA template from the extract was used to run the PCR so as to analyze the genotypes of the malaria parasites (specifically *P. falciparum*). The polymorphic repetitive regions of block 2 of MSP1 (Miller *et al*., 1993; Magesa *et al*., 2001), block 3 of MSP2 (Smythe *et al.,* 1991; Magesa *et al*., 2001) and GLURP region (Borre *et al.,* 1991; Magesa *et al*., 2001) were amplified by nested PCR to access the diversity (allelic families) of the *P. falciparum* in the women in the district. Samples from individual patients were run in adjacent lanes. If there was no amplification for any allelic family, PCR was repeated with two times the quantity of template DNA. If no amplification was detected after this second reaction, amplification was classified as unsuccessful.

The nested PCR products were analyzed by gel electrophoresis using 2% agarose. The PCR products were then visualized under ultraviolet light transillumination after being stained with 0.5 µg/ml ethidium bromide (EtBr) and the results photographed using a paranoid camera. Based on the bands shown, the various allelic genes of MSP1, MSP2 and GLURP were determined.

3.3.3 ORGANIZATION OF STUDY

Haemoglobin level and parasitaemia (peripheral, placental and cord) in study participants were determined. A structured survey form was used to collate data on the pregnant women personal information (including age, gestational age, religious background etc), socioeconomic status, their health conditions and other anthropometric indicators including weight and height, blood pressure. A structured questionnaire containing closed and open-ended questions were administered to a simple randomly selected pregnant women and nursing mothers in the study communities by trained interviewers in the local dialect. The structured questionnaire covered the following areas: socio-demographic characteristics, knowledge of malaria in pregnancy, preventive measures to curb the disease, access and use of antenatal clinics, attitude towards the use of SP in IPTp and other health services. In addition, they were asked whether or not they had received SP at the ANC to protect them from malaria during their most recent pregnancy. If an ANC card was available, information from the card was also abstracted. Routine delivery data for the past three years (delivery data for 2005 to 2007) after the introduction of the IPT programme were analyzed to determine the effect of SP on birthweight of neonates. Distribution of birthweight before the implementation of SP for the past five years (2000 to 2004) was also analyzed.

Filter paper was used to collect blood sample for PCR analysis. Peripheral, placental, and cord blood were taken for PCR analysis as stated earlier.

3.4 QUALITATIVE RESEARCH

Qualitative research was undertaken to assess the knowledge and understanding of study participants on SP in IPTp use and possible outcomes of treatment. In-depth interviews, focus group discussions, case reviews and other tools of qualitative research were used to explore the perceptions, attitudes and practices on malaria/anaemia causation, prevention, control and treatment among pregnant women, health staff, chemists and/or drug store keepers, community leaders and opinion leaders (since they were regarded to be more knowledgeable on health-related matters in their community).

Twenty four IDIs were conducted with midwives at the various health facilities in the Offinso district. Aside midwives, thirteen IDIs were conducted with other health workers and supporting staff. They included: Nurses, Accountants, Administrators, Public Health Nurses, Medical Assistants, Medical Officers, Head of Laboratory Department, Biostatistician and Disease Control Officer. These were all staff of the health facilities in the Offinso District. In addition, three assemblymen, three chiefs, one queen mother, an opinion leader as well as nine chemical sellers in the district were interviewed.

Four focus group discussions (FGDs) of "horse shoe" types were conducted with pregnant women in selected communities within the district. Two were conducted in Offinso Central communities and the other in Akomadan and Afrancho communities. The pregnant women were assigned to one or the other of two categories namely: pregnant women who were less than twenty years of age and those who were twenty years and above.

3.5 ETHICAL CONSIDERATION

Permission was first sought from the District Health Directorate, the District Assembly and opinion leaders in the study communities to conduct the study. This was done after educating them on what the study entailed. Ethical clearance was sought and obtained from the Ghana Health Service and School of Medical Sciences (SMS) Ethic Committees. All study participants were provided with individual informed consent forms to sign or thumbprint after being well educated about the study.

3.6 DATA ANALYSIS AND REPORTING

With the help of health staff at study facilities and team of research assistants, there were compilation of locally relevant information and collection of data using agreed standard procedures including determination of Hb, blood film preparations, anthropometric measurements etc, by the Ministry of Health, Ghana. Datasets were sent to the Department of Biology, KNUST for analysis.

Data entry and preliminary data analysis were done in Microsoft Access.

3.6.1 STATISTICAL METHODS

Verified data were cleaned on regular basis through running programmes on legal values and consistency checks.

All study women were given an eight digit identification number, identifying village, house number, and a randomly computer generated digit. All answers were numerically coded on the questionnaire and responses and laboratory results entered into Microsoft Office Access.

Averages and 95% confidence interval (CI) were used for summarizing of results. Frequencies and percentages were used to compare number of participants associated with a study variable.

Continuous variables were compared using student t-test/anova and discrete variables analyzed using chi sq. (χ^2) in rXn tables and non parametric tests. Multiple regression models were used to control for covariates like age, sex, clinics attended, number of prophylaxis courses, in relation to outcome measures. For continuous variables, the estimates were for differences in means with 95% CI and for binary data, the estimate were for odds ratios with 95% confidence levels. In assessing the effect of SP on birthweights, the effect of potential confounding variables (parity, age of women delivering, gestational age and sex of babies) were controlled for using the Mantel – Haenszel technique, comparing adjusted and crude odd ratios. Values of *p* less than 0.05 were considered significant. Data analysis was done with Stata 10 for Windows (Stata Corporation 4905, Lakeway Drive College Station, Texas 77845 USA).

In the qualitative study, most of the respondents (the health staff exclusive) spoke Asante Twi, the local dialect, and questions asked and the responses were tape-recorded in the local dialect and English. Responses in the local dialect were later translated into English. These responses were initially coded separately for the Asante Twi and English versions and thematic areas were obtained. Data were manually analysed along the defined themes including general knowledge about malaria (causes, symptoms), knowledge of SP in IPTp (usage, benefits and adverse effects), prevention and treatment of malaria, information, communication and education and cost effects in malaria treatment.

CHAPTER FOUR – RESULTS

4.1 THE EFFECTS OF IPT USING SP IN THE CONTROL OF MALARIA IN PREGNANCY

4.1.1 BACKGROUND CHARACTERISTCS

A total of 487 pregnant women, 281(58.0%) in the dry season (November, 2005 – February, 2006) and 206 (42.0%) in the wet season (October, 2005; March – June, 2006), were recruited. An average of 3.4±1.4 (95%CI: 3.33-3.60) people occupied a single room. Forty three (9%) of the pregnant women enrolled were of gestational age <16 weeks and were excluded from the analysis. Four hundred and forty four (91%) of the pregnant women enrolled were of gestational age of 16-36 weeks and included in the analysis. Of these, 190 (43%) took SP (Figure 12).

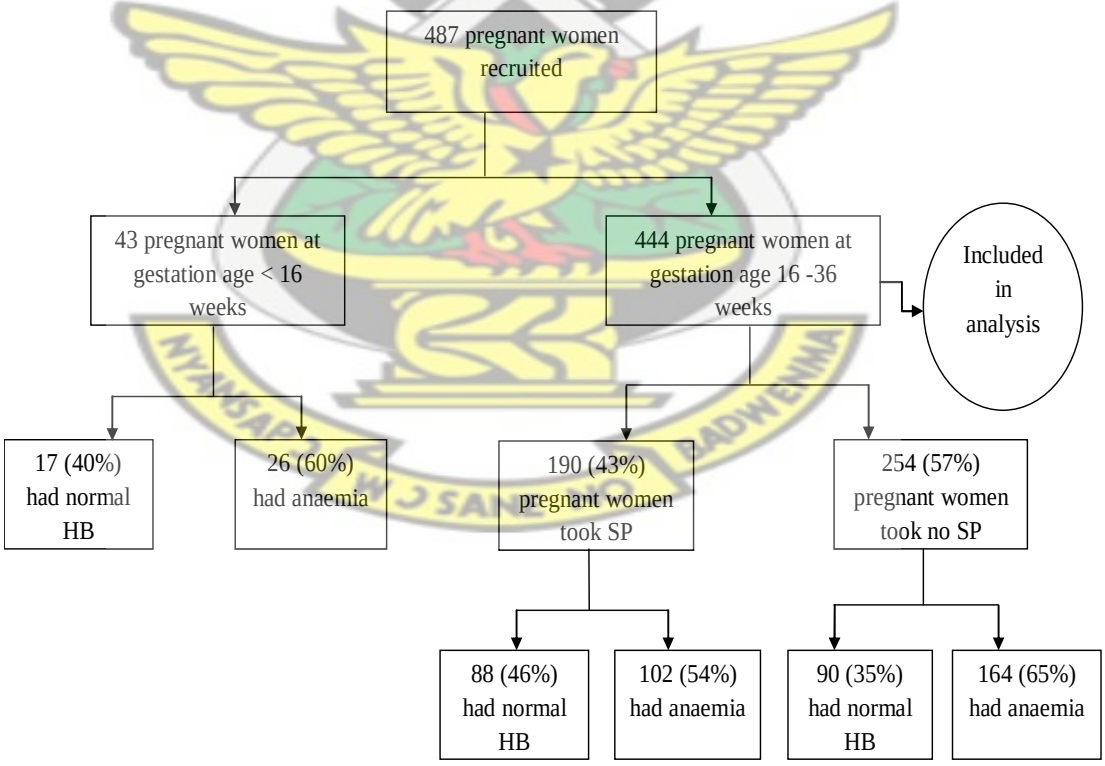

Figure 12: Profile of pregnant women recruited for the study

Fifty four (54) or 12.0% of the pregnant women used traditional medicine including herbs and the bark of trees which they added to foods or used as enemata and which they reported to be helpful as diuretics, for control of nausea and prevention of constipations. The educational level among the pregnant women was low with less than 50% completing Senior Secondary and Middle/Junior Secondary Schools (Table 4). Educational level of the pregnant women had a significant association with haemoglobin level (p=0.032). There were more Christians (75%) as compared to the other religious groups among the study women (Table 4).

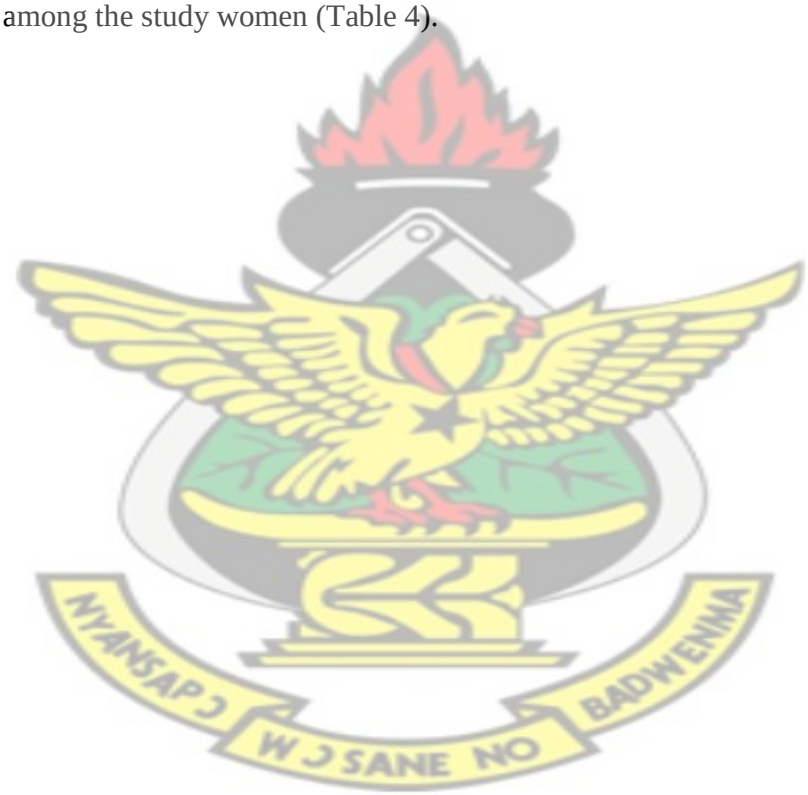

Table 4: Background characteristics of study subjects

	N (444) (%)
Age	
≤19	66 (15.0%)
20-29	237(53.0%)
30-39	125 (28.0%)
≥40	16 (4.0%)
Parity	
Primigravidae	87 (19.6%)
Secundigravidae	91 (20.5%)
Multigravidae	266 (59.9%)
Marital Status	
Married	317(71.0%)
Single	127(29.0%)
Educational Level	
None	157(35.4%)
Primary	86(19.4%)
Middle/J.S.S	185(41.7%)
Secondary	14 (3.1%)
Tertiary	2 (0.4%)
Religion	
Christian	333 (75.0%)
Moslem	80 (18.0%)
Free thinkers	26 (6.0%)
Traditionalist	5 (1.0%)

The socioeconomic statuses of the pregnant women were generally low with few owning properties as shown in Table 5. Over 50% of the pregnant women were farmers; traders and artisans (dressmakers, hairdressers, potters etc) were less than 40%. The "others" under occupation included those unemployed and students who were pregnant. Radio usage was very high among pregnant women as compared to television use i.e. 76% vs. 37%. Only 36% of the women slept in insecticide treated nets (ITNs) (Table 5).

Table 5: Socioeconomic status of study subjects

Occupation	**N (444) (%)**
Farmer	241 (54.0%)
Trader	96 (22.0%)
Artisan	62 (14.0%)
Others	45 (10.0%)
Ownership of Property	
Car	76 (17.0%)
Motorbikes	45 (10.0%)
Bicycles	182 (41.0%)
Radio	336 (76.0%)
Television	163 (36.0%)
Sleep on bed	349 (79.0%)
Windows netted	157 (35.0%)
Sleep in ITNs	158 (36.0%)
Latrine at home	165 (36.0%)
Source of drinking water	
Pipe borne water	153 (34.4%)
Well water	55 (12.0%)
Bore hole water	151 (34.0%)
River water	80 (18.0%)
Animals kept at home	
Goats	96 (22.0%)
Sheep	119 (26.0%)
Poultry	274 (62.0%)

The mean age of the participants was 26.0± 6.2 years. The youngest participant was 14 years and the oldest was 45 years of age. Most of the primigravid women 57/66 (86%) were teenagers. Other anthropometric indicators showed that they were less at risk of complications during delivery since they attained normal height and weight during pregnancy with relatively no hypertensions and obesities (Table 6).

Table 6: Characteristics of pregnant women

	Mean (SD)	95% CI
Age(yrs)	26.0± 6.2	25.4-26.6
Haemoglobin level(g/dl)	10.1±1.7	10.0-10.3
Body mass index (kg/m^2)	22.7±3.7	22.3-23.0
Height (cm)	160.2±9.2	159.3-161.1
Weight (kg)	58.3±8.4	57.5-59.1
Systolic blood pressure (mmHg)	109±11.6	107.9-110.3
Temperature (°C)	36.5±0.6	36.4-36.6

In the SP group, 82 (43%) of the pregnant women took first dose only, 57 (30%) and 51(27%) respectively took second and third doses of SP (Table 7).

4.1.2 THE EFFECT OF SP ON PARASITAEMIA IN PREGNANCY

Of the 123 pregnant women with parasitaemia, 65 (53%) took no dose of SP, 29 (24%), 18 (15%) and 11 (9%) respectively took 1, 2 and 3 doses of SP. Pearson correlation showed poor relation of SP doses taken with malaria infection (r = 0.0008, p = 0.986); thus there was no significant association between SP and parasitaemia (Pearson χ^2 =1.32, $p \geq 0.25$). Parasitaemia in the no SP group was higher than those who took SP (65/123 (53%) as against 58/123 (47%)). Moreover, the proportion of parasitaemia in those who took one dose of SP, 29/82 (35%) was significantly higher than in those who took two and three doses of SP, 18/57 (32%) and 11/51 (22%) respectively (Pearson χ^2 = 11.6, $p \leq 0.02$) (Table 7). Few of the pregnant women, 12/444 had parasite density ≥ 5000 per µl of blood (Table 7).

Table 7: Parasitaemia in pregnant women taking various doses of SP

Parasite density (per µl of blood)	Doses of SP 0	1	2	3	Total
None	189	53	39	40	321
Percentage (%)	74.41	64.63	68.42	78.43	72.30
1-1999	54	24	13	7	98
Percentage (%)	21.26	29.27	22.81	13.73	22.07
2000-4999	6	5	2	0	13
Percentage (%)	2.36	6.10	3.51	0.00	2.93
≥ 5000	5	0	3	4	12
Percentage (%)	1.97	0.00	5.26	7.84	2.70
Total	254	82	57	51	444

Primigravidae were found to have the highest mean parasite density as compared to secundigravidae and the multigravidae; the differences among them were significant ($p < 0.001$). However, parasite densities for doses 2 and 3 in the primigravidae were very high as compared to dose 1 and dose 0 (Table 8). Occupation of the pregnant women did have a significant association with their parasite densities (Pearson $\chi^2 = 18.09$, $p = 0.034$). Parasitaemia in farmers were significantly higher (mean parasite density =2595; $p \leq 0.03$) than the other occupational groups (Table 9). ITN users (36/123; 29%) had less parasitaemia compared to non-users (87/123; 71%). Parasitaemia did not show any significant seasonal variation in pregnant women ($p \geq 0.22$) and thus seasonal differences were also not significant ($r = -0.02$, $p \geq 0.72$). Of the pregnant women with parasitaemia, 2 (2.0%) had severe anaemia, 83 (66.0%) moderate anaemia and 38 (31.0%) had normal haemoglobin (Hb ≥ 11g/dl). However, there was a negative correlation of haemoglobin with parasitaemia ($r = -0.035$, $p = 0.477$).

Table 8: Mean parasite density (per µl of blood) of gravid women by doses of SP taken

SP doses	Parasite density (µl of blood)		
	primigravidae	secundigravidae	multigravidae
0	1090.6	197.6	176.0
1	657.1	674.3	80.7
2	1685.3	966.2	118.6
3	14336.0	40.0	534.5

Table 9: Mean parasite density (per µl of blood) and Occupation of Pregnant women

Occupation	Mean Parasite Density (per µl of blood)	95% Confidence Interval
Farmers	2595	260 -4931
Traders	1009	460-1558
Artisan	1654	312-3996
Others	1523	81-2965

4.1.3 THE EFFECT OF SP ON HAEMOGLOBIN LEVEL IN PREGNANCY

The mean Hb was 10.1±1.8g/dl with the lowest being 6g/dl and highest 17g/dl. Anaemia was found in 266 /444 (60%) of the study subjects. There was a significant positive association between the use of SP in IPTp and haemoglobin level (Pearson χ^2 =16.0; $p \leq 0.01$). The proportion of those who took SP and had anaemia was 102/190 (54%) as compared to those who took no SP but had anaemia 164/254 (65%) [Figure 12]. The mean Hb level for the SP group (10.4±1.69g/dl) was significantly higher than

that (9.9±1.64g/dl) in the no SP group ($p < 0.002$). Among the primigravidae 59/87 (68.0%) were anaemic; 60/91 (66.0%) were anaemic in the secundigravidae whilst 147/266 (55.0%) were anaemic in the multigravidae. There was a significant association of haemoglobin with gravidity (Pearson $\chi^2 = 9.4$; $p \leq 0.05$). Mean haemoglobin levels increased with repeated doses of SP and increasing gravidity. Primigravidae who took 3 doses of SP as against doses 0, 1and 2 had the highest mean haemoglobin level as shown in Table 10. Analysis of variance showed significant difference in mean haemoglobin level by gravidity ($p < 0.0001$); primigravidae had the lowest mean Hb level of 9.4g/dl, with secundigravidae and multigravidae women attaining mean Hb level of 10.1g/dl and 10.4g/dl respectively. Thus, multigravid women were found to have average increase of haemoglobin level (Hb = 0.92g/dl, $p < 0.001$) over primigavid and (Hb = 0.32g/dl, $p = 0.37$) over secundigravid women respectively, using Bonferroni comparison.

Table 10: Mean Hb level among gravid women taking SP

Doses of SP	**Mean Hb content (g/dl)**		
	Primigravidae	Secundigravidae	Multigravidae
0	9.3	9.9	10.1
1	9.0	10.0	10.5
2	9.7	9.8	11.2
3	11.2	10.9	10.9

By Sidak's measure of comparison, the average haemoglobin level for those who took 3 doses of SP increased by 1.02g/dl, ($p < 0.001$) over those who did not take SP, increasing by 0.78g/dl, $p \leq 0.075$, 0.53g/dl, $p = 0.55$ over doses 1 and 2 of SP respectively (Table 11). There was a weak relationship between haemoglobin level and

the use of insecticide treated nets (ITNs) (correlation coefficient, $r = 0.004$, $p \geq 0.90$). There was a mean increase of haemoglobin with increased age of study women but the difference was not significant ($p \geq 0.19$). Seasonal variations did not show significant association with haemoglobin level ($p \geq 0.3$).

Table 11: Relationship between doses of SP and mean Hb level in pregnant women

SP doses taken	Hb mean(SD) g/dl	95% CI
0	9.9 ± 1.64	9.7 - 10.1
1	10.1 ± 1.61	9.8 - 10.5
2	10.4 ± 1.93	9.9 - 10.9
3	10.9 ± 1.43	10.5 - 11.4

4.1.4 ADVERSE EFFECTS OF USE OF SP

One hundred and ninety (190) or 43.0% of the pregnant women took SP as aforementioned; however, the number of pregnant women taking repeated doses decreased. Women who were in their second and subsequent pregnancies took subsequent doses of SP as compared to those in their first pregnancies thus, few primigravid women, 34(18%) took SP as compared to secundigravid women, 40 (21%) and multigravid women, 116 (61%) taking SP.

Thirty six pregnant women (19%) complained of adverse effects from taking SP (as against 154 or 81%) who had no complaints. The adverse effects included general malaise, body weakness, nausea, vomiting, palpitations and itching. These reported cases of side effects in taking SP deterred some of the women from continuing with the second and third doses of the drug. However, there was no significant difference in the adverse effects among those who took the first, second and third doses of SP ($p \geq 0.401$).

4.1.5 OTHER MATERNAL MORBIDNESS

Interviews conducted among the pregnant women indicated 138 (31%) were sick for the past two weeks before their recruitment and were treated at the health centres. These were minor sicknesses. Other conditions experienced by the pregnant women are tabled below (Table 12). Most of these conditions are usual in pregnancy including tiredness, breathlessness, frequent urination, fits and swollen feet etc. Headache, fever, pallor, neck stiff, dizziness and persistent vomiting may indicate presence of malaria and less than 50% of the pregnant women indicated such conditions (Table 12).

Table 12: Conditions complained of by Pregnant women

Conditions	N (444) (%)
Tire easily	267 (60.0%)
Breathless at housework	175 (39.0%)
Neck stiff	57 (13.0%)
Fever	103 (23.0%)
Headaches	180 (41.0%)
Fits	71 (16.0%)
Diuresis	186 (42.0%)
Swollen feet	79 (18.0%)
Pallor	59 (13.0%)
Dizziness	116 (26.0%)
Persistent vomiting	94 (21.0%)

Aside the prophylactic SP, 28 (6%) of the pregnant women took other antimalarial drugs for treatment of malaria. These were artesunate, artesunate–amodiaquine, chloroquine and alaxin. Other drugs taken were analgesics (e.g. paracetamol) and blood tonics.

4.1.6 DISCUSSION

From the study, parasitaemia was more prevalent in the no SP group compared to the SP group. This could be attributed to the taking of SP drug to clear most parasitaemia in the pregnant women. The high parasite density in pregnant women who took two and/or

three subsequent doses of SP could be as a result of possible development of resistance of the parasites to SP. Findings from this study confirm findings from previous studies which showed that pregnant women, particularly primigravidae, were highly susceptible to *P. falciparum* infection and to clinical malaria which could result in maternal anaemia, low birthweight, and preterm delivery (Sullivan *et al*., 1999; Menendez *et al*., 2000; Glover –Amenyor *et al*., 2005; Tagbor *et al*., 2006; Ndyomugyenyi *et al*., 2008). This study also showed that primigravidae had the highest mean parasite density and higher proportion of anaemia. This could be attributed to low immunity and reduced age in them as compared to the relatively high immunity that is found in adult multigravid women who rarely attract highest risk of the disease. The decreased number of primigravid women taking SP may be attributed to lack of attendance to ANC due to the stigma associated to teenage pregnancy in the communities since most, 86% the primigravid women were in their teens.

Seventy two percent (72%) of the pregnant women had body mass index (BMI) below 19kg/m^2 and were anaemic suggesting that malnutrition was a possible major cause of anaemia in pregnancy. Additional negative effects of malnutrition in pregnancy include low birthweight and preterm delivery (Ogunyemi, Hullett and Leeper, 1998; Ehrenberg *et al*., 2003; Neggers and Goldenberg, 2003; Helgstrand and Andersen, 2005). Although, other determinants of anaemia were not part of this study, it is likely that a combination of factors such as malnutrition, helminth infection and other disease conditions in addition to malaria contributed significantly to the observed anaemia in this study (van den Broek, 1996; Steketee, 2003; Agyei, 2005; Glover–Amenyor, Owusu and Akanmori, 2005; Ndyomugyenyi *et al*., 2008).

Given that over 50% of the pregnant women studied were farmers and traders and who had little or no formal education, it is, therefore, possible that most of them had little or no knowledge on malaria, malaria-related anaemia and malnutrition. The low socioeconomic status, many occupants in a room (average, 3.4±1.4) and poor housing of most of the pregnant women (75%) were indicative of poor living conditions which might have contributed to increased exposure to mosquito bites.

The results of the study showed that there was a significant increase in Hb level of pregnant women who took SP compared to the no SP group ($p < 0.002$). Repeated doses of SP were found to be associated with higher Hb levels in the pregnant women, with no significant adverse reactions. This reduction of maternal anaemia and parasitaemia in relation to the number of SP doses taken, thus, confirm the beneficial impact of the drug as reported by WHO (2004) and in other studies (Verhoeff *et al*., 1998; Parise *et al*., 1998; Shulman *et al*., 1999; van Eijk *et al*., 2004; Kayentao *et al*., 2005; Schellenberg *et al*., 2005; Tagbor *et al*., 2006; Mbonye, Bygbjerg and Magnussen, 2008).

For the purpose of this study, SP doses were obtained from the ANC cards, and possible non-recording of doses might have led to an underestimation of doses received. Non-recording of doses was observed at ANCs and was estimated to occur in 2.2–6.5% of attendants. The possible underestimation of doses received is not expected to significantly influence the observed findings (van Eijk *et al*., 2002; van Eijk *et al*., 2004).

The evaluation of SP in IPTp showed a decrease in peripheral parasitaemia with increased dose of SP/IPTp. The study also showed that repeated doses of SP were associated with higher Hb levels in pregnant women. Primigravidae were more susceptible to falciparum malaria with increased morbidity in them. Though the study

was conducted in both the dry and wet seasons there was high malaria-associated maternal morbidity all year round indicating no significant relation between malaria transmission and season, and, thus pointing to the fact that the forest belt region of Ghana is a stable area of malaria transmission. Malaria and anaemia are quintessential diseases of poverty. Hence reducing malaria and malaria-related anaemia in pregnancy in rural Ghana will contribute significantly to Ghana's efforts at poverty reduction.

4.2 ASSESSMENT OF THE EFFECT OF SP, KNOWLEDGE ON MALARIA DURING PREGNANCY AND TRANSPLANCENTAL MALARIA

4.2.1 ASSESSMENT OF THE EFFECT OF SP

4.2.1.1 BACKGROUND CHARACTERISTICS

Three hundred and sixty two women were sampled for the second phase of the study also in the Offinso District of Ashanti Region of Ghana. Out of the baseline data 306 women who took SP were studied and analyzed (Figure 13). The mean age of the 306 study women was 27±6 with a 15 year old being the youngest and 46 year old, the oldest. Over 50% of the age group fell between ages 20 and 29 years with less than 10% being below 20 years (Table 13).

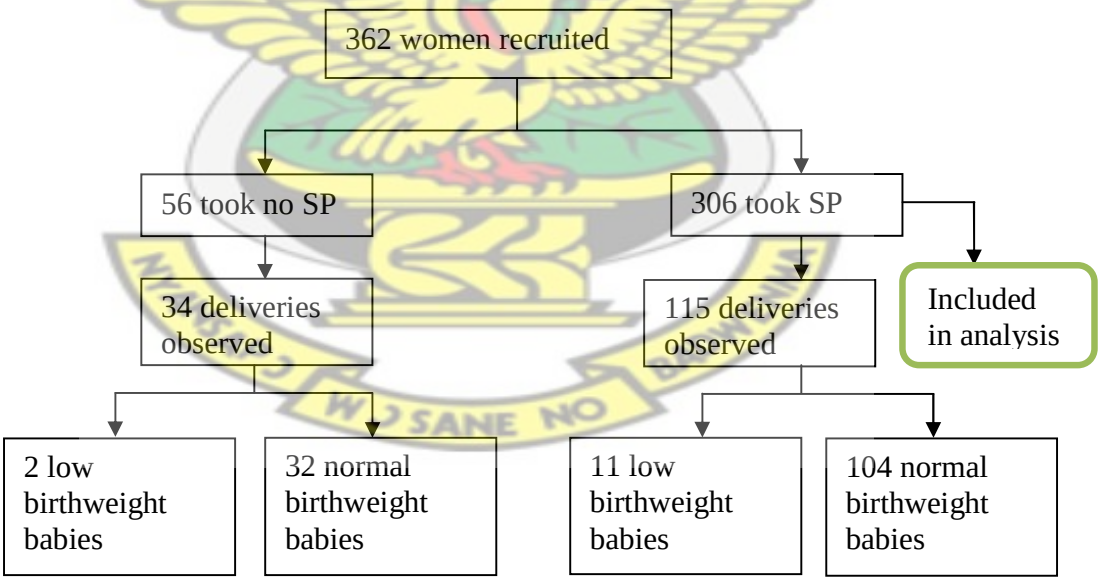

Figure 13: Profile showing the grouping of study women through to delivery

Table 13 Background Characteristics of pregnant women

Age	**N (306) (%)**
≤19	27 (9.0%)
20-29	173 (56.0%)
30-39	102 (33.0%)
≥40	4 (1.0%)
Parity	
Primigravidae	55 (18.0%)
Secundigravidae	75 (24.0%)
Multigravidae	176 (58.0%)
Marital Status	
Married	149 (49.0%)
Single	157 (51.0%)
Educational Level	
None	76 (25.0%)
Primary	67 (22.0%)
Middle/J.H.S	133 (43.0%)
Secondary	23 (8.0%)
Tertiary	7 (2.0%)
Religion	
Christian	218 (71.0%)
Moslem	75 (25.0%)
Free thinkers	11 (3.0%)
Traditionalist	2 (1.0%)

Primigravidae constituted 18% with multigravidae making 58% of the study population. Most of the pregnant women were Christians and less than 50% had completed Middle/Junior High School. Single women who made up 51% of the study subjects included those who have not married under the traditional customs or by laws of the country (Table 13).

The mean body temperature of the pregnant women was 36.4±0.6 ºC (95% CI: 36.2 to 36.4) hence fever could not be attributed to the study subjects though there were complaints of feverishness. The average height was 1.62 ±0.004 m (95% CI: 1.61 to

1.63) and the mean body mass index (BMI) was 24±4.2 kg/m^2 (95% CI: 24 to 25). There were no any hypertensive patients among them since the systolic pressure was found, on average, to be 108 ±12.9 mmHg (95% CI: 106 to 109). The median weight was 63 kg (IQR 57 - 69 kg) with the minimum weight being 30 kg and maximum 94 kg.

Table 14: Socioeconomic status of the pregnant women

Occupation	**N (306) (%)**
Farmer/housewife	79 (26.0%)
Trader	108 (35.0%)
Artisan	49 (16.0%)
Civil servants	12 (4.0%)
Unemployed	58 (19.0%)
Own Properties	
Car	53 (16.0%)
Motorbikes	31 (10.0%)
Bicycles	155(51.0%)
Radio	261(85.0%)
Television	154(50.0%)
Sleep on bed	264(86.0%)
Windows netted	171(56.0%)
Have mosquito nets	183(60.0%)
Have ITNS	173(56.0%)
Sleep in ITNS	145(46.0%)
Latrine at home	118(38.0%)
Source of drinking water	
Pipe borne water	159(52.0%)
Well water	78(25.0%)
Bore-hole water	100(33.0%)
River water	43(14.0%)
Animals kept at home	
Goats	54(17.6%)
Sheep	55(18.0%)
Poultry	188(61.0%)

Traders (35%) formed majority of the pregnant women studied. Artisans included dressmakers, hair dressers, potters and tie-dyers made up 16% of the study women. Civil servants including teachers, nurses, secretaries, etc made up 4% while the unemployed made up 19% of study women (Table 14). Property highly owned by the pregnant women was radio (85%) while motorbikes were least (10%) owned by them. Possession of insecticide treated nets was 57% among the women with less than 50% sleeping in them (Table 14).

The average persons per room were 3±1.5 with the least occupant being one and the most occupants being 13. Twenty eight percent (86 women) lived in houses built with blocks and roofing sheets, whilst 72% (220) of them lived in mud and bricks houses with either roofing sheets or thatches as roof cover (data not shown). One hundred and seventy seven (58%) reported a history of sickness due to malaria, headache, feverishness, abdominal pains, stomach ache, general malaise and other minor health complaints two weeks prior to their recruitment. Seventy four (24%) used traditional medicine which included herbs for enemata and those they added to foods eaten.

4.2.1.2 HAEMOGLOBIN LEVEL

The mean haemoglobin level was 11.3±1.6 g/dl (95% CI: 11.1to 11.4). One hundred and eighteen women (39%) had moderate anaemia (Hb < 11.0 g/dl) whilst most of the pregnant women 187 (61%) had normal haemoglobin level (Hb ≥ 11.0 g/dl). There was no significant association between haemoglobin level and gravida of pregnant women (Pearson's $\chi^2 = 4$ $p \geq 0.14$). Comparing Hb with other socioeconomic status including education, occupation, religion, marital status and use of ITN did not show significant associations (Pearson's $\chi^2 = 0.7$, $p \geq 0.9$; Pearson's $\chi^2 = 1.8$, $p \geq 0.6$; Pearson's $\chi^2 = 6.1$, $p \geq 0.1$; Pearson's $\chi^2 = 1.3$, $p \geq 0.3$; Pearson's $\chi^2 = 1.2$, $p \geq 0.3$) respectively. There was,

however, a significant association between Hb and the doses of SP taken (Pearson's χ^2 =182.2, p = 0.02). Multivariate analysis using regression showed that 2% variance in haemoglobin level was due to age, level of education, occupation, gravid status, and use of ITNS and parasite density of the pregnant women. There was 8% decrease in Hb level with a unit increase of parasite density when all other factors remained constant but this decrease was not significant ($p \geq 0.5$). Number of SP doses taken significantly increased Hb level by 30% on each unit increase when introduced into the model with all other factors being controlled ($p \leq 0.013$).

4.2.1.3 PARASITAEMIA IN PREGNANT WOMEN

Forty seven (15%) of the pregnant women had parasitaemia but there was no significant association between parasitaemia and haemoglobin level of the pregnant women (Fisher's exact = 0.87). Pearson's correlation showed negative relations of the various parasitaemia levels with the number of doses of SP taken but these were not significant ($p \geq 2$) using Bonferroni method of comparison. There was no significant association between parasitaemia and Hb level as aforementioned, however, there was a weak association between gravida and parasite density (Pearson χ^2 = 10.8, $p < 0.09$). About 2.0% and 0.7% of the women who delivered had respectively placental and cord blood parasitaemia (Table 15).

Table 15: Parasite densities in pregnant women

Parasite Density	Peripheral	Placental	Cord blood
1-1999	40 (13.1%)	6 (2.0%)	2 (0.7%)
2000-4999	3 (0.9%)	1 (0.3%)	0
≥5000	4 (1.0%)	1 (0.3%)	0
None	259 (85.0%)	298 (97.4%)	304 (99.3%)

4.2.1.4 USE OF SP

There was significant association between gravida and the doses of SP taken (Pearson χ^2 =18.9, $p < 0.001$). Table 16shows the doses taken by pregnant women according to their gravida status. Multigravid women increasingly took the full dose of SP (dose 3) followed by secundigravid and primigravid women (Table 16). There was significant difference among the gravida of women who took SP doses ($p < 0.001$).

Table 16: Doses of SP taken by pregnant women

Gravida	***Dose 1***	***Dose 2***	***Dose 3***	***Total***
Primigravida	12 (13.0%)	27 (26.0%)	16 (14.0%)	**55 (18.0%)**
Secundigravida	13 (14.0%)	27 (26.0%)	35 (31.0%)	**75 (24.0%)**
Multigravida	67 (73.0%)	46 (45.0%)	63 (55.0%)	**176(58.0%)**
Total (100%)	**92 (100.0%)**	**100(100.0%)**	**114(100.0%)**	**306(100.0%)**

4.2.1.5 ADVERSE EFFECTS EXPERIENCED WITH INTAKE OF SP

With the use of SP-IPT, 113(37%) of the pregnant women reported of adverse effects and below (Table 17) are some of the adverse effects reported. However, these effects had no significant association between the use of SP and the number of doses of SP taken (Pearson's $\chi^2 = 2.3$, $p \geq 0.32$).

Table 17: Adverse effects of SP-IPT in pregnant women

Adverse effects	N (306) (%)
Gastrointestinal	
Nausea	39 (13.0%)
Vomiting	37 (12.0%)
Diarrhoea	9 (3.0%)
Constipation	13 (4.0%)
Neurological	
Headaches	27 (9.0%)
Dizziness	37 (12.0%)
Depression	28 (9.0%)
Confusion	8 (3.0%)
Funny or scary dreams	12 (4.0%)
Dermatological	
Itching	9 (3.0%)
Spots on skin	5 (2.0%)
Change of skin colour	1 (0.3%)
Ocular	
Visual hallucinations	7 (2.0%)
Bad sight	3 (1.0%)
Itchy eyes	1 (0.3)
General	
Fever	9 (3.0%)
Anorexia	20 (6.0%)
General malaise	28 (9.0%)
Musculoskeletal	
Joint ache	6 (2.0%)
Swollen joints	1 (0.3)
Fatigue	15 (5.0%)

4.2.1.6 SP AND PARASITAEMIA

Generally, there was poor negative relationship of doses of SP with peripheral, placental and cord blood parasitaemia (r = -0.07, r = -0.03, r = -0.03) respectively, though not significant when corrected by both Bonferroni and Sidak methods of comparison ($p \geq 1$).

4.2.1.7 SP AND HAEMOGLOBIN LEVEL

There was a significant positive correlation of SP with haemoglobin level (r = 0.15, p < 0.008). Haemoglobin levels among those who took various doses of SP did show significant difference (p<0.007). By Bonferroni method of comparison, the haemoglobin level of the pregnant women who took the first dose of SP was, on average, 0.649 (p < 0.017) and 0.619 (p < 0.019) significantly lower than those who took the second and third doses of SP respectively, whilst the haemoglobin level of those who took the third dose of SP was, on average, (0.03) lower than those who took the second dose of SP but the difference was not significant ($p \geq 1$).

4.2.1.8 OTHER MORBID CONDITIONS IN PREGNANCY

There were other conditions that were reported by the pregnant women; these included feverishness, headache, tiredness etc as shown in Table 18. Over 70% reported of being tired easily during routine house work; more than 50% reported headache, abdominal pains and being breathless during house work. The least reported case was stiff neck which made up 10% (Table 18).

Table 18: Conditions complained of by Pregnant women

Conditions	N (306) (%)
Tire easily	216 (71.0%)
Breathless at housework	169 (55.0%)
Neck stiff	32 (10.0%)
Fever	96 (31.0%)
Headaches	155 (51.0%)
Fits	63 (21.0%)
Swollen feet	64 (21.0%)
Pallor	75 (25.0%)
Dizziness	82 (26.0%)
Persistent vomiting	50 (16.0%)
Abdominal pain	203 (66.0%)
Body weakness	132 (43.0%)

4.2.2 KNOWLEDGE ON MALARIA AND ITS PREVENTION; USE OF ANTENATAL CLINIC SERVICES AMONG PREGNANT WOMEN AND NURSING MOTHERS IN THE COMMUNITIES (QUANTITATIVE SURVEY)

4.2.2.1 BACKGROUND CHARACTERISTICS OF PARTICIPANTS

Three hundred and seven structured questionnaires were administered to pregnant women and nursing mothers in 30 communities in the studied district. The median age of the respondents was 26 (IQR 23-32) years with the youngest being 16 years and the oldest, 46 years. Multigravid women made the majority (70%) of the respondents. Forty three percent of the women had Middle or Junior High School (JHS) education with those at tertiary level, 1% (Table 19).

Table 19: Background Characteristics of respondents

Age	**N (307) (%)**
≤19	25 (8.0%)
20-29	165 (54.0%)
30-39	96 (31.0%)
≥40	21 (6.0%)
Parity	
Primigravidae	12 (4.0%)
Secundigravidae	79 (26.0%)
Multigravidae	216 (70.0%)
Educational Level	
None	55 (18.0%)
Primary	69 (22.4%)
Middle/J.H.S	132 (43.0%)
Secondary	47 (15.3%)
Tertiary	4 (1.3%)
Religion	
Christian	250 (81.4%)
Moslem	44 (14.3%)
Free thinkers	13 (4.2%)

4.2.2.2 GENERAL KNOWLEDGE ON MALARIA

On general knowledge about malaria 232 (76%) participants who responded to the questionnaires were of the view that malaria was a problem in the district. Table 20 shows the respondents' responses on causes and symptoms of malaria.

Table 20: Responses on causes and symptoms of Malaria

Causes of malaria	**Yes (%)**	**No (%)**
Dirt	111 (36.0%)	196 (64.0%)
Food	26 (8.0%)	281 (92.0%)
Drinking water	8 (3.0%)	299 (96.0%)
Mosquitoes	209 (68.0%)	97 (32.0%)
Friends	8 (3.0%)	299 (96.0%)
Symptoms of Malaria		
Fever	196 (64.0%)	111 (36.0%)
Headache	57 (19.0%)	250 (81.0%)
Muscles/joint pains	71 (23.0%)	236 (76.0%)
Shivering	57 (19.0%)	250 (81.0%)
Breathlessness	4 (1.3%)	303 (98.7%)
Dizziness	61 (20.0%)	246 (80.0%)
Drowsiness	3 (1.0%)	304 (99.0%)
Stiff neck	1 (0.3)	306 (99.7%)

Other symptoms of malaria that were given by respondents are coloured or yellowish urine, vomiting, nausea, migraine, body weakness, general malaise, pallor, bitterness in mouth and loss of appetite.

One hundred and fifty five (50%) of the respondents said they went to the Chemist shop (drug store) to buy drugs for treatment, 87 (28%) attended clinics for treatment, 34 (11%) used herbal preparations, 17 (6%) responded to having cold bath and doing self medication whilst 14 (5%) had no idea of treatment on malaria. The most common drugs used for treatment were chloroquine, paracetamol and blood tonics. Others said when they attend clinics they are given artesunate, artesunate amodiaquine, alaxin, quinine,

malafan in combination with blood tonics and/or B-complex and multivitamins for treatment.

On malaria prevention, 277 (90%) of the respondents said malaria could be prevented by draining of stagnant waters, weeding their surroundings, use of insecticide treated nets, mosquito coils, observing personal hygiene and public education on the disease menace and prevention.

Diseases and other problems that were identified with pregnant women according to the respondents were malaria, heart diseases, jaundice, typhoid fever, convulsions, rheumatism, stomach upsets, haemorrhage, anaemia, headaches, palpitation and general malaise and body weakness.

4.2.2.3 MALARIA IN PREGNANCY

From the questionnaires administered, 230 (75%) of the respondents said malaria was a very serious disease that needed to be prevented because it could cause ill health of mother (anaemia) and unborn child (intrauterine growth retardation), miscarriage, abortion, and even the death of both mother and child.

For pregnant women to remain healthy, 214 (70%) of the respondents, said taking balanced diet helps. Other responses were attendance of antenatal care 132 (43%), observance of personal hygiene, 51(17%), regular exercise, 13(4%) and use of ITNs, 61(20%).

There was a 97% (299) response to the need to visit the antenatal care when pregnant. Most gave as reason for this obligation, the examination of the mother's health and that of the foetus in order to avoid complications during delivery.

On time of first visit to ANC when pregnant, 174(57%) of the respondents said two to three months of pregnancy, whilst some said one month, others, four months and others as soon as pregnancy is confirmed.

4.2.2.3 KNOWLEDGE ON SP

On awareness of the new policy adopted by the Ghana Health Service on prevention of malaria in pregnancy, 232 (76%) of the respondents admitted awareness and 165(54%) knew the drug being used for the programme. As to how they got to know about this programme 191 (62%) of the respondents said they heard about it from the ANCs attended. Thirty two (10%) said they heard about it from radio. Less than 10% got the information from community durbars, friends, and market places.

On the use and importance of the drug, 169 (55%) of the respondents said Fansidar® (SP) was a good antimalarial drug that helps prevent malaria in the pregnant women thereby protecting the unborn child also. They further said it improves the health of the pregnant women and enhances good child delivery.

Two hundred and thirty eight (78%) of the respondents said they have taken SP during pregnancy and that it was good. On adverse effects on taking the drug, 50 (16%) reported experiencing some effects which included anorexia, dizziness, headache, vomiting, nausea, depression, confusion, general malaise, and bodily weakness.

About their impression on taking the drug under direct observation at the health centre (i.e. direct observed therapy, DOT), 252 (82%) of the respondents said it was good and helpful because most of them, when given the drugs to take at home, either threw them away or forgot to take them. They said the DOT should continue since by so doing most of the pregnant women took their drugs and got well quickly. The remaining 55 (18%) of the respondents did not comment on the DOT.

4.2.2.4 CHOICE OF PLACE OF DELIVERY

On choice of place of delivery, most (90%) of the respondents said they looked at the availability of experts (trained health personnel including birth attendants), better health facilities and conditions of service. Others said they considered the closeness of the health facilities, patients and health staff relations (one of the respondents stated "*I wanted to avoid insults that is why I don't go to the hospital*"; another said "*I was rejected by one of the hospitals and so, have to deliver at home*"), reason given was delayed attendance to health facility; their financial status ("*lack of money constrained me to stay away from the hospital*" said a respondent); their health conditions ("*to avoid complications*" and "*for the fear of death*" some respondents stated) before choosing their places of delivery.

4.2.2.5 MATERNAL MORTALITY

On death of pregnant women or women at labour, 229 (75%) of the respondents said they normally hear such cases once or twice monthly and most of these deaths were due to haemorrhage, malaria, anaemia, failure to attend ANC or late attendance to hospital. Other causes, said the respondents, were negligence on the part of the health staff to give proper supervision and lack of expertise, some home deliveries, taking of herbal concoctions to ease delivery and other complications of diseases not known of on time. The respondents said these deaths during pregnancy could be averted if the pregnant women attended ANC regularly in time, the health staff were professionally trained and well equipped, patients adhered to the advice given them by health personnel, efforts were made to keep to moderation bleeding during labour to avoid haemorrhage, there were public education on health in pregnancy and personal hygiene. Government should

subvent the care for pregnant women. They also said efforts should be made by government to eradicate poverty among the rural communities.

4.2.3 ASSESSMENT OF THE KNOWLEDGE AND PERCEPTION OF IPT–SP USAGE, MALARIA AND OTHER DISEASE INFECTIONS (QUALITATIVE SURVEY)

4.2.3.1 GENERAL KNOWLEDGE OF DISEASE IN THE COMMUNITY

In almost all the health facilities and communities, common diseases most mentioned by respondents in both the IDIs and the FGDs were malaria/fever, anaemia, diarrhoea, convulsions/seizures and skin diseases. Others were respiratory tract infections (RTI), schistosomiasis, diabetes, hypertension and typhoid fever.

The principal midwife said this:

"The most common diseases are malaria, diarrhoea, anaemia, HIV/AIDS disease, tuberculosis (TB), and as for typhoid it is epidemic, it comes for a period and goes. UTI (Urinary Tract Infection) and RTI (Respiratory Tract Infection) have their season; hypertension and diabetes are common too" (***Principal midwife superintendent***)

In most interactions and discussions, malaria appeared to be the leading and most common and severe disease in the communities.

"*The OPD record reveals that malaria is number one, followed by upper respiratory tract infection, diarrhoea, and skin diseases. These are the top four but the rest keep changing*". (***Disease Control Officer, Offinso District***)

"Our ten or five top diseases, the first one is malaria, (flipping through some documents) we have anaemia, hypertension, typhoid, upper respiratory tract infection,

*sexually transmitted diseases". (**Statistician, St. Patrick's Hospital, Offinso**)*

Respondents named malaria and anaemia as the major disease problems that disturb pregnant women in the district.

This is what the Pharmacist at St. Patrick's hospital had to say:

*"Looking at the folders you see here, I know there are many pregnant women who turn up with malaria because in some cases I see them coming in for quinine, sometimes Artesunate. Aside malaria we also have a lot of diabetes and hypertension cases in this part of the district". (**Pharmacist at St. Patrick's hospital, Offinso**)*

The various interviews and FGDs pointed to the fact that the main disease menace in pregnant women was malaria.

In-depth interviews with opinion leaders and chiefs also confirmed malaria as the most common disease in the district.

"Yes, malaria is the most common disease over here" (***Opinion leader, Mehame, Offinso***)

Most respondents also mentioned that malaria was more rampant during the rainy season. This did not exclude the fact that there were no malaria cases during the dry season.

"It is because this place is in the forest zone and during the rainy season the mosquitoes get a lot of places to lay their eggs and also if a person gets malaria it affects the blood cells and this makes one gets anaemia. So the two go together". (***Midwife, St. Patrick's hospital, Offinso***)

"*They also get the malaria (during the dry season) but you see we stay with them, so we know the periods that malaria cases reported are high or low. In the rainy season the*

malaria cases reported is always high. But during the dry season the cases reported are always low". (***Midwife, St. Patrick's hospital, Offinso***)

The survey revealed that most of the respondents knew the effect malaria could have on the babies born to mothers with malaria.

*"The mother is not able to eat well and the baby too becomes undernourished". (**FGD, pregnant women**)*

4.2.3.2 SIGNS AND SYMPTOMS OF MALARIA

Signs and symptoms of cases of malaria mentioned include chills, whitish/yellowish eyes, headache, loss of appetite, fever and bodily pains amongst others.

"The person has cold, headache, loss of appetite, high body temperature". (***Chemical seller, Offinso***)

"When the person has high temperature, bodily pains, headache, nausea, cold and also by personal observations, I get to know that the person has malaria". (***Chemical seller, Akomadan***)

Another health worker added:

"Basically as soon as there is fever, headache, pains at the joint and loss of appetite; these are some of the basic things the community people get to know and some too will say the urine has changed to yellow colour, then, she talks of malaria. The rest I think when they come to the health facility the laboratory technologist will get to know" (***Disease Control Officer, Offinso District***)

"Oh they come complaining of tiredness, loss of appetite, fever and headache. These are the signs". (***Public Health Nurse, District Health Service, Offinso***)

4.2.3.3 CAUSES OF MALARIA

The causes of malaria based on responses got from various interviews conducted, was sanitation. Most respondents mentioned that their major problem was that they do not keep the environment clean. Because the environment was not kept clean the mosquitoes get a lot of breeding sites which eventually leads to the spread of malaria.

In the FGDs, respondents had diverse perceptions with regards to the cause(s) of malaria. The popular causes mentioned by respondents were: dirt, mosquito bites, bushy environment, and working in the sun. Other causes mentioned were unclean water, hard work, bad eating habits and house flies settling on food before eating. Some explanations given were as follows:

"… because of the unhygienic environment, because of so much filth, containers and weedy areas". (***Public Health Nurse, St. Patrick's hospital, Offinso***)

"*Weedy environment, stagnant water even around the hospital, when entering the hospital that big gutter, is a big breeding ground for mosquitoes*". (***Deputy Director, Midwifery Training College, Offinso***)

"*If one lives in a dirty environment, one is prone to have the disease". **(FGD, pregnant women)***

*"Unclean gutters and stagnant waters breed mosquitoes". **(FGD, pregnant women)***

Most of the pregnant women mentioned that "mosquitoes" are the main cause of malaria.

To buttress this point a health worker made this comment:

"I mentioned earlier that there is a problem with sanitation here especially this town. Indiscriminate disposal of refuse and other unhealthy practices prevailing here make it

conducive for mosquitoes to breed. This explains why this district tops the chart when it comes to malaria". (***Disease Control Officer, Offinso District***)

4.2.3.4 EFFECTS OF MALARIA

During FGDs conducted with pregnant women, they appeared to have knowledge about the effects malaria can have on the pregnant woman and her baby. The pregnant women said malaria in pregnancy could lead to the mother having low haemoglobin level, premature delivery, unhealthy baby or the baby dying a few days after delivery. They also mentioned that it could lead to spontaneous abortion, baby dying in mother's womb (stillbirth) or the mother dying during delivery. They added that it could lead to low birthweight.

One of the pregnant women said; *"Because of the loss of appetite, the mother can die"* (***FGD, pregnant women***)

To buttress this point another pregnant woman also said;

"Because of the loss of appetite on the mother's side, the child suffers from low birthweight when he is born" (***FGD, pregnant women***).

4.2.3.5 KNOWLEDGE OF SP IN IPT AND ITS EFFECTS

When IDIs were conducted with health workers and other opinion leaders, information concerning their knowledge on IPT was sought. Responses showed that aside the midwives who deal directly with the pregnant women in the health facilities, some health workers especially the chemical sellers did not seem to have much knowledge on IPT although they knew what SP was. FGDs with pregnant women also revealed that few of them really knew which drug they were taking and why they took it.

"IPT is where the midwives administer a drug to the pregnant women intermittently to prevent them from getting malaria" (***Administrator, St. Patrick's hospital, Offinso)***

A health worker said this on IPT:

"*Is a process whereby drug is administered to a pregnant woman to prevent her from getting malaria despite the fact that there is treatment; they give the drug to pregnant women to prevent them from getting malaria. This is the preventive aspect but I know the drug can be used in treating malaria …*" (***Disease Control Officer, Offinso District)***

"I have heard about that one and some of them even come here to buy it because when it was given to them in the hospital they realized it was good" ... we know it as Fansidar and in the hospital it's Malafan". (***Chemical seller, Aboasu***)

"Yes. I heard that they are made to take it right there for 3 times. So if a pregnant woman does not attend the antenatal clinic and faces any complications then it is her own problem". (***Chemical seller, Afrancho***)

"I have heard about it on the media but I have not seen one before and my wife has not been pregnant, so I don't know". (***Chemical seller, Afrancho***)

"A doctor from Offinso came to talk to us about it and I think they take it for 3 times before delivery and it is helping them because I have not heard of premature birth since it started". (***Queen mother of Afrancho*)**

When a chemical seller was asked whether he had heard about SP he said he had not heard much about it.

"*I heard that the pregnant women go to the hospital for some chloroquine tablets*". (***Chemical seller, Offinso****)*

This also shows that some people are still ignorant about what is happening in relation to using SP for IPTp. Most of the chemical sellers knew about Fansidar® and Malafan® but

did not know much about SP use in IPTp. Some also did not know that Fansidar® is the same as SP.

Most of the information gathered indicated that there were no major adverse effects on taking SP by the pregnant women. The adverse effects mentioned were vomiting, nausea and body weakness with isolated cases of itching and palpitation. These adverse effects were complained of by just a handful of the respondents.

The head of laboratory in the Offinso St. Patrick's Hospital talked about her own experience when she took SP during pregnancy.

"*The first dose was ok and the second dose when I took it I was having palpitation and I told the woman I won't take it again and that I did not take the third dose*". (***Head of Laboratory Department, St. Patrick's hospital, Offinso***)

"Only a few of them complained of nausea and vomiting and at first some also complained of itching but we have not had such complaints again". (***Medical Assisstant, Akomadan)***

"… Some facilities said if some of the women take it they complain of nausea. I don't think there are any major adverse effects". (***Disease Control Officer, Offinso District***)

A pregnant woman added:

"When you are four months old and you feel the baby quickening, she, the nurse, gives you a drug that will protect both the mother and the baby from malaria. And you are to take the drug every month for three times". (***FGD, pregnant women***)

"When I took the drug, I vomited and became very weak". (***FGD, pregnant women***)

Some of the pregnant women said they get the reaction when they take it for the first time but with the subsequent ones they do not experience those adverse effects. On the other hand, some reported vomiting any time they took it.

"When I took the first dose, I vomited but with the second dose I did not. She, (the midwife) told me to continue taking it. And before I took the drug someone had already explained to me that with the first dose you can vomit or become weak. So I was aware before coming in for the drug". (***FGD, pregnant women***)

Another pregnant woman added:

*"When I took the first dose, I was bodily weak, nauseous and even vomited later on, but when I took the second dose nothing happened". (**FGD, pregnant women**)*

"I didn't vomit when I took the first dose but with the second dose and the third dose, I vomited". (***FGD, pregnant women***)

"When I took the first dose, I felt weak and lost appetite". (***FGD, pregnant women***)

"I felt weak and this continued when I took the second dose but I told the midwife about it and she encouraged me to take the third dose". (***FGD, pregnant women***)

4.2.3.6 BENEFITS OF IPT

The IDIs and FGDs revealed that the IPT programme had been very helpful. Most of the respondents mentioned that the rate at which the pregnant women fell sick had reduced.

A health worker said this:

*"At first, malaria cases were rampant but now it had reduced and even in the whole institution (St. Patrick's Hospital) only 46 had reported with malaria cases; maternal deaths had also reduced. So it has helped a lot. As of April 2007, we had 2,528 pregnant women and only 46 have had malaria" (**Statistician, St. Patrick's Hospital, Offinso**)*

The health workers also mentioned that since the mothers have benefited from the IPT programme then definitely the neonates too would have some benefits because the foetus feeds from the mother's blood.

"The maternal death cases that we used to have are no more". (***Medical Assistant, Akomadan***)

"Looking at the data and the annual reports that we have, it seems it is helping. The rate at which pregnant women use to have the malaria had minimized". (***Administrator, St. Patrick's hospital***)

"It protects us from getting malaria and anaemia". (***FGD, pregnant women***)

"*It has some benefits because now we hardly hear complications in pregnancy and has also reduced stillbirth*". (***Chemical seller, Akomadan***)

"*…Certainly yes. There use to be high malaria cases previously, but now it has reduced, mortality rate too has reduced and the health of mothers and that of the children also have improved". (**Medical Officer, St. Patrick's hospital, Offinso**)*

In-depth interviews with the health workers generally indicated that the SP had benefited the pregnant women and their babies in that they hardly report of malaria and the birthweights of the babies have improved.

4.2.3.7 MALARIA PREVENTION AND TREATMENT

Most of the respondents knew and indicated that malaria could be prevented. Majority of the respondents basically mentioned keeping the environment clean as how to prevent malaria. Others mentioned preparing food under hygienic conditions, washing of hands after visiting the toilet; covering their food to avoid flies resting on them, use of mosquito coils and sprays and using insecticide treated nets. The rest said keeping the environment clean (cleaning gutters, draining stagnant waters, disposing refuse properly), drinking clean water by boiling before use, observing personal hygiene, and driving mosquitoes away with cloth, and avoidance of hanging clothes on cross bars in rooms.

Most of the chemical sellers said they no more combined Artesunate and Amodiaquine because they have been directed by the government not to do so any more. The reason for that was that most of the clients felt very weak after taking the combination therapy; in other words it was too strong.

This was however in contradiction to what other health workers said. They are still using Artesunate–Amodiaquine combination therapy as the standard drug for treating malaria.

A health worker said this:

"Generally we use Artesunate –Amodiaquine. I haven't seen quinine (flipping through some forms) Most of the treatment for general malaria is Artesunate –Amodiaquine" (***Public Health Nurse***)

We are following the national policy and that is the Artesunate –Amodiaquine. (***Medical Assistant, Akomadan Health Centre***)

"*Mostly we use Fansidar, quinine and the protocol drug by the Ghana Health Service and that is the Artesunate –Amodiaquine but in pregnant women during complications we use quinine and Artesunate. …quinine is for the early stage and later we use the Artesunate –Amodiaquine*". **(*Medical Officer, St. Patrick's hospital, Offinso)***

With the issue of prevention and treatment, most of the pregnant women mentioned that they do not take medication on their own but went to hospital any time they fell sick.

"If one is pregnant she does not go to the drug store but if she is not pregnant and is having malaria, she at times goes there for some drug". (***FGD, pregnant women***)

The chiefs, queen mother and assembly men mentioned that they help prevent malaria in their communities by organising communal labour in cleaning their environment to minimise the breeding sites of mosquitoes. Some of the community leaders said they

sometimes invite health workers to come and educate people in their communities and this was done by organising community durbars and also by using the information van.

"We advice the people to keep their environment clean and we have provided bins to the people". **(*Assembly woman, Afrancho*)**

In an IDI, a midwife mentioned that some of the pregnant women resort to herbs for treatment:

"*…most of them use it especially the Northerners. They use these herbs a lot and some of them come to the hospital after these herbs have failed them. Those in the remote villages also use these herbs and the teenagers who get themselves pregnant. These people come to the hospital after these herbs or concoctions have failed them".* (***Midwife in charge, St. Patrick's hospital, Offinso***)

A chief suggested this: "if only there could be mass spraying by the public health officers to control the mosquitoes, I think that will really help us because these mosquito coils do not help". *(*Chief of Kokote*)*

A chemical seller added:

"*Sometimes I clean gutters myself. I do sometimes tell the ladies around to help clean the gutters and educate them on environmental cleanliness so that the rate at which the mosquitoes breed will reduce*". **(*Chemical seller, Afrancho)***

On insecticide treated nets, most of the pregnant women in all the four FGDs said they had one which protects them from mosquito bites. Some do sleep in their nets; others do not while others reserve them for their babies yet to be born.

The following were some of the comments on the use of ITNs:

*"I want to use it when I give birth to my baby" (**FGD, pregnant women***)

"*The weather is too hot".* (***FGD, pregnant women)***

*I itch whenever I sleep in the mosquito nets". (**FGD, pregnant women)***

*"I don't feel the presence of mosquitoes when asleep". **(FGD, pregnant women**)*

4.2.3.8 INFORMATION, EDUCATION AND COMMUNICATION

The study revealed that the main sources through which the community received health news and other information included the radio, television, newspapers, the health facilities (DHMT, CHOs, CDDs, VHCs etc), gong-gong beating, community durbars and mobile vans but the most mentioned were radio, gong-gong beating, and community durbars.

They mentioned that any of the above means and the health facilities could be used in communicating health issues to them. They mostly preferred the use of face-to-face or house-to-house methods, use of video/cinema together with health talks, gong-gong beating, and through community leadership.

The key health issues mostly heard and discussed through the above media included malaria, typhoid, HIV/AIDS, child health care (nutrition), reproductive health, polio/immunization, health insurance scheme and general talks on personal hygiene and environmental cleanliness.

*"The Nurses just educate us on how to protect ourselves against malaria and tell us the causes of malaria" (**Chemical seller, Aboasu**)*

"The media and (we) the chemical sellers too get informed of certain issues through the courses that we attend. And if the chief wants to get information to the people, mostly the information van is what is used". (***Chemical seller, Offinso***)

"People from the Ministry of Health come here when there is an outbreak of disease. They normally talk about Cerebrospinal Meningitis (CSM) and HIV/AIDS.

Information is usually given through the announcement van". (***Chemical seller, Offinso)***

"*We normally have durbars at which health education messages are given".* (***Chemical seller, Abofour***)

"Sometimes the health centres make the information van go round the community educating us on some health issues and also mostly from the media". (***Chemical seller, Afrancho***)

During FGDs with pregnant women their responses indicated that almost all the women who admitted they have heard anything concerning the new policy of the GHS concerning the use of SP in IPT said they heard it on the radio.

4.2.3.9 COSTS OF CARE

It was revealed that the drugs mostly used to treat malaria in the district were Alaxin, Artesunate, Artemos, and Camoquine. According to the chemical sellers the pregnant women usually come with quinine prescription. Some can afford and some also find the drugs very expensive especially artemisinin–based antimalarial drugs.

… "Alaxin is ¢32,000 (GH¢3.20; $2.2 and Artesunate is ¢40,000 (GH¢4.00; $2.7 and Artemos is ¢45,000 (GH¢4.50; $3.1". **(*Chemical seller, Aboasu*)**

"All that I have to say is the drugs should be made less expensive. Artemos for instance at first was given to us at ¢25,000 (GH¢2.50; $1.7) and I was selling it at ¢30,000 (GH¢ 3.00; $2.0) but now they give it to us at ¢40,000 (GH¢4.00; $2.7). And you see the people cannot buy, so the cost should come down a bit for us so that the people too can buy them". ***(Chemical seller, Aboasu)***

"…the price is a bit on the higher side; Artesunate is ¢40,000 (GH¢4.00; $2.7) and they can't buy so unless it is prescribed for someone, we don't give it out". (***Chemical seller, Abofour***)

At first, we were using chloroquine, ORS, paracetamol and B. complex but now the drug of choice is Artesunate–Amodiaquine but it is very expensive and the people do complain.

"In the hospital it is just ¢3,000 or ¢4,000 but those from the pharmacy shops are about ¢10,000 (GH¢1.00; $0.7) and though it is not so expensive, they can't buy". (***Chemical seller, Akomadan***)

A public health nurse at the St. Patrick's Hospital stated that for antenatal visits, the minimum amount a pregnant woman will spend is about ¢15,000 (GH¢1.50; $1.0) and the maximum will depend upon the condition of the pregnant woman and the kind of medical attention she needed.

To add to the comments above a chemical seller at Aboasu said that; *"some can afford and some too find it very expensive"*.

"Our community is a farming community and it is during the harvesting season that they normally come to the hospital for at that time they can afford". (***Midwife, St Patrick's hospital, Offinso***)

4.2.4 ASSESSMENT OF TRANSPLACENTAL TRANSMISSION OF MALARIA

Out of the 115 women who delivered, 83(72%) had their cord blood smear done. Only 2 (2%) of the samples were positive for *P. falciparum* by microscopy with parasite densities within the range of 1-1999 parasites/µl of blood (Table 15). The placenta of

these two samples, however, were found to have very high parasite densities >5000 parasites/µl of blood.

4.2.5 DISCUSSION

Malarial infection during pregnancy increases the risks of severe sequelae for the pregnant woman and the risk of delivering a low birthweight baby and this is evident in the present study as respondents in the quantitative and the qualitative survey talked of malaria as being a great menace to them aside other infections and morbid conditions faced in pregnancy. Most of the respondents were knowledgeable on the causes of malaria and the havoc it brings to pregnant women and their communities at large. Majority of the respondents the quantitative survey were aware of the use of SP and the benefits it brings to them and that they normally get educated on the IPTp during visits to ANC and at community durbars..That SP is used as a preventive treatment drug against malaria in pregnancy is not much known and used among the people in the communities. (*"I heard that the pregnant women go to the hospital for some chloroquine tablets*"; *"I have heard about it on the media but I have not seen one before and my wife has not been pregnant, so I don't know").* Health staff are, however, knowledgeable in the use of SP and the benefits of its use (*"At first malaria cases were rampant but now it had reduced and even in the whole institution only 46 had reported with malaria cases; maternal deaths had also reduced. So it has helped a lot. As of April 2007, we had 2,528 pregnant women and only 46 have had malaria").* Most of the pregnant women said SP was good for their health and even enhances good delivery (*"It protects us from getting malaria and anaemia"; "It has some benefits because now we hardly hear complications in pregnancy and it has also reduced stillbirth*"). The community leaders

did acknowledge the importance of SP in pregnancy in that; there had been reduced maternal mortality and that of the neonates in the district.

The chemical sellers should be cautioned not to sell the SP to pregnant women since it could lead to the abuse of the drug and consequently the parasites resistance (*"I have heard about that one and some of them even come here to buy it because when it was given to them in the hospital they realized it was good" ... we know it as Fansidar and in the hospital it's Malafan").*

This use of SP in the IPTp programme has proven to be effective in reducing anaemia and parasitaemia in pregnant women as discussed by various studies and reports (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.,* 1999; WHO, 2002, 2003, 2004). This was evident as only 39% of the 306 women studied had anaemia. Thus, repeating the doses of SP increases Hb level. There was reduced parasitaemia (15%) in the pregnant women as a result of repeated doses of SP taken. However, primigravid women had high parasitaemia as compared to parasitaemia in the secundigravid and multigravid women.

Although SP is generally considered to be a safe drug when used for IPTp as the present study has shown, it can rarely cause serious skin reactions and haematological side effects (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.,* 1999; Mbaye *et al*., 2006). Most of the pregnant women did not complain much of adverse effects that put them off the drug (*"When I took the first dose, I vomited but with the second dose I did not. And before I took the drug someone had already explained to me that with the first dose you can vomit or become weak. So I was aware before coming in for the drug"; "When I took the first dose, I was bodily weak, nauseous and even vomited later on, but when I took the second dose nothing happened"; "The first dose was ok and the second*

dose when I took it I was having palpitation and I told the woman I won't take it again and that I did not take the third dose"). No serious adverse effects attributable to the administration of SP were seen in the present study as also reported in other studies (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.,* 1999; Mbaye *et al*., 2006).

The study showed that the use of SP enhanced good delivery by the pregnant women by improving birthweight of neonates and with less delivery stress (Apgar score ≥ 5) by the studied women (Figure 13; pg. 96).

The respondents in the questionnaire administration were very critical on the need to make available qualified health personnel and well equipped facilities in the health centres; and relations between the pregnant women and the health staff should be cordial. Again, distant health facilities from their communities and poor transport systems and inaccessible roads were other constraints for their not attending clinics. Generally, the socioeconomic status of the pregnant women was low and they were financially constrained as stated by some of the respondents *"lack of money constrained me to stay away from the hospital"* hence, not visiting the clinics. Maternal mortality according to the respondents in the quantitative survey was very prominent in the district as a result of most the reasons given and thus, they resort to traditional medicines which sometimes results to their death during pregnancy.

In treatment of malaria in the communities, most chemical sellers do not follow the new GHS line of treatment (the use of ACT) but give single therapy drugs on malaria which could lead to early resistance of these malaria parasites to artemisinins–based drugs.

The high cost of the malaria drugs need to be looked at since most of the respondents (particularly the chemical sellers) complained of unaffordability of these drugs by most of their clients (*All that I have to say is the drugs should be made less expensive.*

Artemos for instance at first was given to us at ¢25,000 (GH¢2.50; $1.7) and I was selling it at ¢30,000 (GH¢ 3.00; $2.0) but now they give it to us at ¢40,000 (GH¢4.00; $2.7). And you see the people cannot buy, so the cost should come down a bit for us so that the people too can buy them"; "Our community is a farming community and it is during the harvesting season that they normally come to the hospital for at that time they can afford").

Environmental cleanliness and attitudinal change were the main responses in prevention of malaria aside other responses given by the respondents both in the IDIs and FGDs. The need to intensify education on the causes of malaria and its prevention is important as some of the respondents attributed the causes of malaria to unwholesome foods, dirt and working in the sun.

The use of radio, announcement vans, and gong -gong beating as means for information dissemination and education were common in the rural communities. The preference for the use of cinemas, face to face talks and community durbars for health education was highly emphasized by the respondentsin the qualitative survey.

The use of ITNs was quite encouraging since over 50% of the pregnant women studiedin the quantitative survey had ITNs. However, the use of ITNs by pregnant women in combination with the IPTp programme was not assessed since there were chequered responses in the use of the nets.in the quantitative study. In the FGD, the use of ITNs was not popular among the pregnant women since most complained of discomfort when sleeping in them ("*The weather is too hot", "I itch whenever I sleep in the mosquito nets").* Some kept them till they deliver and others had the wrong perception that mosquitoes were not present in their environments ("*I don't feel the presence of mosquitoes when asleep"*).

Studies by Mbonye *et al*. (2006, 2007) have shown that when pregnant women get malaria, care seeking includes self-medication with antimalarial drugs from drug-shops, or use of herbs whilst visiting a health unit may be a last resort if the illness does not improve. This was evident in the present study as over 50% of the respondents resorted to these self medication options, the result of the health centres being inadequate in terms of drugs or the general quality of health services and distant health centres (Yeneneh, 1993; McCombie 1996; Mbonye, Bygbjerg and Magnussen, 2007).

Parasitaemia presence in the cord blood indicated transplacental transmission of malaria to the neonates thus, congenital malaria do occur in the locality. This was previously thought to be rare or infrequent in sub–Saharan Africa (Ahmed, Cerilli and Sanchez, 1998; Uneke, 2007b; Uneke, 2007c; Rogerson *et al*., 2007); however, several reviewed studies have showed that they do occur in endemic areas as well as non endemic areas (Menendez and Mayor, 2007 Uneke, 2007b).

The small delivery data on the study women made it difficult to make critical judgement on the effect of SP on the birthweight of neonates. Nevertheless, the deliveries of the study women had very few LBW neonates thus, attesting to the possible benefit of SP in reducing incidence of LBW as indicated by other studies (Parise *et al.,* 1998; Shulman *et al*., 1999; Sirima *et al*., 2006; Mbonye, Bygbjerg and Magnussen, 2008).

Pregnant women especially the primigravidae were more vulnerable to infections which correlated with maternal anaemia, since higher parasitaemia levels were associated with decreasing haemoglobin level of the pregnant women. Repeated intake of SP doses significantly improved haemoglobin level; however, repeated doses of SP resulted in reduced parasitaemia of pregnant women.

In pregnancy, the use of SP is effective in improving health of pregnant women and should be effectively implemented in all health facilities in the country. There is the need to intensify education during visits to health care centres when pregnant especially in the rural areas. Intensive education on the new line of treatment should be done to help avoid single drug treatment of malaria cases that could render most drugs ineffective in malaria treatment.

Malaria is a menace in the study area and there is the need to improve education of the public on malaria and how to curb it. There is the need for intensive education on malaria in pregnancy using other methods including public posters, organized durbars encouraging particularly young pregnant women to attend ANC regularly. Effort should be made for cordial relations to exist between the health staff and patients who visit the clinics. The health facilities in the rural areas need to be well equipped to enhance good health care in the rural areas. Transplacental malaria or congenital malaria does occur in Offinso district. Government should do well to give rural health centres ambulance for quick and safe transfer of patients to the larger, well-equipped hospitals when the need arises. Government should provide mobile clinics that could go to the remote areas of the rural areas to help care for the vulnerable especially children and pregnant women.

4.3 VARIATION OF BIRTHWEIGHTS

4.3.1 VARIATION OF BIRTHWEIGHTS IN PRE-IPT PERIOD

4.3.1.1 MATERNAL AND NEONATAL CHARACTERISTICS AT DELIVERY

Routine delivery data comprising of records dated January 2000 to May 2004 were studied. The data comprised of 6,914 singleton born babies born during this period. Most of the singletons (99.9%) were born through spontaneous vagina delivery (SVD) with only one (0.1%) neonate delivered by caesarean section. There were 563 (8%) neonates born with low birthweights (< 2.5 kg) and 6,351 (92%) neonates born with normal birthweight (≥ 2.5 kg). Male babies constituted 49.8 % whilst female babies constituted 50.1 % of all deliveries made (Table 21). Most of the neonates (60%) were born in the wet season (Table 21). The recorded mean age of the mothers were 26 ±6.3 years with the youngest being 13 years and the eldest 49 years.

Women in their twenties formed more than 15% of those delivering and premature deliveries (deliveries at gestation age < 37 weeks) were 1.4% of all the deliveries (Table 21). Primigravidae constituted only 10% of the delivered women. The mean birthweight was 3.1±0.5 kg with the lowest weighted baby being 1 kg and the highest weighted baby 5.1 kg. Student t-test analysis showed that the mean birthweights of the males (3.2±0.42 kg, 95% CI: 3.18-3.21kg) was significantly different from that of their female counterparts (2.9±0.46 kg, 95% CI: 2.92-2.95 kg, $p < 0.0001$). The mean birthweight for babies 3.09±0.45 kg (95% CI: 3.08-3.11) born in the dry season was significantly different from the mean birthweight for babies 3.05 ±0.46 (95% CI: 3.04-3.06) born in the wet season ($p < 0.0001$). Thus, seasonal variations of birthweights was significant;

babies born in the dry season had significantly increased birthweight as compared to those born in the wet season ($z = 2.99$, $p < 0.003$).

Table 21: Maternal and neonatal characteristics at delivery (Variation of Birthweights)

Maternal Characteristics	¶N=6,914(%)
Age(years)	
≤19	343 (5%)
20-29	1,445 (20.9%)
30-39	801 (11.6%)
≥40	77 (1.1%)
***Missing	4,248 (61.4%)
Parity	
Primigravidae	678 (9.8%)
Secundigravidae	548 (7.9%)
Multigravidae	428 (6.2%)
Grand multigravidae	1,013 (14.7%)
***Missing	4,247 (61.4%)
Term of Pregnancy	
Preterm	97(1.4%)
Term	2,685 (38.8%)
***Missing	4,132 (59.8%)
Neonatal Characteristics	
Sex	
Male	3,446 (49.8%)
Female	3,468 (50.1%)
Birthweight	
Low birthweight	563 (8%)
Normal birthweight	6,351 (92%)
†Season of birth	
Dry season	2,799 (40%)
Wet season	4, 115 (60%)

¶ *Total number of singleton deliveries studied*
** Missing records on age of women, parity and term of pregnancy*
†*Dry Season: November to March; Wet Season: April to October*

4.3.1. 2 ASSOCIATION BETWEEN BIRTHWEIGHT AND OTHER VARIABLES

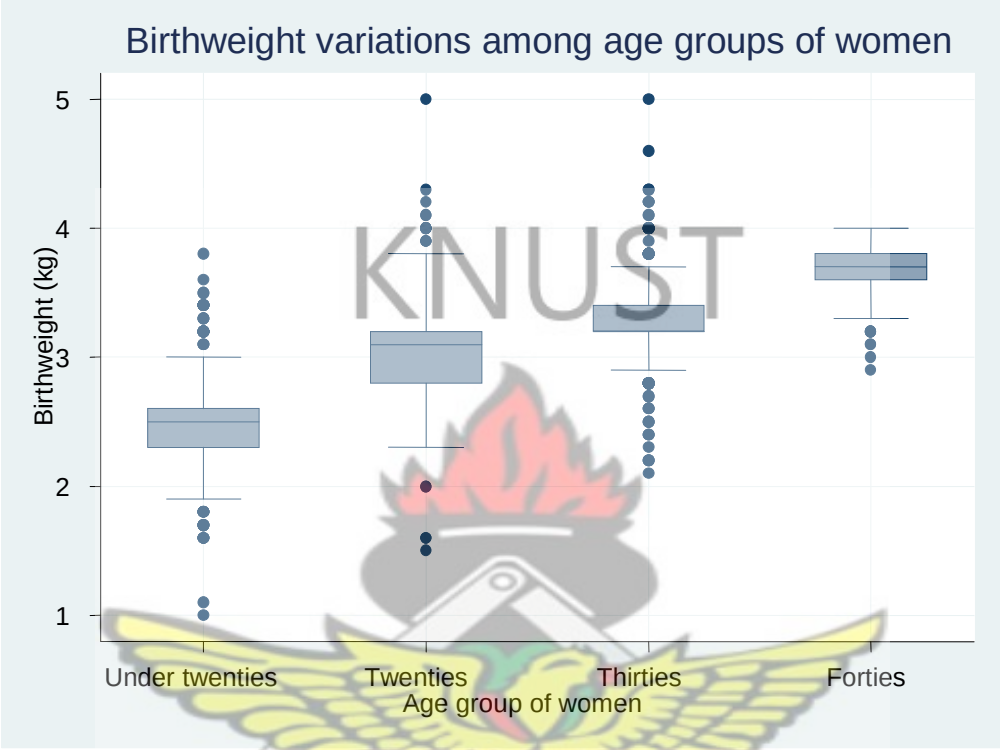

Figure 14: Birthweight variations among age group of delivered women

Median birthweight increased with age and gravida of women (Figures 13 and 14). The median proportion of birthweights of neonates was highest in women in their forties and lowest in women in their teens. Birthweight was more varying in women of the twenties; and those in their thirties had more extreme values (outliers) for birthweights but the very low extreme values of birthweights of neonates were found in women in their teens. The median birthweight for women under twenty years was lower when compared to those of the other age groups (Figure 14). There was significant association between birthweight and age group of women (Pearson $\chi^2 = 1.1$, $p \leq 0.001$). Women in their teens had significantly more low birthweight babies (90.2%) as compared to 5.4% and 4.4%

for the women in their twenties and thirties respectively ($p < 0.001$). Regression analysis did show 4% increase in birthweight with a unit increase in age of women ($p < 0.001$).

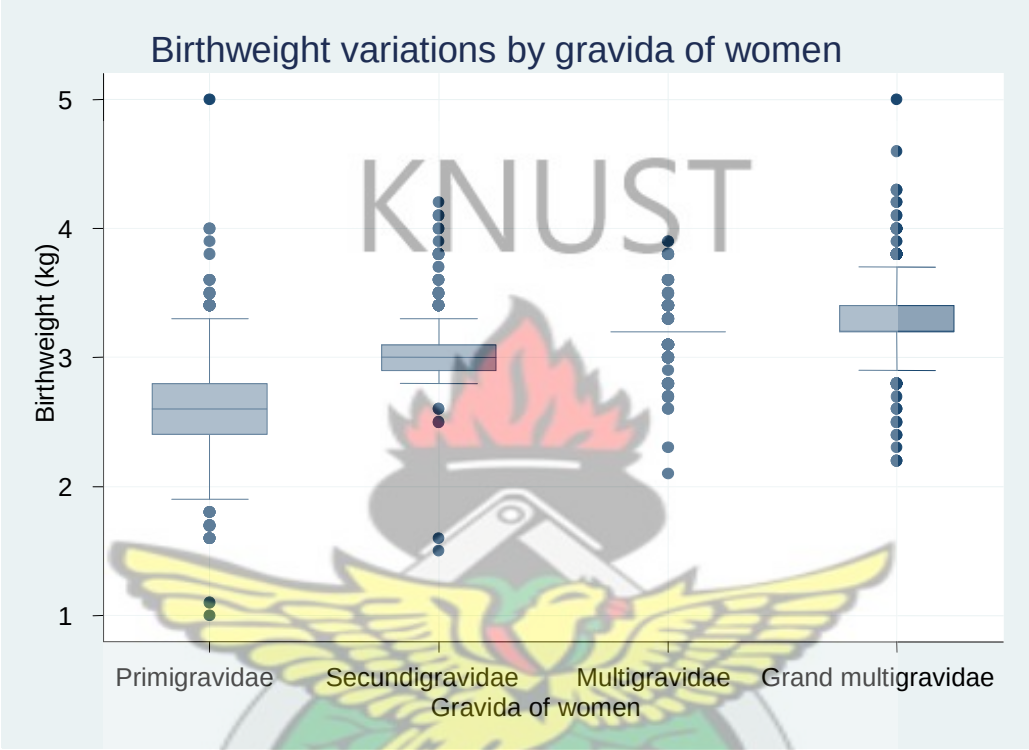

Figure 15: Birthweight variations by gravida of delivered women

In the gravida group, the primigravidae had the lowest median birthweight when compared with the other gravid groups (Figure 15). The median proportion of birthweight of neonates was highest in grand multigravidae and lowest in the primigravidae (Figure 15). On the other hand birthweight of neonates was more variable in the primigravidae. Multigravidae had only median birthweight with several extreme values for birthweight of neonates. The least extreme values for birthweight were found more in the primigravidae followed by the secundigravidae (Figure 15).

This difference of birthweights among the gravida of women was very significant (Pearson χ^2 = 490.6, $p \leq 0.001$) and the primigravidae had more low birthweight neonates (95%) as compared to the other gravida groups. Pearson's correlation coefficient did show a strong positive relation of birthweight with gravida ($r = 0.67$, $p \leq 0.0001$).

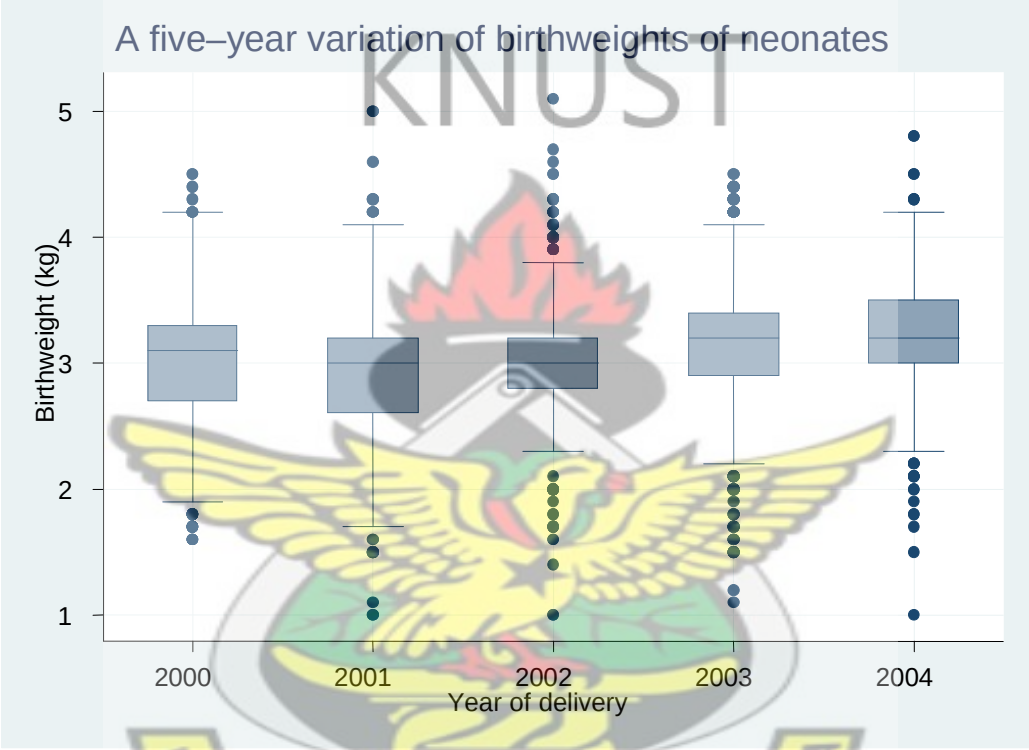

Figure 16: Yearly variations in birthweights of neonates (from 2000 to 2004)

The median proportion of birthweights was highest in year 2004 and lowest in year 2001. Birthweight was more variable in the years 2000 and 2001. The median birthweights for year 2001 and 2002 were the same and that for 2003 and 2004 were not much variable. However, median birthweights for 2003 and 2004 were higher as compared with years 2000, 2001 and 2002. The median birthweight for year 2000 deliveries was higher than those of years 2001and 2002 (Figure 16). Extreme values for

birthweights (outliers) were more common in year 2002 and less common in year 2000. There was significant difference in the yearly variation in birthweights (OR = 1.5 $p \leq$ 0.0001; 95% CI, 1.4–1.6).

Table 22: Interaction between birthweight and the predictor variables

Variables	LBW	NBW	Univariate OR	95% CI	Multivariate OR	95% CI
Sex						
Male	148	3,312	1.0	-	1.0	-
Female	415	3,039	0.33	(0.27-0.39)	0.11	(0.04-0.26)
Age group						
<19	166	177	1.0	-	1.0	-
20-29	10	1,435	134.6	(69.77 -259.61)	44.46	(21.39-92.40)
30-39	8	793	93.0	(44.89-192.51)	4.56	(0.57-36.08)
>40	0	77				
Gravida						
Primigravida	173	505	1.0	-	1.0	-
Secundigravida	2	546	93.5	(23.08-378.92)	9.05	(2.02-40.47)
Multigravida	2	426	73.0	(17.99-295.85)	3.11	(0.50-19.21)
G. multigravida	7	1,006	49.2	(22.95-105.61)	5.35	(0.61-46.79)
Season						
Dry season	186	2,613	1.0	-	1.0	-
Wet season	377	3,738	0.71	(0.59 - 0.85)	0.84	(0.55-1.28)

LBW = low birthweight, NBW = normal birthweight, OR = odd ratio, G. = grand
The value of p was significant for the adjusted odd ratios of all the predictor variables ($p < 0.0001$)

A unit increase of each predictor variable did significantly increase the birthweight of the neonates in the univariate analysis ($p < 0.0001$).

For sex, the birthweight for females was 33% lower than that of males and was significant (z-score = -11.3, $p < 0.001$). Birthweights of neonates for women in their twenties (20-29 years) and thirties (30-39 years) were 134.6 and 93 times respectively, significantly higher than birthweight of neonates of the teenage group women ($p <$

0.001). Women in their forties had no low birthweight babies (Table 22). There was significant increase ($p < 0.001$) in birthweights in the secundigravida, multigravida and grand multigravida women when compared to the primigravida women who had the highest number of low birthweight neonates (Table 22).

In multivariate analysis, there was increase in birthweight with each unit increase in age, sex gravida and season. Male neonates had significant increase in birthweight 11 times over that of their female counterparts ($z = -4.93$, $p<0.001$). Increase in birthweight for stratum specifics for age category (20-29 years) and secundigravidae were significant when compared to the basic group of compares (i.e. women who are ≤ 19 years and primigravidae respectively) ($p < 0.001$ and $p < 0.004$) respectively.

4.3.2 EFFECT OF SP ON BIRTHWEIGHTS

4.3.2.1 MATERNAL AND NEONATAL CHARACTERISTICS AT DELIVERY (BIRTHWEIGHTS DURING SP-IPT PERIOD)

Routine delivery data comprising of records dated 2005 to 2007 were studied. The data comprised of singleton born babies excluding identical and fraternal twin babies at delivery. The recorded median age of the delivering mothers was 26 years (IQR: 21-30 years) with the youngest being 14 years and the eldest 48 years. Women in their twenties formed more than 50% of those who delivered and premature deliveries (deliveries at gestation age <37 weeks) were 2% of the total deliveries (Table 23). Over 60% of the deliveries occurred in the wet season. Primigravidae constituted only 24% of the delivering women. The 2583 singletons were all born through spontaneous vagina delivery (SVD). Twelve percent of the newborns weighed less than 2.5 kg at birth (Table 23). Male newborns constituted 49.8 % with female newborns constituting 50.2% of all deliveries made.

Of the women who delivered, 2081 (81%) took SP while 502 (19%) did not take it before delivery. Forty two percent of the women took the full doses (i.e. one to three doses) of SP before delivery (Table 23). The mean birthweight was 2.9±0.5 kg, range (0.9-5.2 kg). Wilcoxon–Mann–Whitney test showed that the birthweights in male singletons was significantly higher than that of their female counterparts ($z = 6.45$, $p < 0.0001$).

Table 23: Maternal and neonatal characteristics at delivery (Effect of SP on Birthweights)

	N (2583) (%)
Maternal Characteristics	
Age(years)	
≤19	369 (14.0%)
20-29	1,390 (54.0%)
30-39	710 (28.0%)
≥40	114 (4.0%)
Parity	
Primigravidae	628 (24.3%)
Secundigravidae	559 (21.6%)
Multigravidae	1023 (39.6%)
Grand multigravidae	373 (14.4%)
Doses of SP taken	
0	502 (19.4%)
1	314 (12.2%)
2	674 (26.1%)
3	1,093 (42.3%)
Term of Pregnancy	
Preterm	58 (2.0%)
Term	2,525 (98.0%)
Neonatal Characteristics	
Sex	
Male	1,286 (49.8%)
Female	1,297 (50.2%)
Birthweight	
Low birthweight	310 (12.0%)
Normal birthweight	2,273 (88.0%)
Season of birth	
Dry season	1,007 (39.0%)
Wet season	1,576 (61.0%)

Table 24: Effect of SP on birthweight of neonates

Year	2005		2006		2007	
SP	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Mean birthweight						
	2.91±0.46	2.89±0.48	2.89±0.44	2.87±0.45	2.98±0.55	3.15±0.66
Proportion of low birthweight						
	78(10%)	24(15%)	92(14%)	28 (13%)	78 (13%)	10 (8%)
Mean birthweight of babies by age groups of women						
<19	2.68±0.46	2.59±0.52	2.69±0.42	2.56±0.26	2.68±0.44	3.0±0.59
20-29	2.9±0.43	2.87±0.46	2.88±0.42	2.9±0.45	2.98±0.57	3.17±0.59
30-39	3.01±0.45	3.04±0.3	2.99±0.44	2.93±0.36	3.1±0.52	3.1±0.84
≥40	3.14±0.54	3.15±0.64	2.97±0.53	2.92±0.57	3.05±0.54	3.6±0.91
Proportion of low birthweight in women by age group of women						
<19	24 (22%)	9 (38%)	25 (24%)	6 (25%)	24 (25%)	1 (8%)
20-29	43 (10%)	12 (14%)	44 (13%)	15 (12%)	42 (13%)	6 (8%)
30-39	10 (5%)	1 (3%)	17 (9%)	5 (10%)	10 (6%)	3 (10)
≥40	1 (3%)	1 (8%)	6 (18%)	2 (18%)	2 (13%)	-
Mean birthweight of babies by gravida of women						
Primigravida	2.71±45	2.57±0.49	2.66±0.39	2.59±0.44	2.65±0.46	2.84±0.47
Secundigravida	2.91±0.41	2.93±0.47	2.89±0.47	2.93±0.33	3.1±0.54	3.1±0.72
Multigravida	2.97±0.42	2.95±0.35	2.96±0.42	2.95±0.55	3.1±0.56	3.3±0.66
Grand Multigravida	3.03±0.47	3.08±0.4	3.0±0.44	2.9±0.39	3.09±0.53	3.25±0.69
Proportion of low birthweight by gravida						
Primigravida	40 (20%)	15 (35%)	44 (27%)	13 (30%)	44 (29%)	3 (14%)
Secundigravida	13 (8%)	5 (13%)	15 (10%)	3 (7%)	9 (7%)	4 (12%)
Multigravida	10 (7%)	1 (4%)	9 (11%)	6 (13)	10 (8%)	1 (4%)
Grand Multigravida	15 (5%)	2 (4%)	24 (9%)	6 (8%)	15 (7%)	2 (4%)
Mean birthweight by season of birth						
Dry season	2.97±0.47	2.91±0.49	2.92±0.46	2.87±0.46	2.95±0.49	3.0±0.63
Wet season	2.88±0.45	2.87±0.47	2.86±0.42	2.87±0.45	2.99±0.58	3.2±0.68
Proportion of low birthweight by season of birth						
Dry season	24 (8%)	7 (11%)	36 (12%)	11 (14%)	26 (12%)	6 (14%)
Wet season	54 (11%)	17 (17%)	56 (15%)	17 (13%)	52 (14%)	4 (5%)
Mean birthweight by doses of SP						
0	2.89±0.48		2.87±0.45		3.15±0.67	
1	2.76±0.61		2.92±0.45		2.96±0.59	
2	2.91±0.48		2.9±0.46		2.98±0.55	
3	2.94±0.41		2.87±0.42		2.98±0.54	
Proportion of low birthweight by doses of SP						
0	24 (15%)		28 (13%)		10 (8%)	
1	22 (25%)		14 (13%)		21 (17%)	
2	32 (14%)		27 (12%)		31 (14%)	
3	24 (5%)		51 (15%)		26 (10%)	

Yes – Taken SP dliveries **No – Have not taken SP deliveries**

The proportion of LBW newborns was more profound in the no SP women deliveries than deliveries in women who took SP (Table 24). Generally, there was a decrease in LBW of newborns from year 2005 to 2007. Low birthweight was more common during the wet season than in the dry season. There was reduced LBW in women of higher age groups and gravida as compared to the teenage group and low gravida women. Though there was no significant difference in mean birthweights of babies by doses of SP ($p \geq 0.48$), there was a reduced proportion of LBW with repeated doses of SP (Table 24). There was also a significant association between birthweight of neonates and the doses of SP with repeated doses of SP decreasing the proportion of LBW in the neonates ($p < 0.001$).

4.3.2.2 ASSOCIATION OF BIRTHWEIGHT WITH DOSES OF SP TAKEN BY WOMEN WHO DELIVERED AND OTHER PREDICTOR VARIABLES

Pearson chi square test showed significant associations between birthweight and doses of SP, term of pregnancy and sex of neonates (Pearson χ^2 = 20.4, 197.4, 13.5; $p \leq 0.001$) respectively. Seasonal variation in birthweight did not show any significant difference (Pearson χ^2 =1.82, $p \geq 1.8$).

Median birthweight increased with age and high gravida of women. Birthweight of neonates was more variable in women (mothers) in their forties (Figures 16 and 17).

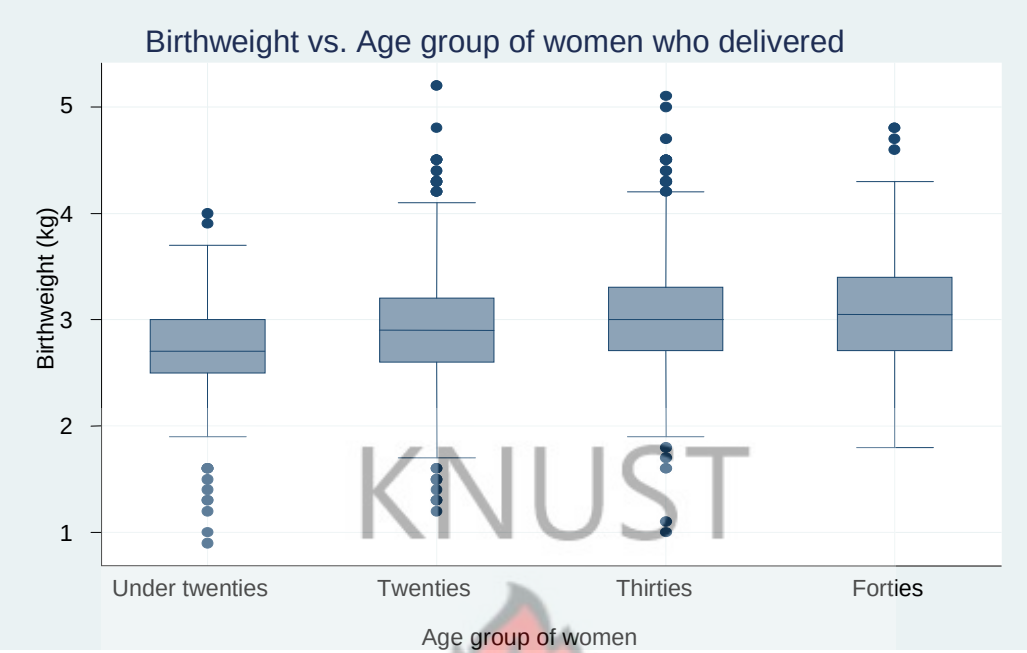

Figure 17: Birthweight variations among age group of women

There was significant association between birthweight of neonates and age group of women who delivered (Pearson $\chi^2 = 72.3$, $p \leq 0.001$). Women in their teens had more LBW babies (24%) as compared to 12%, 6% and 11% for the women in their twenties, thirties and forties age group respectively. The median birthweight for women under twenties was lower as compared to the other age groups (Figure 17). The primigravidae had the lowest median birthweight (Figure 18) as compared with the other gravida group. This difference of birthweight among the gravida of women was very significant (Pearson $\chi^2 = 142.8$, $p \leq 0.001$). Pearson's correlation did also show significant positive relation of birthweight with gravida ($r = 0.27$, $p \leq 0.0001$). The primigravidae had more LBW neonates (25%) as compared to 9%, 8% and 7% for secundigravidae, multigravidae and grand multigravidae, respectively.

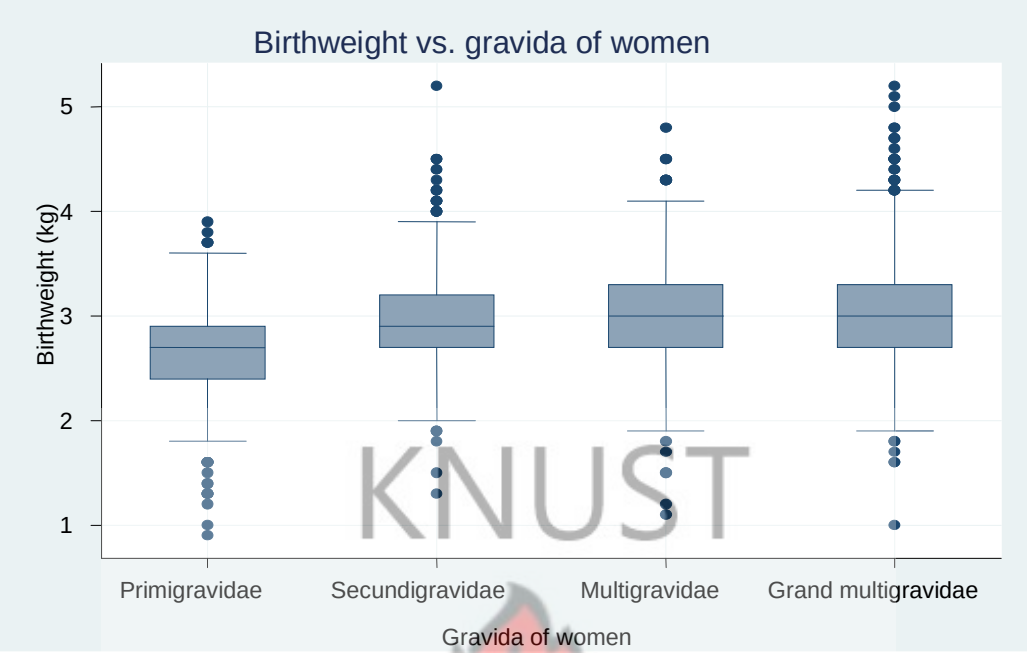

Figure 18: Birthweight variations among gravida of women

The variation in median birthweights during the three years (2005, 2006 and 2007) was insignificant (OR = 0.91, 95% CI, 0.8 – 1.1; $p \geq 0.26$) although it appeared highest in year 2007 (Figure 19).

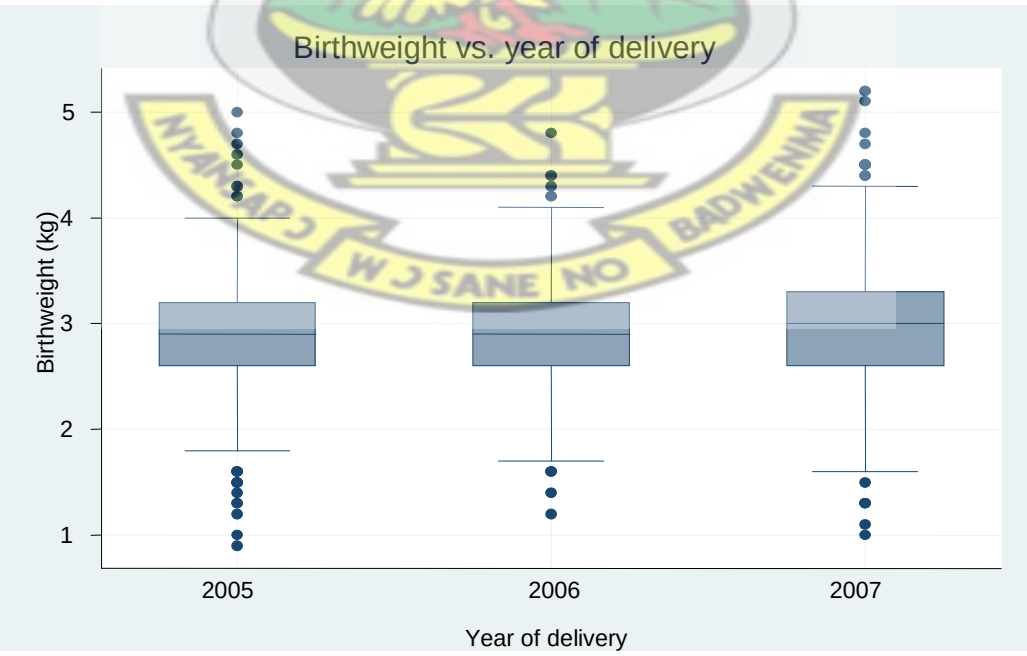

Figure 19: Birthweights of neonates (year 2005-2007)

4.3.2.3 RELATIONSHIP BETWEEN BIRTHWEIGHT AND THE PREDICTOR VARIABLES

Table 25: Relationship between birthweight and the predictor variables

Variables	LBW (%)	NBW (%)	Crude OR	Adjusted OR at 95% CI
IPT Dose				
0	62 (12.0%)	440 (88.0%)	1.0	1.16
1	57 (18.0%)	257 (82.0%)	0.64	
2	90 (13.0%)	584 (86.0%)	0.91	
3	101 (9.0%)	992 (91.0%)	1.38	
Sex				
Male	124 (10.0%)	1,162 (90.0%)	1.0	0.64
Female	186 (14.0%)	1,111 (86.0%)	0.64	
Age group				
<19	89 (24.0%)	280 (76.0%)	1.0	1.79
20-29	162 (12.0%)	1,225 (88.0%)	2.4	
30-39	46 (6.0%)	664 (94.0%)	4.59	
>40	12 (11.0%)	102 (89.0)	2.7	
Gravida				
Primigravida	159 (25.0%)	467 (75.0%)	1.0	1.66
Secundigravida	49 (9.0%)	510 (91.0%)	3.54	
Multigravida	37 (8.0%)	410 (92.0%)	3.72	
G. multigravida	64 (6.0%)	884 (93.0%)	4.7	
Term of Pregnancy				
Preterm	41(71.0%)	17 (29.0%)	1.0	21.43
Term	268 (11.0%)	2,242 (89.0%)	21.43	
Season of birth				
Dry season	110 (11.0%)	897 (89.0%)	1.0	1.8
Wet season	200 (13.0%)	1,376 (86.0%)	0.84	

LBW = low birthweight, NBW = normal birthweight, OR = odd ratio, G. = grand
The value of p was significant for the adjusted odd ratios for all the variables ($p < 0.0001$) excluding season of birth ($p \geq 0.18$) CI= Confidence Interval

The unit increase in each of the predictors' variables including the main exposure variable (the SP) significantly increased the birthweight of neonates ($p < 0.0001$). Women in their twenties gave birth to neonates with significantly higher birthweights than those in their teens (OR=2.4, $p < 0.001$). There was 37% increase in birthweight of

neonates born to multigravid women as compared with primigravid women ($p < 0.001$) (Table 25). A significantly larger proportion of women, who took doses of SP, generally gave birth to normal birthweight neonates than those who took none (Table 25).

4.3.2.4 RELATIONSHIP BETWEEN BIRTHWEIGHT AND SP WITH OTHER PREDICTOR VARIABLES

Table 26: Potential confounders/effect modifiers for birthweight and SP

	OR for effect of BWT and SP (95%CI)	Test for effect modification	Stratum specific estimates
Adjusted for age	1.16	p = 0.66	<19 = 1.28 20-29 = 1.09 30-39 = 1.15 ≥ 40 = 1.31
Adjusted for sex	1.15	p = 0.004	Male = 1.39 Female = 1.02
Adjusted for gravida	1.19	p = 0.61	Primigravida = 1.28 Secundigravida = 1.24 Multigravida = 1.16 G. Multigravida = 1.08
Adjusted for term of pregnancy	1.15	p = 0.18	Preterm = 1.81 Term = 1.12

Sex was found to be the only effect modifier (Table 26). Upon adjusting for the effects of the other predictors on birthweight and SP using logistic regression models and the likelihood–ratio test (LR), it was found that, the fits of reduced models of term of pregnancy (LR χ^2 =103.9, $p < 0.0001$), sex (LR χ^2 = 12.98, $p < 0.0003$), gravida of women (LR χ^2 = 67.1, $p < 0.0001$), and age of women (LR χ^2 = 64.57, $p < 0.0001$) significantly differ from that of the full model and thus these predictors significantly contributed to increase of birthweights as SP remained constant, thus, none of these variables confounded the use of SP by the women and the birthweight of neonates.

Sex of neonates and term of pregnancy did not show significant interaction between SP and birthweight of neonates (Pearson χ^2 = 4.6, 5.6; $p \geq 0.2$, 0.14) respectively, however, age of pregnant women showed significant interaction (Pearson χ^2 = 17.9, $p < 0.035$). There was a weak association between gravid status of pregnant women with SP and weight of neonates (Pearson χ^2 =15.2, $p \leq 0.086$).

4.3.3 DISCUSSION

This study has shown that the use of SP in IPTp helps improve the birthweight of neonates as indicated by other studies (Parise *et al*., 1998; Shulman *et al*., 1999; Guyatt and Snow, 2004; WHO, 2004; Sirima *et al*., 2006; Mbonye, Bygbjerg and Magnussen, 2008).

The present study showed that low birthweights of neonates are common in primigravidae and young mothers. Age of mother, parity of women, age of pregnancy and sex of babies tend to have great influence on birthweight of neonates. It was found that women of older age and high parity had normal birthweight babies which were statistically significant ($p < 0.001$). This could be attributed to the relatively high immunity in them as compared to teenage primigravid women who has no exposure to pregnancy related diseases to generate enough antibodies against them. Primigravidae women and those whose ages are below twenty years are prone to have LBW newborns as shown in other studies (Brabin *et al*., 1999; Taylor *et al*., 2000; Guyatt and Snow 2004; Garner and Gulmezoglu, 2006; Sirima *et al*., 2006; Mbonye, Bygbjerg and Magnussen, 2008). Male–born neonates had significantly higher birthweights as compared to their female counterparts. Studies on LBW of neonates have shown that LBW is a risk factor for poor neurosensory, cognitive, and behavioural development, as

well as for limited school performance and academic achievement (Taylor *et al.*, 2000) and that prevention of LBW in neonates is important, hence it should be prevented.

The yearly variation of birthweight was significant and that of 2004 showed highest median proportion of birthweight (Figure 16). This yearly increase of birthweight may be attributed to the increased education on health care especially in pregnant women as shown in the qualitative aspect of the study and the questionnaire administration in Section II of this volume. With the introduction of SP-IPTp the yearly variation in of birthweights was not significant at any point; they all had almost equal median birthweights, during the 2005 and 2007 three year study period.

Seasonal variations had significant influence on birthweight of neonates. This may be due to intense malaria incidence in the wet season resulting in high parasite densities both peripheral and placental in pregnant women as compared to the dry season. This placental parasitaemia may result in uterine growth retardation of the foetus and consequently low birthweight babies as shown in other studies (Parise *et al*, 1998: Guyatt and Snow, 2004). However, seasonal variations during the IPTp period did not have significant association with birthweights. This may be due to the increased education on prevention of malaria in these recent times and the implementation of IPTp which has proven to be effective in reducing LBW in the newborns.

There has been an increased delivery in the health centres in recent years but records of few delivery data on IPT usage were due to improper management of delivery records in delivery units. Thus, these records were either torn away or were not found at all. Furthermore, other factors including haemoglobin level, body mass index of mothers though have effect on birthweight of neonates as indicated by other studies (Shaheen, 1997; Shaheen *et al*., 1999; Steketee, 2003; Jane, 2004; WHO, 2004), these were not

found in the data reviewed, although, this does not in any way bias the results of the present study.

The present study, therefore, has shown that the use of IPTp with SP in rural communities in sub-Saharan Africa is essential in improving birthweights of neonates. Seasonal variations have no influence on birthweight of neonates so far as there is effective implementation of IPTp programme. Primigravidae women and teenage mothers are prone to giving birth to LBW babies and this requires that intensive care be given to these women during pregnancy to improve their health and that of the babies born to them. However, other factors including parity, age of women, term of pregnancy and sex of the neonates have significant effects on birthweight of neonates. This indicates the multifactorial nature of birthweight of neonates, and thus, the need to monitor every stage in pregnancy so as to improve the health of the mother and the neonate.

4.4 DIVERSITY OF *PLASMODIUM FALCIPARUM*

PCR genotyping was done for 126 randomly but purposefully selected microscopy positive samples. PCR amplifications were successful in 22%, 43% and 56% of samples for MSP1, MSP2 and GLURP, respectively and in 84% of samples when all the 3 genes were combined.

To estimate the genetic diversity of MSP1, MSP2, and GLURP in the parasite population, the frequency distribution of alleles were determined for the studied samples (Figure 20).

MSP1 (11 alleles) and MSP2 (16 alleles) revealed considerably greater parasite diversity than GLURP (5 genes). In each sample, MSP2 alleles especially the FC alleles exhibited extensive parasite diversity as compared to the other markers (Figures 20b and 21).

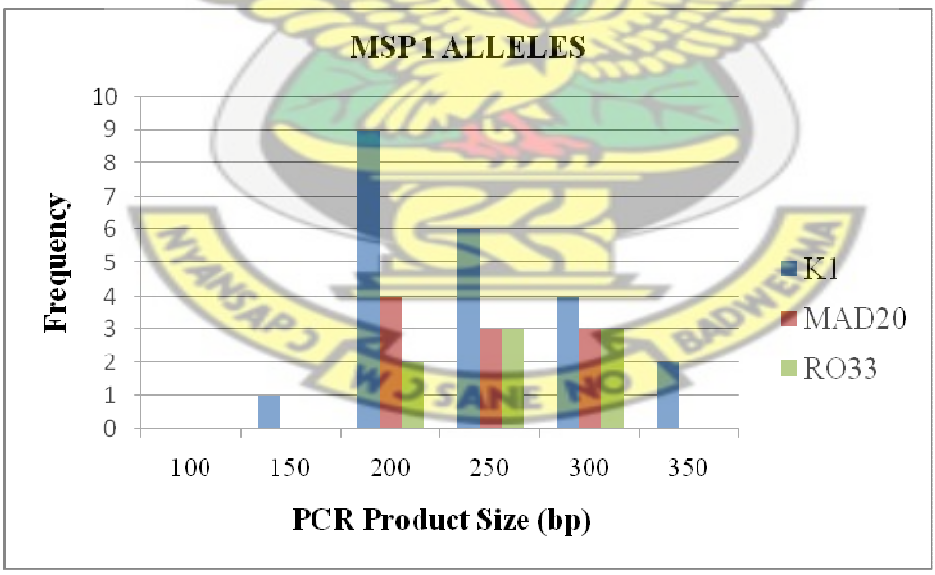

Figure 20a: Frequency Distribution of MSP1 Alleles

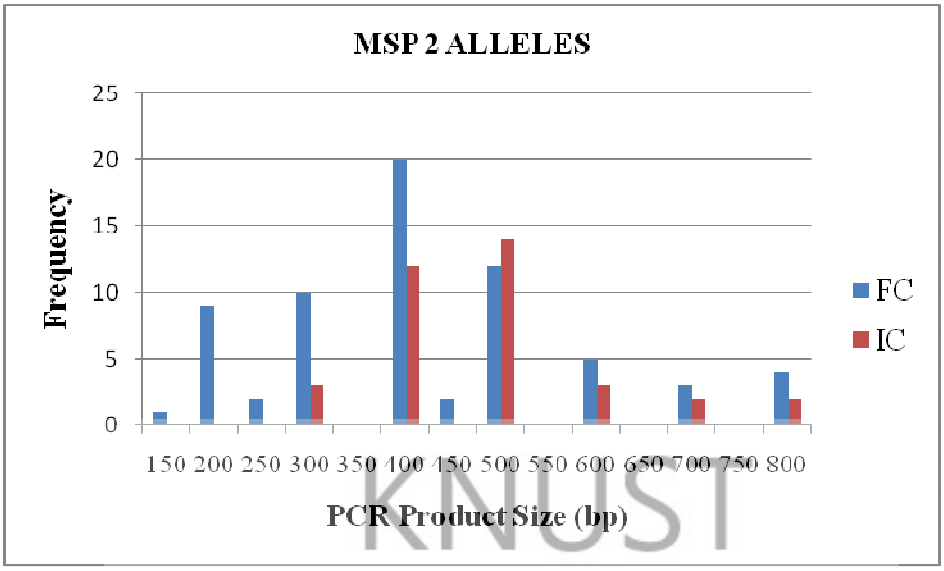

Figure 20b: Frequency Distribution of MSP2 Alleles

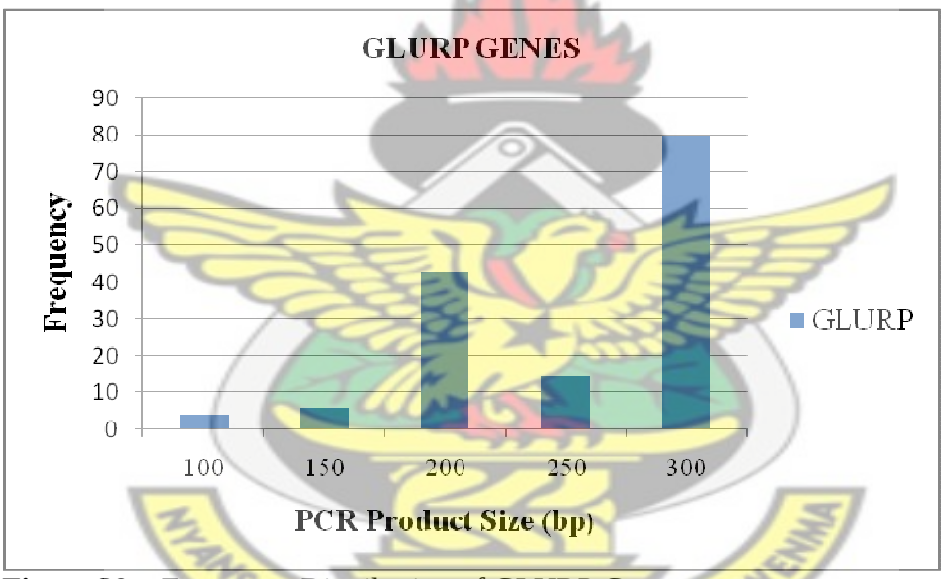

Figure 20c: Frequency Distribution of GLURP Genes

Figure 20: Parasite genetic diversity detected by MSP1, MSP2, and GLURP. Polymerase chain reaction (PCR) products were categorized into molecular weight groups differing by 50 bp for MSP1, MSP2 and GLURP. **(a)** MSP1. **Blue bars** represent K1; **indigo bars**, MAD-20; and **green bars**, RO33 allelic families. The 22 K1 alleles ranged in size from 150 to 350 bp; the 10 MAD20 alleles, 200 to 300 bp; and the 8 RO33 alleles, 200 to 300 bp. **(b)** MSP2. **Blue bars** represent FC and **indigo bars** represent IC allelic families. The 68 FC alleles ranged in size from 150 to 800 bp, and the 36 IC alleles ranged in size from 300 to 800 bp. **(c)** GLURP. The 148 GLURP genes ranged in size from 100 to 300 bp.

The majority of the samples analyzed in MSP2 harboured ≥ 2 parasite lines. Undifferentiated parasite lines of 2 were common in most (98%) of the samples for GLURP genes hence it showed lesser degree of polymorphism. However, GLURP genes were highly (56%) detected in the pregnant women as compared with MSP 2(43%) and MSP1 (22%) markers.

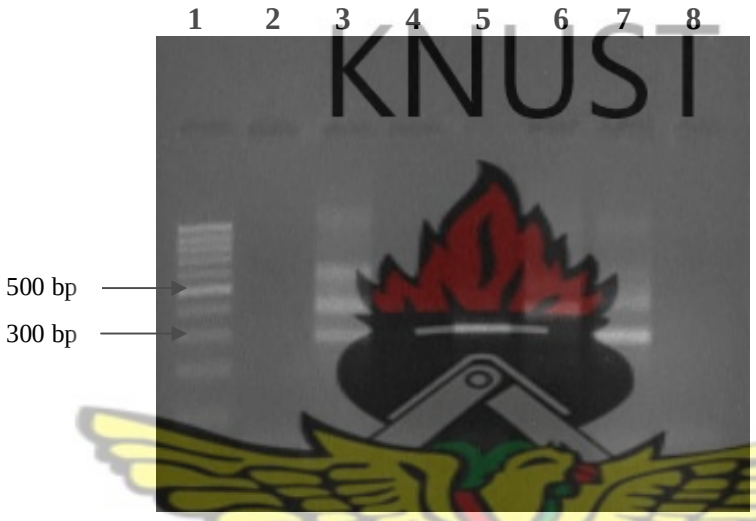

Figure 21: Electrophoregram of MSP2 PCR products of *P. falciparum* malaria: Lane 1 is a 100 base pair DNA Marker; DNA fragments 3, 4(bands faint), 5, 6 and 7 are diverse MSP2 gene FC alleles. Lanes 2 and 8 showed no presence of DNA fragments.

4.4.2 DISCUSSION

Plasmodium falciparum is very diverse in the Offinso District. MSP1 and MSP2 were found to be more diverse as compared to GLURP genes although the later was the most frequently found parasite gene in the pregnant women samples studied. FC alleles of the MSP2 in the samples studied were extensively variable as compared with the IC alleles. Those of the MSP1 polymorphic genome were less diverse in comparison. Thus, alleles of the MSP2 genome were highly diverse in the pregnant women as compared to the

MSP1 alleles in the pregnant women in the district. This highly diverse nature of *P. falciparum* is indicative of a great potential for the development of resistance to the SP drug which may render it less effective as a preventive treatment drug. Studies by Cano *et al*. (2007) and Conway *et al.* (1999) have shown that there is genetic recombination during the sexual phase of the life cycle of the parasite and this enhances the diverse nature of the parasite. Hence there is need for effective measures to control the entomological inoculation rate, for instance, by avoiding overcrowding in homes.

Very diverse genetic strains of *P. falciparum* are infecting the pregnant women. MSP2 allelic families are more diverse as compared with MSP1 and GLURP in the women. However, GLURP parasite genes are the most common in the women in the district. Presence of parasitaemia in the pregnant women did show that the drug SP needs to be well monitored to avoid resistance of the parasite to the drug.

CHAPTER FIVE– GENERAL DISCUSSION

5.1 EFFECTS OF SP ON MATERNAL MORBIDITY AND MALARIA ASSOCIATED ANAEMIA IN PREGNANCY

Pregnant women, especially the primigravidae (mostly in their teens) were more vulnerable to infections which correlated with maternal anaemia, since higher parasitaemia levels were associated with decreasing haemoglobin level of the pregnant women. This affirms studies by Mutabingwa *et al.* (2005) that lower parity and younger age increase susceptibility to malaria. This could be as a result of initial hormonal changes of which they are not used to, coupled with with none exposure to most diseases in pregnancy; thus, leading to low/poor immunity among the primigravid young.

The reduced parasitaemia in the pregnant women reported in the two cross sectional studies of this thesis may be attributed to the effectiveness of the SP usage by the women, which led to reduced anaemia. This is supported by the FGDs with the pregnant women (*"It protects us from getting malaria and anaemia")* and the IDI among the health staff *"At first malaria cases were rampant but now it had reduced and even in the whole institution only 46 had reported with malaria cases; maternal deaths had also reduced. So it has helped a lot. As of April 2007, we had 2,528 pregnant women and only 46 have had malaria")* and chemical sellers (*"It has some benefits because now we hardly hear complications in pregnancy and it has also reduced stillbirth*"); all these and the study by van Eijk *et al*. (2005) attest to the fact that SP is helpful. Repeated doses of SP significantly improved haemoglobin level and the two cross sectional studies support other studies undertaken in other countries on the effectiveness of SP (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.*, 1999; Challis *et al*., 2004; Kenyatao *et al*.,

2005; Sirima *et al*., 2006). However, in Ghana IPT2 coverage nationwide is < 40% (GHS, 2007), necessitating a concerted effort being made to encourage repeated doses of SP intake by pregnant women. Studies (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.,* 1999), have shown that there are no serious adverse effects associated with the use of SP in pregnancy, however, in this present study, one of the respondents in the qualitative studies reported of palpitation after taking the second dose of SP " *The first dose was ok and the second dose when I took it I was having palpitation and I told the woman I won't take it again and that I did not take the third dose*". There could be possible serious adverse effects but these may be rare.

5.2 EFFECTS OF SP ON BIRTHWEIGHTS OF NEONATES

Study on birthweight variation during the pre-IPTp period showed that low birthweights of neonates were common in primigravidae and young mothers as also reported in studies by Brabin *et al.* (1999). Low birthweight is associated with high infant mortality (Steketee *et al*., 2001; Guyatt and Snow, 2001; Murphy and Breman, 2001) which is profound in high malaria transmission areas (Guyatt and Snow, 2004). However, the use of SP in the IPTp programme helped improve birthweight as repeated doses resulted in a reduction in the number of LBW newborns. Garner and Gülmexoglu, (2006) reported that IPTp in paucigravidae is effective in malaria prevention with reduction of LBW by as much as 43%. Recent study by Gies *et al*. (2009) reported that primigravidae who were mostly adolescent women experienced great benefits from complete IPTp–SP in terms of reduction of anaemia and birthweights gains. The present study also showed that age of mother, parity of women, age of pregnancy and sex of babies have great influence on birthweight of neonates. Male born neonates had higher birthweights than

their female counterparts; however, no reason could be attributed to this in the present findings. Seasonal variations have no effect on the birthweights of neonates with the implementation of SP in IPTp programme.

Again, the qualitative studies conducted and other studies (Schultz *et al*., 1994; Parise *et al*., 1998; Shulman *et al.*, 1999; WHO, 2002, 2004; van Eijk *et al*., 2005) have shown that SP in IPTp programme helps improve the birthweights of neonates.

The low deliveries (38%) in the health centres (please see Chapter Five; Cross Sectional Study II: Assessment of the Effect of SP, Knowledge on Malaria and ANC attendance during Pregnancy) indicate the very poor attendance of pregnant women to health centres. Some of the pregnant women and nursing mothers in the quantitative study attributed this to the poor health staff and patient relations ("*I wanted to avoid insults that is why I don't go to the hospital*"); financial problems ("*lack of money constrained me to stay away from the hospital*"); unequipped health facilities and inexperienced health staff ("*ignorance and negligence on the part of health staff leads to maternal death*") and distance of health facilities were some of the reasons given by most of the women for non–attendance at health facilities. These problems were common and nationwide so that the annual deliveries by skilled personnel were 35.1%; higher maternal mortality and increased maternal mortality ratio (229.9/100,000 live births) in the year 2007 as compared to the preceding two years (GHS, 2007). These lack of "quality services" in conjunction with inefficient management of deliveries and lack of essential care to the newborns could lead to high neonatal mortality as reported in other studies (Kulmala, 2000; Lawn, Cousens and Zupan, 2005; Adam *et al*., 2005).

"Quality services" in this context included all services pertaining to customer care such as health workers' behaviour when dealing with their clients, waiting time at the service

facility, availability of drugs and other basic services. Quality of health care also includes the expertise of a provider in delivering the care. Studies in India and elsewhere have found that good obstetric and antenatal care are fundamental to decreasing case fatality due to pregnancy–related complications (Mubyazi *et al*., 2005). Although the respondents' perceptions of the quality of care were highly subjective, patients should rightly expect courtesy and attention from health service providers as well as proper clinical examination and medical advice.

5.3 KNOWLEDGE AND PERCEPTION OF IPT-SP AND MALARIA IN OFFINSO DISTRICT

Knowledge on malaria and its causes were high among the pregnant women and the people in the communities as both the questionnaire administration and the qualitative studies showed, for example, (*"Unclean gutters and stagnant waters breed mosquitoes"; "If one lives in a dirty environment, one is prone to be having the disease")* were some of the statements made. However, there is the need to intensify education of the public on malaria since some were attributing causes of malaria to poor drinking water, dirt, uncovered foods, personal hygiene and others. There was chequered information on the treatment of malaria as few (28%) in the quantitative study went to the health centres for treatment whereas most of them including some of the pregnant women either went to the drug store or used herbs. This was evident as some respondents in the qualitative study stated: *"…most of them use it especially the Northerners. They use these herbs a lot and some of them come to the hospital after these herbs have failed them. Those in the remote villages also use these herbs and the teenagers who get themselves pregnant. These people come to the hospital after these*

herbs or concoctions have failed them"; "If one is pregnant she does not go to the drug store but if she is not pregnant and is having malaria, she at times goes there (the hospital) for some drug".

That SP is used as a preventive treatment drug for malaria in pregnancy is not well known among the people in the communities (particularly the chemical sellers) and, thus, they were less informed and educated about it "*I have heard about that one and some of them even come here (the drug store) to buy it because when it was given to them in the hospital they realized it is good", "... we know it as Fansidar and in the hospital it's Malafan"*. A comment from one chemical seller: *"I heard that the pregnant women go to the hospital for some chloroquine tablets*" indicates that most of the people are less knowledgeable about the use of SP in the IPTp programme.

Health staff on the other hand were knowledgeable about the use of SP and the benefits of its use as they were the "spear headers" of it, encouraging the pregnant women to come and take the drugs "*There used to be high malaria cases previously, but now it has reduced, mortality rate too has reduced and the health of mothers and that of the children also have improved"*. The use of SP by pregnant women was found to be good for their health, thus enhancing good delivery and improving birthweight of their babies as mentioned by most interviewees in both the quantitative and qualitative studies. This confirms similar findings in other countries on the effectiveness of SP (Schultz *et al*., 1994: Parise *et al*., 1998; Shulman *et al*., 1999; Challis *et al*., 2004; Kenyatao *et al*., 2005, Gies *et al*., 2009).

The use of ITNs was not popular among the pregnant women since most complained of discomfort when sleeping in them as reported in other studies (Browne *et al*., 1996, 2001; van Eijk *et al*., 2005) whilst some keep them till they deliver and others had the

wrong perception that mosquitoes are not present in their environments (*"I don't feel the presence of mosquitoes when asleep"*).

The findings of the present study attest to the fact that for success of any health intervention, other factors such as the knowledge and skills of service providers and users, their motivation, attitudes, practices and a range of other socioeconomic factors play very important role (Newman *et al.*, 2003; Mubyazi *et al*., 2005).

5.4 TRANSPLACENTAL TRANSMISSION OF MALARIA

Transplacental transmission of *P. falciparum* has been well described, and the reported frequency of this event in babies born in malaria-exposed pregnancies has ranged from 0 percent to more than 25 % (Uneke, 2007b; Menendez and Mayor, 2007). Thus, placental malaria is known to be a major determinant of congenital malaria. It was thought to be a rarity in sub-Saharan Africa, however, recent reviews have indicated that congenital malaria is more common than previously thought (Menendez and Mayor, 2007; Uneke, 2007b, Uneke, 2007c). Congenital malaria occurs when malaria parasites cross the placenta either during pregnancy or at the time of delivery and it may be defined as the presence of asexual stages of *P. falciparum* in cord blood smear at delivery or in peripheral blood smear of the infant in the first seven days of life, irrespective of clinical symptoms (Menendez and Mayor, 2007; Uneke, 2007b, Uneke, 2007c). Thus, parasitaemia presence in the cord blood in the studied women indicates transplacental transmission of the malaria parasites to the neonates which may be related to increased risk of anaemia in infancy as suggested in a study by Ndyomugyenyi and Magnussen, (2000) in western Uganda. These transplacental transmissions are common in endemic areas as well as non endemic areas (Menendez and Mayor, 2007). More studies are

needed to look at the effects congenital malaria have on neonates since there is dearth of information on it.

5.5 GENETIC DIVERSITY OF *PLASMODIUM FALCIPARUM*

Plasmodium falciparum showed wide diversity and the MSP2 allelic families were more diverse than all the other genes of the parasite investigated. Studies have shown that high infection rates would increase the number of possible sexual recombination within the mosquito and, therefore, would favour the circulation of a greater variety of allelic forms (Conway *et al*., 1999; Cano *et al*., 2007), which could explain the high variability of the MSP2 genes observed. GLURP genes were, however, very common in the study women.

The genetic diversity of the parasite in the district could show possible high transmission of malaria as a result of high prevalence of infection multiplicity as reported in other studies (Konate *et al*., 1999; Paganotti *et al*., 2004; Cano *et al*., 2007). The great diversity of the parasite, thus, poses a threat to the effectiveness of the SP and hence, the need to look at other antimalarial drugs used in pregnancy. There is also the need to introduce efficient control measures which would result in a reduction in the population heterogeneity of the parasite. Notwithstanding this, attitudinal change and proper sanitary conditions are of great importance if the malaria menace is to be curbed.

CHAPTER SIX– CONCLUSION AND RECOMMENDATIONS

CONCLUSION

Repeated doses of SP were effective in improving haemoglobin level of pregnant women. The evaluation of SP with IPTp indicated a reduction in parasitaemia with repeated doses of SP/IPTp in pregnant women thereby improving birthweight of the neonates born to them. Primigravidae and women in their teens were more susceptible to malaria during pregnancy.

Other factors including sex of baby, age and gravida of women and term of pregnancy influenced the birthweight of babies. Primigravid women and teenage mothers were prone to giving birth to LBW babies and male neonates had higher birthweight than their female counterparts. Seasonal variations had no effects on birthweight of neonates with the implementation of IPTp using SP.

The study results suggested that successful implementation of the IPTp strategy will go a long way to improve the birthweight of neonates and the health of pregnant women especially among the paucigravidae and women in their teens.

In the present study the pregnant women readily accepted the SP drug in the IPTp programme when they were educated on the aims of the study. The result was improvement on maternal health, reduced parasitaemia, increased Hb level and neonatal birthweights. This indicates that educated on the benefits of the IPTp-SP programme, patronage would be improved in Ghana.

Knowledge of malaria and IPTp using SP was relatively high among the people in the district. However, the health staff had full knowledge of malaria in pregnancy and the

use of SP in IPTp. They supported the use of the drug in IPTp and advocated for effective implementation of the programme.

Transplacental transmissions of malaria or congenital malaria do occur with possible increased risk of anaemia in the neonates. It has been shown to be common in endemic areas of malaria transmission.

Plasmodium falciparum parasites were very diverse in the pregnant women and the MSP2 gene of the parasite was most diverse compared to MSP1 and GLURP genes. GLURP genes of the parasite were, however, very common in the pregnant women.

RECOMMENDATIONS

There is need for members in the family to motivate family members who are pregnant, particularly the primigravidae and women in their teens, to attend ANC regularly to avoid any complications in them and the consequent death of mother and child.

The leaders in the communities need to organize regular community meetings and durbars to educate their people on health issues, particularly the risk of malaria in pregnancy and the need to attend ANC or health facilities when pregnant to protect both the mother and the unborn child from this deadly disease. Communal labours have to be organized on regular basis to clean the environment, by weeding surroundings, draining stagnant waters, removing empty cans as a way of removing the breeding sites of the mosquito vectors that transmit this and other diseases.

Chemical sellers in the communities should be educated to avoid selling SP to pregnant women but rather encourage them to attend ANC for regular checkups to avoid abuse of the drug. They should also be educated to follow the national policy of treatment of malaria, particularly during pregnancy.

Health staff should make it a point to be friendly with patients especially pregnant women to encourage their attendance at the health facilities for treatment and deliveries of their children. Effective implementation of SP in IPTp relies on the health staff so there is the need for them to educate the pregnant women on the importance of the programme and encourage them to patronize the SP at the right time. They should make sure the pregnant women take the SP before they leave the health facilities. Again, health staff should not delay in attending to emergencies particularly in pregnancy and be quick to refer the patient if not skilled in a special field to help the patient. Use of ITNs by pregnant women should be promoted.

There is need for proper recording and upkeep of data in the health facilities to enhance easy reference and for research.

Strategies should be designed and implemented to increase the proportion of pregnant women who take all three doses of SP during pregnancy at the district, regional and national levels. The IPTp programme should be maintained and effectively implemented nationwide.

Malaria-related anaemia in pregnancy is a killer, and the effective implementation of IPTp would, in a way, contribute significantly towards achieving the Millennium Development Goal by reducing maternal and neonatal mortalities resulting from malaria.

Data in hospitals and health centres should be well kept for easy access for research and reference purposes.

Intensive care should be given to the primigravid and teenage mothers during pregnancy to improve their health and that of the babies born to them. Concerted efforts should be made to enable them attend ANC and have safe deliveries since most of the maternal deaths mentioned in the IDI and the quantitative studies affected them. A new strategy

should be adopted by the Ghana Health Service to train volunteers to go to distant communities to provide mobile antenatal care to the pregnant women given the SP by DOT to the asymptomatic women among them and effectively treat other ailments as they pay attention to face -to -face health education, focussed antenatal care and better social mobilization.

Malaria and anaemia are quintessential diseases of poverty and, therefore, a reduced burden of anaemia (and malaria) in the rural folk would be an extremely cost-effective way of promoting development and reducing poverty.

A standardized procedure should be adopted nationwide in recording information and events (particularly visits to ANC and deliveries) in the hospitals and health centres.

There is the need to improve education of the public on malaria in pregnancy (especially the rural communities) and the need to attend health care (ANC) when pregnant..

The malaria menace could be curbed if proper sanitary conditions are adhered to through effective education, communication and attitudinal change.

International agencies such as the WHO, UNICEF and others should do well to promote the use of SP for IPTp in areas where resistance to the drug has not developed and make the well–being of pregnant women, mother and child health care a priority on their agenda. They should also promote the three–prong approach to control of malaria, namely: effective case management, control of the infective parasites in the mosquitoes through the use of ITNs and indoor residual spraying and attack on the mosquito vectors in the environment through national and regional spraying programmes and good sanitation strategies.

Limitations

Missing records and non-standardized format for recording of delivery outcomes among the health staff in the health centres and in the district at large generated some variables for analysing the pre-IPTp and IPTp delivery data. Poor record keeping and data management in the health centres was a great problem, leading to loss of relevant information

Distant health centres in the district, poor road networks (especially in the communities in the district) and financial burden (particularly in transportation and for molecular studies) were constraints to recruitment of a larger number of pregnant women for the study; thus, the change of the study design from analytical cohort to analytical cross sectional studies. These and other limitations did not in any way, however, bias the results of the present study.

Further Research

There is need for further research on the effects of SP on birthweights, for example, follow up study on pregnant women taking SP in comparison with those not taking SP to delivery to further ascertain the effect of SP on birthweights of neonates.

Congenital malaria is known to be common in endemic areas, however, information on its effects on the neonates or infants is very scanty, hence the need for further research in this area.

Plasmodium falciparum genetic strain is very diverse, hence, studies should be conducted frequently to monitor possible development of resistance by the parasite to the drug SP and a search for other alternative drugs should be initiated. Again, further studies are needed to look at the diversity of the parasite in pregnant women so as to target particular genes for vaccine development for pregnant women.

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APPENDICES

APPENDIX 1 – CONSENT FORM

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

CONSENT FORM

(To be translated into Asante Twi)

Study Woman Identification Code

The Project Staff has described the study to me and explained that I am volunteering for a research on Intermittent Preventive Treatment in Pregnancy and Its Effects on malaria–associated Maternal and Neonatal Morbidity birthweights in Offinso District. He has explained that I would receive the usual recommended care during pregnancy, whether well or ill, based on Ministry of Health, Ghana /Ghana Health Service standard protocols even if I did not volunteer for the study.

During the study, I will have a number of examinations and laboratory tests, not different than if I was treated at any clinic or hospital or was not part of the study.

I understand that I will be provided medical care and treatment based on the rules and regulation of the local health facility that cares for me. If I have any questions about the study, I can ask the Project Staff for answers. I understand I have the right to withdraw from the study at anytime.

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.

_____ _____

Signature or Right Thumb Print of Pregnant Woman. Project Staff (Witness).

Date:

APPENDIX 2 – CERTIFICATE OF CONSENT FORM FOR PREGNANT WOMAN

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

CERTIFICATE OF CONSENT FORM FOR PREGNANT WOMAN
(To be translated into Asante Twi)

Study Woman Identification Code

The Project Staff has described the study to me and explained that I am volunteering for a research on Intermittent Preventive Treatment in Pregnancy and Its Effects on malaria–associated Maternal Morbidity and Neonatal birthweight. He has explained that I would receive the usual recommended care during pregnancy, whether well or ill, based on Ministry of Health, Ghana /Ghana Health Service standard protocols even if I did not volunteer for the study.

During the study, I will have a number of examinations and laboratory tests, not different than if I was treated at any clinic or hospital or was not part of the study.

I understand that I will be provided medical care and treatment based on the rules and regulation of the local health facility that cares for me. If I have any questions about the study, I can ask the Project Staff for answers. I understand I have the right to withdraw from the study at anytime.

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
Mr. Osei Tutu Emmanuel, Department of Community Health KNUST, Kumasi Mobile is 024 3451631 and email address is oseitutu17@yahoo.com.
Dr. Nii Laryea Browne Department of Community Health, KNUST, Kumasi Mobile is 024 4383927 and email address is enlbrowne@yahoo.com
Mr. Osei Francis, District Director of Health Service, Ghana Health Service, Offinso

_____ _____

Signature or Right Thumb Print of Pregnant Woman.

Project Staff (Witness).

Date:

APPENDIX 3 – SURVEY FORM FOR PREGNANT WOMEN

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

SURVEY FORM FOR PREGNANT WOMEN

STUDY NUMBER ☐☐☐☐ **IDENTITY NUMBER** ☐☐☐☐☐☐

DATE OF VISIT ☐☐☐☐2 0 0☐

I) NAME OF HEALTH FACILITY:…… GESTATIONAL AGE (WKS)……

NAME OF PREGNANT WOMAN:……..

ADDRESS:……

AGE: ☐

NAME OF TOWN/ VILLAGE:…….

II) GRAVID STATUS

PRIMIGRAVID	YES		NO	
SECUNDIGRAVID	YES		NO	
MULTIGRAVID	YES		NO	

IF YES	NO.OF CHILDREN ALIVE	
	NO. OF CHILDREN DEAD	
	NO.OF ABORTIONS	

III) EDUCATIONAL LEVEL

1. NONE ☐ 2. PRIMARY ☐
3. MIDDLE/J.S.S ☐ 4. SECONDARY ☐
5. TERTIARY ☐

IV) MARITAL STATUS

1. MARRIED ☐ 2. SINGLE ☐
3. DIVORCED ☐ 4. WIDOW ☐

V) RELIGION	
1	CHRISTIAN
2	TRADITIONAL
3	ISLAM
4	OTHERS(NANE IT)

HB(g/l)			
Weight (kg)			
Height (m)			
Blood Pressure (mmHg)			
Temperature (°C)			
SAMPLES TAKEN			
Blood	Yes	No	

VI) OCCUPATION

1. FARMER ☐ 3. ARTISAN ☐

2. TRADER ☐ 4. OTHERS (NAME IT):

VII) SOCIOECONOMIC INDICATORS

	YES	NO
SOURCE OF INFORMATION		
1.RADIO		
2.TELEVISION		
3.DAILIES		
4.FRIEND/FAMILY		
SLEEPS ON BED		
SLEEPS ON FLOOR		
WINDOWS NETTED		
HAVE BED NET		
INSECTICIDE TREATED NET (ITNS)		
UNTREATED NET		
SLEEPS IN ITNS		
SLEEPS IN UNTREATED NET		
ACCESS TO LATRINE AT HOME		
DRINKING WATER		
1.PIPE BORNE		
2.WELL		
3.RIVER		
4.BORE HOLE		
CARS		
MOTORBIKES		
BICYCLES IN HOUSE		
NUMBER OF PEOPLE PER ROOM		
GOAT IN HOUSE		
SHEEP IN HOUSE		
POULTRY IN HOUSE		

What type of house do you live in?

- Mud with thatch
- Mud with iron sheets
- Bricks with thatch
- Other (Please, explain)
- Bricks with iron sheets
- Blocks with thatch
- Blocks with iron sheets

VIII) DISEASE BURDEN

1. Have you been sick in the course of the pregnancy?

Yes/ No

If yes what type of sickness……

How did you treat it?.....

2. Do you tire easily? **Yes/ No**

3. Are you breathless during routine household work?

Yes /No

4. Is your neck look to be stiff? Yes /No

5. Have you taking any anti-malaria drug**? YES/NO**

6. What type of drug you took?

1. Chloroquine ☐ **2.** Fansidar (SP) ☐

3. Artesunate ☐ 4. artesunate-amodiaquine ☐

5. Others (Check the drugs being brought by the pregnant woman)……

……

…..

7. Have you taking sulphadoxine–pyrimethamine (SP)**?**

Yes/No

If **Yes** indicate the number of times and dates/gestational age of drug intake in this pregnancy (check antenatal card for IPT status)

8. Do you have problem in taking SP? **Yes/No**

9. If **Yes** describe the problem…….....

10. Do you use traditional medicine for treatment?

Yes ☐ No ☐

NUMBER OF TIMES	GESTATIONAL AGE(WKS)
IPT 1	
IPT 2	
IPT 3	

11. Do you experience any of these conditions?

CONDITIONS	**YES (S)**	**YES (P)**	**NO (P)**
FEVER			
HEADACHES			
FITS			
SWOLLEN FEET			
PALLOR			
DIZZINESS			
PERSISTENT VOMITTING			
ABDOMINAL PAINS			
BODY WEAKNESS			

Probed-**P** Spontaneous-**S**

12. Do you take/do the following	**Yes**	**No**
I. Apeteshie		
II. Pito		
III. Nsa fufuo		
IV. Coffee		
V. Cola		
VI. Tea (Lipton)		
VII. Cocoa / Chocolate		

APPENDIX 4 – SIDE EFFECT FORM

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

Side Effect Form

Study Number | | | | | **Identity No.** | | | | | | |

Name of Pregnant woman…….. Date of Visit…../…../…….

Address……. Name of Recorder……

Gravida……..Para ……. Age of Pregnancy (wks) …….

What side effects occur in taking SP?

Number of SP taken……

EFFECTS	Yes (S)	Yes (P)	No (S)	No (P)
Gastrointestinal • Nausea • Vomiting • Diarrhoea • Constipation				
Neurological • Headache • Dizziness • Depression • Confusion • Funny or scary dreams				
Dermatological • Itching • Spots on skin • Colour of skin change				
Ocular • Visual hallucinations • Bad sight • Itchy eyes				
General • Fever • Anorexia • Difficulty in breathing • Any pain				
Musculoskeletal • Joint ache • Swollen joints • fatigue				
Other: (specify)				
Describe the adverse event in detail (including all relevant laboratory results):				

Describe how the reaction was treated:

Haemoglobin level (g/l)…….

Weight of woman (kg)……..

Blood Pressure (mmHg)……

Temperature (°C)……..

APPENDIX 5 – QUESTIONNAIRE

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

QUESTIONNAIRE

STUDY NUMBER ☐☐☐ **IDENTITY NUMBER** ☐☐☐☐☐☐

DATE OF VISIT ☐☐☐☐2 0 0☐

SECTION A: BACKGROUND CHARACTERISTICS

Address:……

Age: ☐☐

Name of town/ village:……

Locality:……

Occupation……

No. of children:

Religion:……..

Level of Education

1. None ☐ 2.Primary ☐

3. JSS/Middle ☐ 4. Secondary ☐

5. Tertiary ☐

SECTION B: GENERAL VIEW ON MALARIA

1. Is malaria a problem in this community?

Yes No

2. What causes malaria?

i) Dirt ii) food iii) drinking water

iv) Mosquitoes v) friends

vi)Others

(specify)……..

3. How would you know someone has malaria?

(Multiple response)

1. fever
2. headaches
3. muscle/joint pain
4. shivering
5. breathlessness
6. dizziness
7. sleepy
8. stiff neck

Name of interview……

Others (specify)……

4. When you have malaria what do you do first?.....

.....

.....

5. Where do you go for treatment?

1. health facilities
2. herbalists
3. chemist shops
4. Pastors/Mallam

Others (specify)…….

6. How do you treat malaria?

1. chloroquine only

2. chloroquine + paracetamol
3. chloroquine + paracetamol + blood tonic
4. fansidar only
5. fansidar + paracetamol
6. Artesunate / Artemisinin (Artemox)
8. Artesunate + amodiaquine
9. Herbal preparations

Others (specify)……..

7. Can malaria be prevented? Yes No

If yes, how can you prevent malaria? (Multiple response)

1. draining and cleaning of choked gutters/cans
2. weeding surroundings regularly
3. Using of insecticide sprays
4. Praying regularly

Others(specify)……

SECTION C: MALARIA IN PREGNANCY

8. How would you describe malaria in pregnant women?

Serious Not serious

Why?.....

9. What should a pregnant woman do to remain healthy? (Multiple response)

1. eat balanced diet
2. exercise regularly
3. observe personal hygiene
4. use herbal preparations
5. attend antenatal clinic
6. sleep in mosquito nets

Others

(specify)……

10. Do you think it is necessary for pregnant women to attend clinic? Yes No

Why?.....

11. When do you think pregnant women should first report at clinic? When pregnancy is

1. one month old
2. two month old
3. three month old
4. four month old
5. as soon as pregnancy is confirmed
6. Others (specify)……

Give reasons to your answer.....

12. What diseases are usually identified with pregnant women in this community? (Multiple response)

1. anaemia
2. malaria
3. fever
4. diarrhoea
5. stomach upsets

Others (specify)…….

13. Are you aware of the Ghana Health Service's new preventive treatment of malaria in pregnancy? Yes No

14. What drug is used?

1. fansidar (SP)
2. chloroquine
3. artesunuate
4. quinine

Others (specify)…….

15. Where did you hear about the new drug (SP)? (Multiple response)

1. ANC
2. Community durbar
3. church
4. markets
5. friends
6. radio /FM

Others (specify)……

16. How often do you hear about the new drug (SP)?

1. everyday
2. once a week

3. once a month
4. once every three months

Others (specify)……

17.What did you hear about the new drug?.....

18. Have you ever taken fansidar during pregnancy?

Yes No

19. Do you experience any adverse events?

Yes No

If yes list them (multiple responses)

1. hypersensitivity reactions
2. anorexia
3. dizziness
4. disturbed visual accommodation
5. headache
6. confusion
7. depression
8. skin rashes
9. exfoliative dermatitis
10. vomiting

Others (specify)……..

20. When was the last time you took SP?.....

21. What are your impressions about taking drug by observation in a hospital/clinic?

……

22. Where do pregnant women go to deliver?

1. ST Patrick Hospital
2. Nkenkasu Gov.Hospital
3. Abofour Health Centre
4. Afrancho Health Centre
5. Akomadan Health Centre
6. At Home

Others(specify)……

23. What determines one's choice of place to deliver?

.....

.....……

……

24. How far is facility from your home?

1. less than 5km
2. 5km
3. <10km
4. 10km
5. Others (specify)

25. What are your impressions about malaria control in pregnancy?

1. Is of importance
2. Is not necessary
3. Is full of spurious things

Other comments…….

26. Do you sometimes hear the death of a pregnant woman doing delivery? Yes /No

How many times do you hear this?

1. Once every month
2. Twice every month
3. Thrice every month

Others (specify)…….

27. What causes death in pregnant woman?

1. haemorrhage
2. malnutrition
3. malaria
4. jaundice
5. accident
6. superstitious powers

Others (specify)……

28. Could the cause of death be prevented? Yes No

How could it be prevented?

……

29. Traditionally, how is pregnancy in women cared for?.....

APPENDIX 6 – IN–DEPTH INTERVIEW WITH OPINION LEADERS/ALTERNATIVE PROVIDERS IN THE COMMUNITY

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

IN–DEPTH INTERVIEW WITH OPINION LEADERS/ALTERNATIVE PROVIDERS IN THE COMMUNITY

INTRODUCTION

Good morning/afternoon and thank you all for coming. We are with the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi. My name is ..... and these are my colleagues.....(let them introduce themselves). We are conducting several meetings with people like yourselves to find out your views about the effect of IPT use in pregnancy on malaria-associated maternal morbidity and neonatal birthweight in Offinso District. Your opinions are very important and they will help us to improve the kind of care we provide.

There are no right or wrong answers. Your contribution is valuable. Whatever you say will be confidential so feel at ease to express your opinion, one person at a time.

BACKGROUND INFORMATION

Name:

Community: Date:

Sex: Age:

Occupation:

Highest level of education: Marital Status:

No. of children: Religion:

Length of stay in community:

Role in community: Ethnicity:

GENERAL KNOWLEDGE ABOUT DISEASES IN COMMUNITY

1. What do you think are the most common diseases in your community and why?

2. How about malaria (use local term which would have been elicited from previous interviews). Does it affect pregnant women? Children?
3. How do you know that someone has malaria? (Probe for adults and children)

4. How do the community members recognise severity and complications of the disease (malaria)? Probe for:

- fever
- headache
- tiredness
- Increased Pallor (Anaemia)
- Dizziness
- Abdominal pains

5. How do you treat malaria? How effective is this treatment? What if the pregnant woman does not get well, what do you do next?

FOR ALTERNATIVE PROVIDERS OF HEALTH CARE.

6. How much does your treatment cost for a pregnant woman with malaria? Are community members able to pay? What is the mode of payment? (Probe for cash, credit, and kind)

7. Where do you get your drug supplies? Are there any problems with these? What are they? How do you think these can be solved?

FOR OPINION LEADERS AND OTHER LEADERS OF IDENTIFIABLE GROUPS

8. What role do you (community leaders) play in the control of malaria?

9. What do you think about IPT using SP in pregnancy in health centres?

INFORMATION, EDUCATION AND COMMUNICATION

10. What are the usual ways of getting information in this community? (Probe friends, rumours, chief's gong-gong beater, etc.)

11. Who normally gives talks in this community on health issues? (Probe BD, TBA, CCA, preachers, teachers, health workers, community development workers, information services, drug peddlers, chemical sellers, and other)

- What issues are normally discussed? (Probe for malaria in pregnancy if not mentioned)
- How often do you receive this information?
- Where do you normally receive the information?

12. How has this education helped you and your family?

13. How has this helped you in caring for malaria in pregnancy?

14. Supposing we want to educate you on fevers/malaria, what information (new/extra) would you like to know?

15. What communication channels have been used to give you education? (Probe on one-on-one, durbars, posters, radio, TV, video, reading literature etc.)

16. Supposing we want to educate you on malaria /fevers? Which of the methods would you or your community prefer. (Can include others not mentioned)

17. Who are those who need information on malaria? Why?

18. Which people would you prefer to give you information on malaria?

19. Are there any other issues in relation to malaria that you would like us to talk about?

APPENDIX 7 – IN –DEPTH INTERVIEW WITH HEALTH WORKERS IN THE COMMUNITY

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

IN–DEPTH INTERVIEW WITH HEALTH WORKERS IN THE COMMUNITY

INTRODUCTION

Good morning/afternoon and thank you all for coming. We are with the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi. My name is ..... and these are my colleagues..... (Let them introduce themselves). We are conducting several meetings with people like yourselves to find out your views about the effect of IPT use in pregnancy on malaria-associated maternal morbidity and neonatal birthweight in Offinso District.

Your opinions are very important and they will help us to improve the kind of care we provide.
There are no right or wrong answers. Your contribution is valuable. Whatever you say will be confidential so feel at ease to express your opinion, one person at a time.

BACKGROUND INFORMATION
Name:

Community: Date

Sex: Age:

Designation: Number of years working with the health facility:

PART ONE

GENERAL KNOWLEDGE OF DISEASES IN COMMUNITY
1. What do you think are the most common diseases in pregnant women in this community you serve and why?

2. What about malaria? (If not mentioned)

3. Are there any diseases that the pregnant women think cannot be treated in hospital?

4. How do the pregnant women recognise severity and complications of Malaria? Probe for:
- fever
- headache
- tiredness
- Increased Pallor (Anaemia)
- Dizziness
- Abdominal pains

Treatment for Malaria

5. How do you treat malaria in this health facility? Probe for
    - Type of antimalarial drugs used/prescribed and why?
    - Find out the different treatments for pregnant women?
    - How much does it cost (every cost included) to treat a pregnant woman with malaria at this facility?
    - Is this affordable for community people?

Intermittent Preventive Treatment Programme

1. How do you see malaria in pregnancy
    - Considering Maternal Health (morbidity, mortality)?
    - Considering Neonatal Health?
2. When was the IPT program introduced in this health centre?
3. What are some of the benefits accruing as far as pregnancy is concerned?
4. What are the problems in the programme?
5. What are some of the difficulties in administering the drug to pregnant women? (probe for gestational age at which SP is given to pregnant women)
6. Are pregnant women hesitant in taking the drug? Why?
7. Have there been reports of side effects of the drug? What are some of the reports? (probe for the treatment of the side effects)
8. Is there improvement of health of mothers who took doses of SP at delivery?
9. Is there improvement of birthweights and health in neonates since the IPT programme started?
10. Do you wish the IPT program to continue?

APPENDIX 8 - FOCUS GROUP GUIDE

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, SMS-KNUST & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY, KNUST

Intermittent Preventive Treatment of Malaria in Pregnancy its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region, Ghana

FOCUS GROUP GUIDE

INTRODUCTION

Good morning/afternoon and thank you all for coming. We are with the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi. My name is ..... and these are my colleagues..... (Let them introduce themselves). We are conducting several meetings with people like yourselves to find out your views about the effect of IPT use in pregnancy on malaria-associated maternal morbidity and neonatal birthweight in Offinso District. Your opinions are very important and they will help us to improve the kind of care we provide.

There are no right or wrong answers. Your contribution is valuable. Whatever you say will be confidential so feel at ease to express your opinion, one person at a time.

Background Information

Name:

Age:

Occupation:

Marital status:

Educational level:

Number of children:

1. What diseases are usually identified with pregnant women in this community and why?
2. Do you know anything on malaria in pregnancy? (probe for the signs and symptoms
3. What are some of the effects of malaria on the pregnant woman and her baby if she does not seek early treatment?
4. Do you see malaria as a problem in pregnant women that we have to prevent and control it?
5. How do you treat malaria? (Probe for where they go for treatment and the kind of drugs given them).
6. How could you prevent malaria? (Look for prevention in pregnant women including taking of SP and sleeping in bed nets).
7. What type of bed nets; do they normally sleep in the nets if not why?

8. Are you aware of the Ghana Health Service new policy on treating malaria in general and that of pregnant women? (probe for where they got the information -and the type of drugs adopted in the policy – artesunate amodiaquine and SP)

9. How do the midwives administer the drug SP to you?

10. How many doses do you take in the cause of pregnancy? (Probe whether they take all full doses if they discontinue why so).

11. What benefits do you get from taking this SP (on maternal side and neonatal side)?

12. Do you experience any adverse events?

13. What are the midwives responses when you complain of any adverse event to them?

14. How do the midwives/health workers relate to you?

15. Do you normally go to the Drug stores to buy drugs? (Probe for the kind of drugs bought and why they buy search drugs).

16. Do you use traditional medicine? Why?

17. The traditional medicine and the modern medicine, which one do you prefer? Why?

18. Any other health problems you want us to discuss.

19. Your final comments.

APPENDIX 9 – LABORATORY FORM (PERIPHERAL SMEAR)

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

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[IPT STUDY]

LABORATORY FORM (PERIPHERAL SMEAR)

IDENTITY No. | | | | | | | **STUDY No.** | | | | |

Name of Pregnant woman …….

Age of Pregnant woman……

Address .....…….....

Date of Visit/Exam | | | | | | |

Axillary Temp ^{0}C | | | . | |

Laboratory No. | | | | | |

Staff code | | |

Name of Recorder .....

HEMOCUE RESULTS

Date | | | | | | |

Haemoglobin (g/l) | | | |

BLOOD FILM EXAMINATION

Date | | | | | | |

Malaria Parasites seen | 1. Yes | 2. No |

Parasite count per 200 wbcs | | | | | | |

P. Falciparum (ASEXUAL) | | | | | | |

P. Falciparum (GAMETOCYTES) | | | |

P. Malariae | | | |

P. Ovale | | | |

P. Vivax | | | |

CERTIFIED CORRECT BY DATE...../...../...../ | | | CCB

APPENDIX 10 – LABORATORY FORM (PLACENTAL SMEAR)

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

LABORATORY FORM (PLACENTAL SMEAR)

IDENTITY No. | | | | | | |

STUDY No. | | | | |

BLOOD FILM EXAMINATION

Name of Mother ……

Date | | | | | | |

Age of Mother……..

Malaria Parasites seen 1. Yes | 2. No

Term of Pregnancy……

Address ……

Parasite count per 200 wbcs | | | | | | |

P. Falciparum (ASEXUAL) | | | | | | |

Date of Visit/Exam | | | | | | |

P. Falciparum (GAMETOCYTES) | | |

Date of Delivery | | | | | | |

P. Malariae | | |

Axillary Temp ^{0}C | | . |

P. Ovale | | |

Laboratory No. | | | | |

P. Vivax | | |

Name of Recorder .....

HEMOCUE RESULTS

Date | | | | | | |

Haemoglobin (g/l) | | |

CERTIFIED CORRECT BY DATE...../...../...../ | | CCB

APPENDIX 11- LABORATORY FORM: PCR (PERIPHERAL BLOOD)

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

LABORATORY FORM: PCR (PERIPHERAL BLOOD)

IDENTITY No. | | | | | | | **STUDY No.** | | | | |

BLOOD FILM EXAMINATION

Name of Pregnant woman …….. Date | | | | | | |

Age of Pregnant woman……

Address .....……..... Malaria Parasites seen | 1. Yes | 2. No |

Date Received | | | | | | | P. Falciparum (ASEXUAL) | | | | | | |

Date DNA Extracted | | | | | | | P. Falciparum (GAMETOCYTES) | | |

Laboratory No. | | | | P. Malariae | | |

Staff code | | P. Ovale | | |

Name of Recorder ..... P. Vivax | | |

PCR RESULTS

Date | | | | | | |

REMARKS:

Primer set used	**Positive**	**Negative**

CERTIFIED CORRECT BY DATE...../...../...../ | | CCB

APPENDIX 12 – LABORATORY FORM: PCR (PLACENTAL BLOOD)

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

[IPT STUDY]

LABORATORY FORM: PCR (PLACENTAL BLOOD)

IDENTITY No. | | | | | | |

STUDY No. | | | | |

BLOOD FILM EXAMINATION

Name of Pregnant woman ……

Date | | | | | | |

Date of Birth | | | | | | | | |

Malaria Parasites seen 1. Yes 2. No

Address ……

P. Falciparum (ASEXUAL) | | | | | | |

Date Received | | | | | | |

P. Falciparum (GAMETOCYTES) | | |

Date DNA Extracted | | | | | | |

P. Malariae | | |

Laboratory No | | | | |

P. Ovale | | |

Staff code | |

P. Vivax | |

Name of Recorder…..

PCR RESULTS

Primer set used	Positive	Negative

Date | | | | | | |

REMARKS:

CERTIFIED CORRECT BY DATE...../...../...../ | | CCB

APPENDIX 13 – DELIVERY FORM

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

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[IPT STUDY]

DELIVERY FORM

IDENTITY No. | | | | | | | **STUDY No.** | | | | |

Name of Pregnant woman ……

Age of pregnant woman……

Gravida ……. Para……

Number of SP taken……

Address.....…….....

Place of Delivery…….

GestationalAge(weeks)……

Date of Admission | | | | | | |

Haemoglobin level (g/dl)……..

Active Labour ☐

Not in active Labour ☐

Time active labour started:……

Timemembranes ruptured:……..

Time second stage starts:……

Time delivered: ……

Estimated blood loss (ml): ……

Mode of delivery……

Oxytocin – time given:…….

Placenta complete Yes/No

Live Birth	
Stillbirth –Fresh	
Stillbirth –Macerated	

Resuscitation | Yes | No |

Birthweight in first 3hours ____ kg

Birth length (cm) ____

Head circumference (cm) ____

Chest length (cm) ____

Date of Birth (Child) | | | | | | |

Sex	1. male	2. female

Attendant at Delivery		
1.Midwife	2. Doctor	3. Other…
Any complication during delivery		
PPH	Fits	Fever	None	NK
Others (specify):		
Referred with reason		

PPH: Postpartum haemorrhage NK: Not known

DELIVERY FINDINGS

Is Baby very small? Yes No

Condition of Baby

Apgar score 5 minutes after delivery (*scores 0, 1, and 2*)

a. Heart rate [ ]
b. Skin colour [ ]
c. Breathing [ ]
d. Response to stimulus [ ]
e. Muscle tone [ ]

Total score [ ]

Baby has **(*tick any*)**

a) Fever
b) Feels cold
c) Not able to suck
d) Yellowish conjunctiva

Body temperature of baby…….

Other comments on the baby's health condition……
……

Planned treatment of the baby……..

Condition of mother within Six hours

a. Weak after delivery
b. Fever
c. Good
d. Dead
e. Referral for Further Intensive Health Care

Blood pressure of mother……..

Body temperature of mother…….

Haemoglobin level of mother after delivery
……..

Other comments on mother's health condition
……

Planned treatment of the mother……

Date of Discharge……..

CERTIFIED CORRECT BY DATE...../...../...../ | | | CCB

APPENDIX 14 – INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH OF MOTHER

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH OF MOTHER

Study Number | | | | | **Identity No.** | | | | | | |

CAUSE OF DEATH

I (a) . . . . . .

Disease or condition directly leading to death*

b). Due to (or as consequence of). . . . . .

. .

Antecedent causes

Morbid conditions if any, giving rise to the above cause, stating

(c) Due to (or as consequence of. . . . . .

. . . . . .

(d) Due to (or as consequence of). . . . . .

. . . . . .

II

Other significant conditions contributing to the death, but not related to the disease or condition causing it.

. . . . . .

. . . . . .

This does not mean the mode of dying, e.g. heart failure, respiratory failure.

It means the disease, injury or complication that caused death.

CONSIDER COLLECTING THE FOLLOWING INFORMATION

III

- If the deceased is a female, was she
    1. Not pregnant
    2. Not pregnant, but pregnant within 42 days of death
    3. Pregnant at the time of death
    4. Unknown if pregnant or was pregnant within 42 days of death

Approximate interval between onset and death……

APPENDIX 15 – INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH OF NEONATE

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY, DEPARTMENT OF COMMUNITY HEALTH, KNUST-SMS & DEPARTMENT OF THEORETICAL AND APPLIED BIOLOGY KNUST

Intermittent Preventive Treatment for Malaria in Pregnancy and its Effects on Maternal Morbidity and Neonatal Birthweight: a study in Offinso District, Ashanti Region Ghana

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH OF NEONATE

Study Number | | | | | **Identity No.** | | | | | | |

CAUSE OF DEATH

I (a) . . . . . .

Disease or condition directly leading to death*

b). Due to (or as consequence of). . . . . .

Antecedent causes

Morbid conditions if any, giving rise to the above cause, stating

(c) Due to (or as consequence of. . . . . .

. . . . . .

(d) Due to (or as consequence of). . . . . .

. . . . . .

II

Other significant conditions contributing to the death, but not related to the disease or condition causing it.

. . . . . .

This does not mean the mode of dying, e.g. heart failure, respiratory failure.

It means the disease, injury or complication that caused death.

CONSIDER COLLECTING THE FOLLOWING INFORMATION

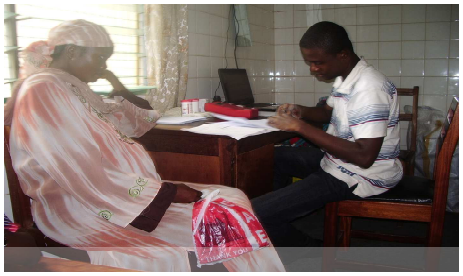
III

- If the deceased is an infant and less than one month old
  - What was the birthweight: . . . . . g
- If exact birthweight not known, was baby weighing:
  - ■ 2500 g or more
  - ■ Less than 2500 g

Approximate interval between onset and death……

APPENDIX 16 – FIELD PICTURES

SOME FIELD PICTURES



Field staff at work St Patrick Hospital, Offinso

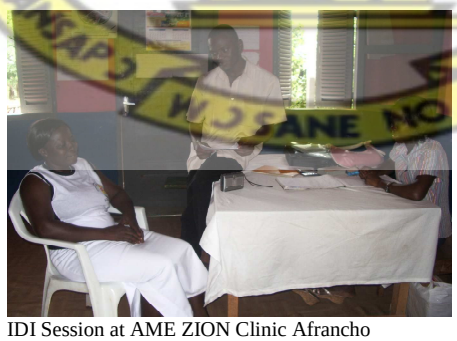
Pregnant women at ANC, St Patrick Hospital, Offinso

Offinso DHMT

Attendance at stakeholders workshop,Offinso

Prof Lawson (Co –investigator) handing over drugs to DHD

FGD session in Akomadan- Afrancho



IDI Session at AME ZION Clinic Afrancho

Field staff at work at Abofour Health Centre

Field Staff at work at Abofour Health Centre

Pregnant women waiting to be attended to at Akomadan Health centre

Work in a molecular laboratory

Midwife poised during IDI session

Midwife looking on as a pregnant woman takes the SP drug

Training session in Offinso