SEX DIFFERENCES IN THE EFFICACY OF ANTIMALARIAL DRUGS AND RELATED CHANGES IN THE
HAE MOGLOBIN LEVELS OF CHILDREN UNDER FIVE IN GHANA

BY

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MSc. CLINICAL TRIALS DEGREE

JULY, 2012
DECLARATION

I, Nagumo Walter-Rodney declare that except for the other people’s investigations which I have duly acknowledged in this dissertation. This document is a result of my own original research which was carried out as dissertation for the award of a Master of Science (Clinical Trials) degree between May-July 2012. This dissertation has not been presented elsewhere either in whole or in part for another degree.

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DEDICATION

This piece of work is dedicated to my dad, Mike Nagumo and my mum, Cedonia Tang for their relentless support. I say God richly bless you for taking keen interest in my education and wellbeing. Also, to my brother, Thomas-More and my sister, Carine-Truce for their encouragement.
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# TABLE OF CONTENTS

DECLARATION ................................................................. i
DEDICATION ...................................................................... ii
ACKNOWLEDGMENT ........................................................ iii
TABLE OF CONTENTS ....................................................... iv
LIST OF TABLES ............................................................. vii
LIST OF FIGURES ........................................................... viii
LIST OF ABBREVIATIONS ................................................ ix
ABSTRACT ........................................................................ x

## CHAPTER ONE ............................................................. 1

1.0 INTRODUCTION .......................................................... 1

1.1 Background .............................................................. 1

1.2 Statement of the problem .......................................... 2

1.3 Rationale .................................................................. 3

1.4 Study Objectives ....................................................... 5

1.4.1 General Objective ................................................ 5

1.4.2 Specific Objectives ............................................... 5

## CHAPTER TWO ............................................................. 6

2.0 LITERATURE REVIEW ............................................... 6

2.1 Anaemia Associated with Malaria ............................. 6
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 Sex Difference in Haemoglobin Levels</td>
<td>8</td>
</tr>
<tr>
<td>2.3 Antimalarial Drug Resistance</td>
<td>9</td>
</tr>
<tr>
<td>CHAPTER THREE</td>
<td>13</td>
</tr>
<tr>
<td>3.0 METHODS</td>
<td>13</td>
</tr>
<tr>
<td>3.1 Study Location</td>
<td>13</td>
</tr>
<tr>
<td>3.2 Study Design</td>
<td>14</td>
</tr>
<tr>
<td>3.3 Sample Size and Power</td>
<td>14</td>
</tr>
<tr>
<td>3.4 Research Questions</td>
<td>14</td>
</tr>
<tr>
<td>3.5 Outcome Measures</td>
<td>15</td>
</tr>
<tr>
<td>3.6. Statistical Analysis Plan</td>
<td>15</td>
</tr>
<tr>
<td>3.6.1 Data Description and Extraction</td>
<td>15</td>
</tr>
<tr>
<td>3.7 Analysis of Data</td>
<td>15</td>
</tr>
<tr>
<td>3.8 Limitations</td>
<td>16</td>
</tr>
<tr>
<td>3.9 Ethical Considerations</td>
<td>16</td>
</tr>
<tr>
<td>3.9.1 Privacy and confidentiality</td>
<td>17</td>
</tr>
<tr>
<td>CHAPTER FOUR</td>
<td>18</td>
</tr>
<tr>
<td>4.0 RESULTS</td>
<td>18</td>
</tr>
<tr>
<td>4.1 Background characteristics of study participants</td>
<td>18</td>
</tr>
<tr>
<td>4.2 Sex differences in the efficacy of antimalarial by clinical response on day 14</td>
<td>21</td>
</tr>
<tr>
<td>4.3 Sex differences in the efficacy of antimalarial by clinical response on day 28</td>
<td>23</td>
</tr>
<tr>
<td>4.4 Sex differences in mean haemoglobin levels by treatment</td>
<td>25</td>
</tr>
</tbody>
</table>
4.5 Prevalence of anaemia in all treatment groups…………………………………… 24
4.6 Comparing sex differences haemoglobin levels by treatment (day 0 and 7)………… 28
4.7 Comparing sex differences haemoglobin levels by treatment (day 0 and 28)………… 28
4.8 Comparing sex differences haemoglobin levels by treatment (day 7 and 28)………. 29

CHAPTER FIVE……………………………………………………………………………… 31
5.0 DISCUSSION……………………………………………………………………………… 31
5.1 Summary………………………………………………………………………………… 31
5.2 Sex differences in antimalarial efficacy……………………………………………… 31
5.3 Prevalence of anaemia in study population………………………………………... 33
5.4 Sex differences haemoglobin levels before, during and after antimalarial treatment 34

CHAPTER SIX……………………………………………………………………………… 36
6.0 CONCLUSION AND RECOMMENDATION ……………………………………… 36
6.1 Conclusion……………………………………………………………………………….. 36
6.2 Recommendation………………………………………………………………………. 37
REFERENCE………………………………………………………………………………38

LIST OF TABLES

Table 1: Baseline characteristics of antimalarial drugs used in children………… 19

Table 2: Sex differences in efficacies of antimalarials on day 14 .................... 21

Table 3: Sex differences in efficacies of antimalarials on day 28 .................... 23

Table 4: Changes in Hb levels by antimalarial, day of assessment and sex......... 30
LIST OF FIGURES

Figure 1: Over view of sex differences Hb levels in all treatments......................... 25

Figure 2: Sex differences in the Hb level of treatment groups ............................ 27
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP</td>
<td>Sulphadoxine-Pyrimethamine</td>
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<td>CQ</td>
<td>Chloroquine</td>
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<td>AL</td>
<td>Artemether Lumefantrin</td>
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<td>ART/AMQ</td>
<td>Artesunate Amodiaquine</td>
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<td>AMFm</td>
<td>Affordable Medicine Facility- Malaria</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>ACT</td>
<td>Artemisinin combination therapies</td>
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<td>Hb</td>
<td>Haemoglobin</td>
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<td>IFCC</td>
<td>International Federation for Clinical Chemistry</td>
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<td>ETF</td>
<td>Early Treatment Failure</td>
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<td>LCF</td>
<td>Late Clinical Failure</td>
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<td>LPF</td>
<td>Late Parasitological Failure</td>
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<tr>
<td>ACPR</td>
<td>Adequate Clinical and Parasitological Response.</td>
</tr>
<tr>
<td>M</td>
<td>Mean</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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</tbody>
</table>
ABSTRACT

Background: One of the consequences of drug resistance to malaria parasites, is poor haematological recovery (Bloland et al., 1993; Verhoeff et al., 1997; Ekvall et al., 1998). Use of the right antimalarial is the key to avert this situation. Few studies have explored sex differences of these drug interventions in pediatric populations. (Domellöf M et al 2002 and Songül S et al 2009).

Methods: This study is a descriptive study analyzing secondary data collected from a primary comparative efficacy study of four antimalarials in Ghanaian children under five in 2005. Age, sex, haemoglobin levels, parasite counts and temperature between sexes were used for the analysis. Pearson Chi square test, ANOVA and paired t-test were performed between sexes and day of treatment. Comparison of means, standard deviation, risk difference and mean difference were done where it applies stating p values of <0.05 as significant and 95% confidence intervals.

Results: The treatment groups were distributed as follows at baseline; Chloroquine (CQ) 36, Artesunate-Amodiaquine (ART/AMQ) 27, Sulphadoxine-Pyrimethamine (SP) 29, and Artemether –Lumefantrine (AL) 19. The mean age was highest in the AL group 38.6 months (SD±9.9). Adequate Clinical and Parasitological Response for evaluable patients was also highest among females in the AL group 72% (13/18) at day 14 and followed a similar trend at day 28; 69.23% (9/18).

About 70% (62/94) of all males in all treatment groups were anaemic while 43% (40/94) of all females were anaemic at baseline. A total of 88.3% in both sexes and treatment groups were still anaemic by day 7 assessment. Haemoglobin (Hb) levels increased in both sexes and all groups during and after treatment but the cross comparisons between days were mostly significant among ACT females. Among the ACT’s, females in AL were always significant comparing Hb’s levels on any day of treatments but only significant at day 0 and 28 for ART/AMQ (p=0.0188).

Conclusion: No significant difference in efficacy was found between males and females and between antimalarial treatment groups. This could be attributed to a small sample size used in the evaluation. Considering the permuted days of comparisons in both ACT groups, females were found to have a statistically significant haematological recovery than boys with mean ages in months of 35.1 and 31.5 respectively. Further studies to establish local haematological reference values, followed by studies to ascertain haematological recovery rates among Ghanaian children are recommended.
CHAPTER ONE
1.0 INTRODUCTION

1.1 Background

In Africa drug resistance is a major bottleneck in the combat of malaria. The World Health Organization (WHO), defines drug resistance as “the ability of a parasite strain to multiply or to survive in the presence of concentrations of a drug that normally destroys parasites of the same species or prevent their multiplication” (WHO, 2002). Many failing monotherapies for malaria treatment have been replaced by Artemisinin based Combination Therapies (ACTs). The resistance of P. falciparum parasite to monotherapies like Chloroquine in endemic areas has been a major reason for this decision. In Ghana, the drug policy was changed from Chloroquine as first line treatment for uncomplicated malaria to Artesunate Amodiaquine in 2002 due to the fact that it was failing to kill parasites effectively. The decline in efficacy was first observed in 1986 from 91.1% to 38.2% in 2003 (Koram et al 2005). By June 2006, 37 countries in Africa had adopted ACT as the first or second-line treatment policy (WHO, 2007). There are a number of registered co-formulated ACTs that are produced to internationally recognized good manufacturing practice standards that are used in sub-Saharan Africa. These include; Artemether-Lumefantrine (AL), Artesunate-Amodiaquine (AS + AQ), Artesunate-Amodiaquine (AS + AQ) and Artesunate-Sulphadoxine Pyrimethamine (AS + SP) (Adjuik et al, 2002; AMFm report, 2012). They are used in various countries according to their drug policy and affordability.

It is estimated that 655,000 people died from malaria in 2010 making it the fifth biggest killer in low income countries even though others argue a double of about 1.24 million deaths (Gulland A-BMJ., 2012). Children under five years are the most vulnerable population in terms of malaria
infection. The red blood cells are usually destroyed by the parasites which lowers the haemoglobin levels and then gives way for anaemia (Hb<11g/dL) to set in (Ekvall et. al. 1998). This situation usually can be curtailed by administration of the right antimalarial at the right time. The most effective antimalarial is able to kill the parasites in a shorter time.

1.2 Statement of the problem

The escalating prevalence of malaria-associated anemia and mortality in African children is attributed partly to the rise in antimalarial drug resistance (Hedberg et.al., 1993., Slutsker et.al., 1994., Trape et.al. 1998., Bjorkman 2002)

The resistance of *P. falciparum* to antimalarials that are often used in the treatment of malaria in Ghana has shown similar trends across Sub-Saharan Africa (Amukoye et al., 1997; Sowunmi et al., 2001). The problem of antimalarial drug resistance has prompted the search for a safe, good quality, affordable, acceptable and newer antimalarial drugs with the purpose of providing, among other benefits, long lasting clinical cure for individuals suffering from malaria, thereby preventing progression of uncomplicated malaria to severe disease and death. (Koram et al 2005).

Few studies have explored sex differences to these drug interventions in pediatric populations (Domellöf M. et al 2002 and Songül S. et al 2009). This study analyzes data collected from a primary comparative efficacy study of four antimalarial drugs in 2003. This was done to review the antimalarial drug treatment policy in Ghana to support the National Malaria Control Programme in the fight against non effective treatments. It seeks to support the hypothesis that the most effective antimalarial will improve haemoglobin levels significantly with difference in
sex. The sex difference in the efficacy of Amodiaquine Artesunate (AMQ/ART), Sulphadoxine Pyrimethamine (SP), Artemether-Lumefantrin (AL) and Chloroquine (CQ) and related effects on haemoglobin levels in Ghanaian children will contribute to knowledge in the treatment and diagnosis of *P. falciparium* infected malaria.

### 1.3 Rationale of the Study

Prompt diagnosis and early effective therapy are important in the reduction of malaria and anaemia related deaths. The methods used to define what makes up an effective course of therapy have been well established and still keeps improving which includes assessments of parasitological and clinical cure.

Anaemia due to malaria has been perceived to be secondary to direct damage of both infected and non-infected red blood cells and also to suppression of bone marrow function as a result of the infection (Owusu-Agyei S. *et al* 2002). In The Gambia it was shown that the seasonal fall in haemoglobin values in adults could be prevented if malaria parasitemia is cleared or reduced by use to appropriate antimalarial.

The use of Sulphadoxine Pyrimethamine, Chloroquine, Artemether-Lumefantrin and Artesunate-Amodiaquine as antimalarials are well known (Oduro A.R. *et al* 2000, Owusu-Agyei S. *et al* 2002, Ehrhardt S. *et al* 2003, Koram *et al* 2005). There are few studies that seek to evaluate the sex difference in the efficacy and on the haemoglobin levels of children treated with antimalarials. Thus there is a need to carry out this study to add to knowledge about sex differences in effective diagnosis and treatment of malaria cases despite the general hypothesis that there is usually no difference is sexes.
An Affordable Medicine Facility- Malaria (AMFm) survey was conducted by the Ghana Pharmacy Council from March to May 2011. This was to determine among other things the proportion of Pharmacists and Licensed Chemical sellers who are sentient of the co-paid AMFm Artemisinin-based combination therapies (ACTs), access and availability in community retail outlets and observed retail prices. It revealed that, Chloroquine even though not used as the first line therapy for uncomplicated malaria, continues to be the second most preferred choice of drug used in the treatment of malaria. It may be assumed that, some people are aware of treating malaria with ACTs but are not conscious of the fading out of Chloroquine and its resistance. Chloroquine is now used largely for preventive purposes in some parts of the world.

The introduction of ACT has been very effective and World Health Organization (WHO) has therefore approved the use of Artemisinin-based combination therapy (ACT) as the standard of care in the treatment of uncomplicated falciparum malaria (WHO 2005). However, the widespread implementation of ACTs is bound to face serious limitations of availability, familiarity and affordability (Bloland 2003). A survey by Affordable Medicine Facility- Malaria (AMFm) in 2010 revealed that about over 88% of facilities in eight different African countries showed that private for profit sectors had in stock non artemisine therapies than they had quality assured ACT’s (AMfm Baseline Report 2012). Effective antimalarial therapy should lead to better treatment outcomes (cure, survival, haematological recovery and reductions in the prevalence of malaria-associated anaemia). It is therefore imperative to investigate the existence of any differences in sexes since male and female are physiologically different in terms of growth, metabolism and catabolism.
1.4 Study Objectives

1.4.1 General Objective

To determine sex differences in the efficacy of four antimalarials and related haemoglobin levels in Ghanaian children.

1.4.2 Specific Objectives

1. To compare the sex differences in therapeutic efficacy by clinical response on day 14 and 28 in children under five with uncomplicated malaria treated with an antimalarial; Amodiaquine-Artesunate (AMQ/ART), Sulphadoxine-Pyrimethamine (SP), Artemether -Lumefantrine (AL) and Chloroquine (CQ).

2. To determine the sex differences in haemoglobin levels at days 0, 7 and 28 in relation to treatment response.
CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 ANAEMIA ASSOCIATED WITH MALARIA

Malaria and anemia in children has been a major public health concern in malaria holoendemic areas. They have been a leading cause of childhood sickness and deaths especially in malaria prone areas. In many malaria endemic areas like Ghana, anemia is among the leading causes of morbidity and mortality in patients admitted in hospitals. It has been observed that in these areas, the incidence of severe anemia and age-specific rates of anemia strongly correlate with the intensity of Plasmodium falciparum transmission and that, significant improvements in hematological indices such as haemoglobin levels have been seen after interventions from malaria control trials (WHO, 2005). The main strategy for the reduction of malaria-related morbidity and mortality in Africa is early diagnosis and institution of effective treatment (WHO, 1993).

Malaria induced anemia has been postulated to be secondary to direct destruction of both infected and non-infected red blood cells and also to suppression of bone marrow function as a result of the infection. (Owusu–Agyei S. et al., 2002). In The Gambia it was shown that the seasonal fall in haemoglobin values in adults could be prevented if malaria parasitemia was cleared or reduced by prophylaxis.

It is very important that children maintain sufficient red blood cell counts to support oxygenation growth, development and the fight against malaria.

While there may be several causes for the anemia, *P. falciparum* infection is believed to be a major contributory factor to the etiology of severe anemia seen in malaria endemic areas.
The severity of malaria infection can vary from mild (uncomplicated) to life threatening (severe malaria). One of the most inevitable manifestations of malaria is anaemia—the reduction of haemoglobin concentration below the normal range for age and sex.

The relatively high prevalence of anemia observed at the end of the high transmission season opens up the possibility of using incidence of anemia as a primary outcome variable for the effects of new intervention tools such as vaccines, at least in areas of high malaria transmission.

Because anaemia presents with non-specific signs and symptoms, the condition is often unrecognized and under-treated (Schellenberg et al., 2003). If left untreated, anaemia is a major risk factor for mortality (Mabeza et al., 1998). Up to three quarters of African children are estimated to be anaemic, mainly from malaria or iron deficiency. (DeMaeyer and Adielstegman, 1985). Malaria-related anaemia affects an estimated 1.5 to 6 million African children, causing a case fatality rate of 15% (Murphy and Breman, 2001). In areas of high malaria transmission, young children bear the brunt of malaria and in these settings the commonest presentation of malaria is (severe) anaemia. Malarial anaemia is thought to develop through increased destruction or reduced production of red blood cells or a combination of both processes. However, the predominant pathogenetic mechanism is incompletely understood (Obonyo et. al. 2003).

According to the World Health Organization, a normal haemoglobin level for children age 6 months to 4 years is at or above 11 g/dL thus haemoglobin <11.0 g/dL is considered anaemic. A normal levels for children ages 5 to 12 years is at or above 11.5 g/dL. A normal level for adolescents ages 12 to 15 is at or above 12.0 g/dL. Any haemoglobin values below these cut-points may be diagnosed as anaemia (WHO, 2008).
Reference values, when used with clinical history and physical examination provide useful information for the diagnosis and management of diseases. Thus it is recommended by the International Federation for Clinical Chemistry (IFCC) to establish laboratory reference values using the population it intends to serve. Thus a study by D.K Dosoo and colleagues established pediatric haemoglobin reference in central Ghana as 8.1g/dL to 13.5 for males and 7.8 to 13.3 for females (Dosoo et al 2010) but suggested an average of 10.8 g/dl for male and 10.6 g/dL for female.

2.2 SEX DIFFERENCE IN HAEMOGLOBIN LEVELS

To detect anemia, age-appropriate cut-offs of haemoglobin (Hb) values are necessary and if present, any physiological changes should be defined. However, there have been a limited number of studies addressing the difference in Hb status between male and female infants. There have been some studies about Hb changes by season in adults; however, there are very few published studies on infants and children (Songül S. et al 2009).

Haemoglobin levels are influenced by a number of factors including nutritional status of children, age, sex and parasitemia. This invariably reflects a child’s anemic status as stated earlier and it’s influenced mainly by malaria transmission intensity of the area.

In two surveys to assess the characteristics of severe malaria in Ghanaian infants between 6–19-month, haemoglobin levels were categorized into severely anemic (Hb < 6.0g/dL), moderately anemic (Hb 6.0–7.9 g/dL), and normal (Hb >8.0 g/dL) groups. It was found that severely anemic group of children in both surveys were older and predominantly males. The point prevalence of parasitemia was higher in both moderate and severe groups. A positive correlation was found to
exist between age and proportion with Hb < 6.0 g/dL in the population attesting to a stronger relationship in girls (Owusu-Agyei S. et al 2002).

In a similar study carried out in Turkey, to evaluate seasonal and gender differences in haemoglobin value in infants at 5-7 months of age. Infants were divided into three groups according to their Hb values at 5-7 months of age. Hb values at 5-7 months of age of ≥10.5 g/dl were determined as normal between 9.5 and 10.4 g/dl as mild anemic and <9.5 g/dl as moderate anemic showed that, the prevalence of anemia was 41.4% and boys had significantly lower Hb than girls (10.5±0.9 g/dl and 10.8±0.9 g/dl respectively p=0.003) (Songül S. et al 2009). These all together indicate some level of sex differences in Hb which could be attributed to malaria.

### 2.3 Antimalarial Drug Resistance

The increasing prevalence of malaria-associated anaemia and mortality in African children is attributed partly to the increase in antimalarial drug resistance (Hedberg et al., 1993; Slutsker et al., 1994; Trape et al., 1998; Bjorkman 2002). One of the consequences of drug resistance is poor haematological recovery (Bloland et al., 1993; Verhoeff et al., 1997; Ekvall et al., 1998). Failed treatment contributes to malarial anaemia by persistence of parasitaemia, recrudescent infections, and continued bone marrow suppression. Consequently, the incidence of severe anaemia requiring admission and treatment with blood transfusion has increased globally (Greenberg et al., 1988; Zucker et al., 1996). In some settings 20 to 50% of pediatric admissions received transfusion (Greenberg et al., 1988; Lackritz et al., 1992).

Chloroquine is currently is a failed monotherapy in sub Saharan Africa (Koram K.A et al. 2005) and most parts of the globe and ACT’s are now recommended (WHO 2002). Notwithstanding, Chloroquine has been much favored for its affordability. Studies have shown in Malawi where
Chloroquine was banned that it is possible for it to be reintroduced ideally in combination with other antimalarials where affordable alternatives are nonexistent. The study showed that after banning the use of Chloroquine and ensuring strict compliance for a long time, Chloroquine resistant *P. falciparum* is now being sensitive again and could be reintroduced in combination with other drugs for a more effective therapy. (Kublin *et al* 2003).

The prevalence of Chloroquine-resistant *P. falciparum* malaria has been increasing in sub-Saharan Africa and parts of South America over the last 2 decades, and has been associated with increased anaemia-associated morbidity and higher mortality rates. The proportion of Chloroquine treatment failures (combined early and late treatment failures) is higher in the central-eastern Africa (Tanzania, 53%; Uganda, 80%; Zambia, 57%) and Ecuador (54%) than in Ghana (36%). Analysis showed that most of the children at baseline were anaemic (Hb>110g/L) and Hb levels declined from day zero to day seven from a mean level of 92.6g/L to 87.2g/L which then began to increase from 95.5 to 100.9g/L on day 14 and 28 respectively (Hamer D.H. *et al.* 2002).

A study in Tanzania showed no sex differences in mean haemoglobin p=0.26 or prevalence of anaemia at any level but there was difference in age groups in children under five. More than three quarters of the children had some degree of anaemia. A different study in the same region also showed that, Chloroquine treatment for uncomplicated childhood malaria in an area with drug resistance gives an early treatment failure which aggravates anaemia. The evidence that Chloroquine treatment could not prevent an exacerbation of anaemia was evident in the fall of haemoglobin levels after day 3. This was significantly greater in children with early treatment failure. Those with late treatment failure and an adequate clinical response, and the absence of
any haematological improvement at follow-up in children receiving Chloroquine alone, even in true treatment successes (Ekvall H. et al, 1998).

Without an effective vaccine for the prevention of malaria, a fundamental component of the strategy for the control of this disease is based on prompt and effective treatment. Due to the high resistance level of *P. falciparum* to the most affordable drugs such as Chloroquine and Sulfadoxine–pyrimethamine, Artemisinin-based combination therapies are presently used in many countries including Ghana or are being developed for registration.

One Artemisinin combination therapy that is drawing a certain degree of interest is the combination of Artesunate (a short half-life drug) plus Amodiaquine (a long half-life drug that is presently used in loose combination in many countries). The short half-life drug achieves substantial and rapid parasite killing, while a high concentration of the long half-life drug kills off the remaining malaria parasites. In addition to the effectiveness of seventy two hours of treatment (rapid clearance of fever and malaria parasites) in western and central Africa, where resistance to Amodiaquine is low, the combination of Artesunate plus Amodiaquine may delay or prevent the emergence of resistance to both drugs. (Bienvenu S. 2007). This invariably tells us that haemoglobin levels are supposed to be improved once the parasites are cleared from the blood preventing further depletion of the red blood cells in affected children. A study in Ghana to test the efficacy of Artesunate Amodiaquine alone showed a 99.8 % parasite clearance by 72 hours and significant improvements in the mean haemoglobin levels 14 and 28 days after treatment. Overall, the mean haemoglobin at enrolment of 9.58 g/dL improved to 10.15 g/dL at day 14 and to 10.96 g/dL on day 28 (p=0.001) among subjects. This enhancement was also seen among the different treatment outcome groups, with the most improvement seen in those who had Adequate Clinical and Parasitological Response (Koram et al 2008). This confirmed
previous studies carried out earlier by the same author who showed that mean haemoglobin level had improvement for both Chloroquine and Amodiaquine Artesunate from baseline to day 28 even though the improvements for Chloroquine was not significant (p=0.67).

Three categories for treatment failure (Early Treatment Failure, Late Clinical Failure, and Late Parasitological Failure) and one for treatment success (Adequate Clinical and Parasitological Response) have been used for classification of therapeutic response according to WHO guidelines (WHO 2003): These are defined as follows:

- **Early treatment failure (ETF)** in cases of development of severe malaria in the presence of parasitaemia on day 3 with axillary temperature =37.5°C parasitaemia on day 2 > day 0 irrespective of axillary temperature; parasitaemia on day 3 =25% of day 0; fever and parasitaemia on day 3.

- **Late clinical failure (LCF)**. Cases of development of danger signs or severe malaria after day 3 in the presence of parasitaemia; presence of parasitaemia and axillary temperature =37.5°C anytime from day 4.

- **Late parasitological failure (LPF)**. Cases of parasitaemia with axillary temperature <37.5°C on day 14 or 28 without previously meeting any of the criteria of ETF or LCF.

- **Adequate clinical and parasitological response (ACPR)**. Cases of absence of parasitaemia on day 14 or 28 irrespective of axillary temperature without previously meeting any of the criteria of ETF of LCF.

Treatment failure will help determine the sex differences in efficacy of Amodiaquine-Artesunate (AMQ/ART), Sulphadoxine-Pyrimethamine (SP), Artemether-Lumifantrine (AL) and Chloroquine (CQ) and related haemoglobin levels of children under five.
CHAPTER THREE

3.0 METHODS

3.1 Study Location

The original study was conducted at two sites namely, Hohoe and Navrongo. Hohoe Municipality is situated in the centre of the Volta Region. On to the north-west is Jasikan District and to the south is Ho Municipal. The Municipality houses part of the Akwapim-Togo ranges extending beyond the country’s eastern boundary all the way to Western Nigeria. The Republic of Togo borders the Municipality to the east, while to the west is Kpando District with Hohoe as its capital. Hohoe lies in the middle belt of the country with two rainy seasons – a major season from March/April to August/September and a minor one from October–November/December. Malaria occurs all year round but with some seasonal variation that closely follows the months of rainfall.

The therapeutic efficacy of Amodiaquine in the district is not known. However, clinical and parasitological response to Chloroquine in 2001 was estimated to be about 68% (Koram et al 2003).

Navrongo is located in the Kassena – Nankana District (KND) in the northern region of Ghana. The KND lies within the Guinea Savannah woodland of northern Ghana and are among the districts with the worst social economic status in the country. The district covers a land area of 1675 square kilometers and shares borders with Burkina Faso in the Upper East region of Ghana. The KND has a population of 140000 people living in approximately 13000 dispersed compounds. The KND is one of the most arid districts in northern Ghana with a long dry season punctuated with only three months of rains and average temperatures ranging between 20 and 40 degrees Celsius (Parashar et al 2009). Malaria transmission here is markedly seasonal with most
infections occurring during the period of the rains. Adequate clinical and parasitological response rate for Chloroquine in the district was 63% in 2001 (Koram 2003).

3.2 Study Design

The original study design was a randomized open label comparative study of four antimalarial including ACT’s in the treatment of uncomplicated malaria in Ghanaian children. This study is a secondary analysis of sex difference in the efficacy of antimalarial drugs related to changes in the haemoglobin levels in Ghanaian children under five.

3.3 Sample Size and Power

With an estimated PCR-corrected cure rate of 93% for ACTs and 69% for Chloroquine or Sulphadoxine-Pyrimethamine, at 80% power, 95% confidence interval and a sample ratio of 1:1, a sample size of 49 children per arm was needed to detect a difference in cure rate of 81%. Allowing for a dropout rate of 10%, a minimum of 54 patients were to be recruited for each arm of the study (Koram et al 2005).

3.4 Research Questions

➢ Are there differences in therapeutic response between males and female who received an antimalarial?

➢ Which antimalarial drug has a better clinical response?

➢ Are there any sex differences in haemoglobin concentrations before, during and after treatment?
3.5 Outcome Measures

The outcome measure for efficacy was adequate clinical and parasitological response at day 14 and 28. Haematological recovery was assessed by comparing haemoglobin (Hb) levels with the WHO standard (ref) at days 0, 7 and 28 of drug administration. These outcome measures were compared between males and females.

3.6 Statistical Analysis Plan

3.6.1 Data Description and Extraction

The original data was in SPSS software and was transferred using to STATA 11.0 Software for analysis. Children’s baseline characteristics were explored in the dataset using simple descriptive methods such as summary statistics and frequency distributions.

All variables to be used were identified and described. The main variables used were clinical response, Hb at day 0, day 7 and 28, treatment groups, temperature, parasite density, age and sex.

Data quality checks were performed to screen for any outliers and missing values. Missing values were only reported at baseline and not in subsequent analysis.

3.6.2 Statistical Analysis

The baseline data that were analyzed include age (months), sex, haemoglobin levels, parasite counts and temperature. Pearson Chi square test, analysis of variance and paired t-test were done for all treatments and days of treatments. Comparison of means and mean difference were done where it applies stating p values and confidence intervals. Statistical significance level was set at alpha 0.05 (p<0.05).
Anaemia was categorized into haemoglobin levels greater than 11g/dL as normal and less than 11g/dL as anaemic according to WHO criteria while age was in less than 12months, 12 to 24 month, 25 to 48month, 48 to 59 months for exploratory purposes.

3.7 Analysis of Data
STATA version 11.0 was used during the data analysis. Simple proportions, mean/median, standard deviations and confidence intervals were used to estimate the haemoglobin levels and efficacy of the drug using WHO protocol for assessment of efficacy in malaria endemic areas.

3.8 Limitations
This is a secondary data analysis and was therefore limited to what was available in the database. Also, missing values caused an imbalance in the treatment arms making them uneven and subject to bias. There were also still cases of drop outs in the various arms further worsening the situation.

3.9 Ethical Considerations
In the original study, approval was sought from The WHO Secretariat Committee on Research Involving Human Subjects (SCRIHS) and the Institutional Review Board of the Noguchi Memorial Institute for Medical Research, University of Ghana.

In this study, approval for this study was sought from the Ghana Health Service Ethical Review Committee of the Research and Development Division of the Ghana Health Service and approval has been solicited from the principal investigator of whom the data was acquired.
3.9.1 Privacy and Confidentiality

In the original study, written, signed/thumb printed and dated informed consent was used to obtain the consent of mothers/care givers. Each mother was informed of the objectives, methods, anticipated benefits and potential hazards of the study. They were also informed that they were at liberty to withdraw their children from the study at any time without penalty.

In this study, in order to protect the privacy and confidentiality of participants no study identifications, names or any information traceable to subject was used in the analysis.
CHAPTER FOUR

4.0 RESULTS

4.1 Background characteristics of study participants

The dataset contained a total of 168 observations that were originally randomized into four treatment group. A total of 111 (66.1%) observations were in all the treatments and 57 (33.9%) observations were with either missing or incomplete. Two monotherapies and two ACT’s were used as treatments (Table 1).

The characteristics of children at enrolment are presented on Table 1. The mean age was highest in the AL group 38.6 months (SD±9.9). This was because of the WHO recommendation of it being given to children above 10kg who are definitely older (WHO 2001; Koram et al 2005). Mean temperature was also highest in the SP group (M=38.5, SD±8), p=0.326. Mean haemoglobin level was highest in AL group 9.6g/dL, (SD±1.1) while the least was in the SP group 8.7g/dL, (SD±1.6), p=0.273. Overall, majority were females 55.36 % (93/168).

Parasite density at baseline was highest in the AL group 32,230.5 parasites/uL. Further comparison by sex showed that males in the AL group had the higher parasite densities 39,670.56 parasites/uL. Among females in the different groups, SP recorded the highest parasite densities 34,606.42 parasites/uL while the least was in the CQ group with 28,502.5 parasites/uL (Table 1).
### Table 1: Baseline characteristic of children in treatment arms

<table>
<thead>
<tr>
<th></th>
<th>CQ N=36</th>
<th>SP N=29</th>
<th>ART/AMQ N=27</th>
<th>AL N=19</th>
<th>INCOMPLETE DATA N=57</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in months (Mean/±SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26.5 (±13.8)</td>
<td>31.1 (±13.3)</td>
<td>28.8 (±13.5)</td>
<td>38.6 (±9.9)</td>
<td>30.9 (±13.8)</td>
</tr>
<tr>
<td>Female</td>
<td>24.8 (16.7)</td>
<td>31.1 (12.1)</td>
<td>30.5 (13.9)</td>
<td>39.7 (9.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Parasite Density/uL (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27664.5 (17434.24, 43897.78)</td>
<td>25064.14 (14334.58, 43824.86)</td>
<td>23453.4 (15551.19, 35371.06)</td>
<td>32230.51 (17062.01, 60884.11)</td>
<td>20619.27 (14639.68, 29041.22)</td>
</tr>
<tr>
<td>Female</td>
<td>20670.56 (12582, 57663.9)</td>
<td>34606.42 (15220.2, 78685.2)</td>
<td>32399.21 (21190.91, 49535.8)</td>
<td>29051.37 (11356.58, 74316.57)</td>
<td>22201.03 (13672.11, 36050.47)</td>
</tr>
<tr>
<td><strong>Temperature °C (Mean/±SD)</strong></td>
<td>37.2 (±6.3)</td>
<td>38.5 (±8)</td>
<td>38.3 (±7)</td>
<td>38.1 (±6)</td>
<td>38.3 (±7)</td>
</tr>
<tr>
<td><strong>Haemoglobin/g/dL (Mean/±SD)</strong></td>
<td>8.9 (±1.7)</td>
<td>8.7 (±1.6)</td>
<td>9.1 (±1.5)</td>
<td>9.6 (±1.1)</td>
<td>8.8 (±1.7)</td>
</tr>
</tbody>
</table>
4.2 Sex differences in the efficacy of antimalarial by clinical response on day 14

The complete available data for assessment of clinical response was 104 children. The data was used for the classification by clinical response into Early Treatment Failure (ETF), Late Parasitological Failure (LPF), Late Clinical Failure (LCF) and Adequate Clinical and Parasitological Response (ACPR). This further reduction in figure from the 168 baseline occurred due to missing values, incomplete data and those not accessed. 55 children were classified as ACPR even though they were in no treatment group. 9 participants were not accessed. Two monotherapies and two ACT’s were used. The treatment groups were distributed as shown in table 2.

At day 14 the cure rate/Adequate Clinical and Parasitological Response (ACPR) for evaluable patients was highest among female in the AL group 72% (13/18) (Table 2). For the monotherapies males recorded higher cure rate/ACPR 20.59% (7/34) and 46.15% (12/26) for CQ and SP respectively than their female counterparts while it was the reverse in the ACT’s with females recording 72.2% (13/18) and 53.85% (5/18) for AL and ART/AMQ respectively. Non of the treatment groups was statistically significant.

All who had Chloroquine (CQ) had Late Parasitological Failure (LPF) and Late Clinical Failure (LCF). Early Treatment Failure (ETF), was same for both sexes 5.9 % (2/34) and LCF was higher in males 5.9% (2/34) compared to 2.9% (1/34) in female. LPF was highest in only the two monotherapies. In both groups, males recorded the higher percentages in the CQ group 23.53% (8/34) and females were the least for SP group 7.69% (2/26). All differences were not statistically significant for any of the treatment groups or responses (Table 2).
Table 2: Sex differences in efficacies of antimalarials on day 14

<table>
<thead>
<tr>
<th></th>
<th>CQ (N/%)</th>
<th>SP (N/%)</th>
<th>ART/AMQ (N/%)</th>
<th>AL (N/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34(32.7)</td>
<td>26(25.0)</td>
<td>26(25.0)</td>
<td>18(17.3)</td>
</tr>
<tr>
<td>MALE</td>
<td>19(55.88)</td>
<td>15(57.69)</td>
<td>12(46.15)</td>
<td>5(27.78)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>15(44.22)</td>
<td>11(42.31)</td>
<td>14(53.85)</td>
<td>13(72.22)</td>
</tr>
<tr>
<td>ETF</td>
<td>2(5.90)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>LCF</td>
<td>2(5.90)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>LPF</td>
<td>8(23.53)</td>
<td>3(11.54)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>ACPR</td>
<td>7(20.59)</td>
<td>12(46.15)</td>
<td>12(46.15)</td>
<td>5(27.8)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.973</td>
<td>0.907</td>
<td>0.520</td>
<td>0.657</td>
</tr>
</tbody>
</table>

**TERMS**

ETF - early treatment failure, LCF – late clinical failure, LPF-late parasitological failure, ACPR-adequate clinical and parasitological response.
4.3 Sex differences in the efficacy of antimalarial by clinical response on day 28

The numbers and proportions used for evaluation of day 28 clinical response was the same as those used to evaluate day 14 (Table 3). A total of 104 children’s data that had a treatment group were used for the classification by clinical response into ETF, LPF, LCF and ACPR.

Clinical response at day 28 showed a general decrease in cure rate/ACPR of all antimalarials against the different sexes compared to day 14. Mono-therapies had low cure rates, CQ recorded the least cure rate which was same for both sexes 8.8% (3/34) while SP was highest 23.1% (6/26) in males.

Among ACT’s females, cure rates were better; 50% (9/18) and 30.8% (8/26) for AL and ART/AMQ respectively. Nonetheless, they were still less than the day 14 classification. The AL group recorded the high efficacy even though there was a decrease of 22.2% while the least was CQ showing a decrease of 11.29% in males and 8.8% for females meaning males still had more protection than females.

There was also a general increase in LPF’s across all sexes and antimalarials compared to day 14 (Table 3). The highest increase was in CQ males 32.4% (11/34) with difference of 8.9% and the least in AL female 11.1% (2/18) which has no LPF at day 14.

For LCF females recorded the highest efficacies in SP 7.69% (2/26), ART/AMQ 11.54% (3/26) and AL 11.1% (2/18) but not CQ 5.9% (2/34). No males experienced LCF in ART/AMQ and AL same at day 14 and there was no statistical difference in sexes (Table 3). None of the treatment groups was statistically significant for sex.
Table 3: Sex differences in efficacies of antimalarials on day 28

<table>
<thead>
<tr>
<th></th>
<th>CQ (N/%)</th>
<th>SP (N/%)</th>
<th>ART/AMQ (N/%)</th>
<th>AL (N/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34(32.7)</td>
<td>26(25.0)</td>
<td>26(25.0)</td>
<td>18(17.3)</td>
</tr>
<tr>
<td>MALE</td>
<td>19(55.88)</td>
<td>15(57.69)</td>
<td>12(46.15)</td>
<td>5(27.78)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>15(44.22)</td>
<td>11(42.31)</td>
<td>14(53.85)</td>
<td>13(72.22)</td>
</tr>
<tr>
<td>ETF</td>
<td>2(5.9)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>LCF</td>
<td>3(8.82)</td>
<td>1(3.85)</td>
<td>2(7.69)</td>
<td>3(11.54)</td>
</tr>
<tr>
<td>LPF</td>
<td>11(32.4)</td>
<td>8(23.53)</td>
<td>6(23.1)</td>
<td>1(5.55)</td>
</tr>
<tr>
<td>ACPR</td>
<td>3(8.82)</td>
<td>6(23.08)</td>
<td>7(26.92)</td>
<td>4(22.2)</td>
</tr>
<tr>
<td></td>
<td>0.977</td>
<td>0.598</td>
<td>0.180</td>
<td>0.646</td>
</tr>
</tbody>
</table>

TERMS

ETF- early treatment failure, LCF – late clinical failure, LPF-late parasitological failure, ACPR-adequate clinical and parasitological response.
4.4 Sex differences in mean haemoglobin levels by treatment

A total of 166 observations were in the dataset with Hb values at baseline, 34.3% were missing values and 2 children were not assessed. One hundred and nine (109) Hb’s of children were analyzed; 67.9% (74/109) were males and 84.4% (92/109) females. A median of 8.9 g/dL and standard deviation (SD) of ±1.6 with minimum value of 5.0g/dL and maximum value of 14.1g/dL were used for the assessment. Fifty seven (57) cases of incomplete data were excluded from the analysis.

Hb’s had increased considerably comparing before treatment at day 0, and after treatment at day 28. Female Hb’s were higher than male Hb’s after treatment at day 28, and day 0 and day 7 comparison showed improvements in only females. Using WHO reference of <11.0g/dL Hb for anaemia, it was observed that anaemia was prevalent in the population irrespective of time treatment was taken. But using internal reference values of <8.1 for male and < 7.8 for female as anaemic, (Dooso et al 2010) a drastic improvement in Hb levels after antimalarial treatment was observed (See Figure.1).

4.5 Prevalence of anaemia in all treatment groups

At day 0, Hb classification according to WHO classification (<11g/dl) showed that all males were anaemic in the ACT’s group but not in monotherapies (See Fig 2). In the CQ female group 93.75% (15/35) were anaemic and a total prevalence of 88.1% cases were observed but none of the groups showed any statistical significant differences. About 70% (62/94) of all males in all treatment groups were anaemic while 43% (40/94) of all female were also anaemic. A total of 88.3% in both sexes and treatment groups were anaemic by day 7 assessment (See Fig. 1).
By day 28 AL marked the highest haematological recovery within its group with 75% (3/4) male and 80% (8/10) females becoming normal. The least improvements were in the ART/AMQ males 33% (2/6). In totality 43% (22% male and 20.4% female) were still anaemic after day 28 treatment. The differences observed were not statistically significant (See Fig. 1).

Figure 1. Overview of sex differences in Hb levels of all treatments

WHO cut off for anaemia (<11g/dl)

Central Ghana cut off (Male) (<8.1g/dl)

Central Ghana cut off (Female) (<7.8g/dl)

(Dooso et al. 2010)
At day 0, mean Hb levels was highest in the AL female group ($M=9.6 \ SD\ 1.2$) and least in the CQ female ($M=8.4 \ SD\ 1.7$).

At day 7, mean Hb was still highest in the AL female group 10.2 g/dL SD 1.5 and least in CQ male group 8.7 g/dL SD1.4. Sex difference in Hb at day 7 was statistically significant $F(3,\ 45)=3.26\ (P=0.030)$ in AL female group when ANOVA was done for all treatments. Further test to confirm the difference with bonferroni showed a borderline difference between CQ and AL ($M=11.15 \ SD\ 0.5$) and ($M=9.3 \ SD2.9$) $P=0.049$.

At day 7, CQ males had improved to 9.3 g/dL and mean Hb in AL males group became 11.2 g/dL better than female Hb 10.3 g/dL. The least haematological recovery at day 7 was in the CQ female group 8.8 g/dL despite the improvement from Hb level of 8.4 g/dL at day 0. Sex differences for all treatments were performed using a Pearson chi square test. Males had a $P$ value of 0.047 but further test showed no difference between treatments.

On day 28 there was a general increase in mean Hb levels in all treatment groups (Figure 2). Overall, males recorded ($M=10.5,\ SD\ 1.78$) and females ($M=11.07,\ SD\ 1.34$) with $F$ test of $F(3,18)=1.12, p=0.368$ and $F(3,23)=1.36,\ p=0.281$ respectively. The highest increases were recorded in the female AL group ($M=11.69,\ SD\ 0.9$) while the least were in the CQ males ($M=9.3\ SD\ 2.9$) (Figure 2).
Figure 2: Sex differences in the Hb level of treatment groups.

SEX DIFFERENCES IN HB LEVELS OF TREATMENT GROUPS

Hb levels (g/dL)

male female male female male female male female

CQ ART/AMQ SP AL

day 0 hb day 7 hb day 28 hb

FIG2
4.6 Comparing sex differences in Haemoglobin levels by treatment (day 0 and 7)

Using a paired t-test, showed that mean Hb at day0 which was 8.75g/dL (SD 1.4) had improved by day7 to 8.90g/dL (SD1.3) in male. Females had mean Hb at day 0 improved from 9.0 g/dL (SD 1.6) to 9.5g/dL (SD1.3) by day 7 but increase in females were significant p<0001 while the males were not p=0.37. Further comparison showed statically significance figures for only AL group males and females. Males Hb at day 0, 9.3g/dL (SD 0.6) became better by day 7 10.03 g/dL (SD 0.5), t (2)= -4.6, p=0.044. This was similar to improvements in AL group mean female Hb at day 0 (M=9.6 SD1.3) and day7 (M=10.3 SD1.5), t (12)= -3.088, p=0.0094 but all hematological recoveries were not more than 1g/dL (Table 4)

4.7 Comparing Sex Differences in Haemoglobin Levels By Treatment (Day 0 And 28)

All antimalarials showed increase in Hb more than 1g/dl for all treatment groups and sexes except CQ. Both ACT’s had statistically significant difference between day 0 and day 28. ART/AMQ were better generally but male group had better improvements in Hb at day 0, 8.6g/dL (SD1.0) and day 28, 10.5g/dL (SD1.4), t(5)= -3.369, p=0.02 than females at day 0, 9.59g/dL (SD1.3) and day 28, 10.94g/dL (SD1.53), t(7)= -3.0432, p=0.0188. Mean Hb for AL male group at day 0 was less 9.3g/dL, (SD0.5) than day 28, 11.1g/dL, (SD0.5), t(3)= -1.83, p=0.0177 and females were also lesser 9.8g/dL,(SD1.4) compared to day 28 11.7g/dL,(SD0.9), t(9)= -6.0144, p=0.0002 respectively. Among the monotherapies only SP group males had a statistically significant difference between day 0, 9.5g/dL, (SD1.2) and day 28, 10.97g/dL (SD1.3), t(6)= -2.7754, p=0.0322. (Table 4)
4.8 Comparing sex differences haemoglobin levels by treatment (day 7 and 28)

Changes in Hb between day 7 and day 28 were generally higher compared to day 0 and 7 and day 0 and 28. Among the monotherapies, CQ males group was not statistically significant \( p=0.947 \) but females in the CQ group was statistically significant \( t(3) = -3.5746, p=0.0374 \) with increase of about 2.5g/dL in Hb level. SP male group was also statistically significant \( p=0.0027 \) but female was not. Among ACT’s the strongest association was among females in AL group \( p=0.003 \) but not males \( p=0.1900 \) and ART/AMQ was not significant in both sexes (Table 4).
Table 4: Changes in Hb levels by antimalarial, day of assessment and sex

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean Hb (g/dl)</th>
<th>Standard deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td><strong>CQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Day 7</td>
<td>29</td>
<td>9.1/8.7</td>
<td>8.5/8.8</td>
<td>1.6/1.4</td>
</tr>
<tr>
<td>Day 0/Day 28</td>
<td>9</td>
<td>9.1/9.3</td>
<td>7.9/10.7</td>
<td>1.1/3.0</td>
</tr>
<tr>
<td>Day 7/Day 28</td>
<td>9</td>
<td>9.2/9.3</td>
<td>8.2/10.7</td>
<td>1.2/2.9</td>
</tr>
<tr>
<td><strong>ART/AMQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Day 7</td>
<td>25</td>
<td>8.8/8.7</td>
<td>9.7/9.9</td>
<td>1.1/1.4</td>
</tr>
<tr>
<td>Day 0/Day 28</td>
<td>14</td>
<td>8.6/10.5</td>
<td>9.6/10.9</td>
<td>1.0/1.4</td>
</tr>
<tr>
<td>Day 7/Day 28</td>
<td>13</td>
<td>8.6/10.5</td>
<td>9.7/10.7</td>
<td>1.14/1.4</td>
</tr>
<tr>
<td><strong>SP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Day 7</td>
<td>24</td>
<td>8.8/9.1</td>
<td>8.7/9.1</td>
<td>1.6/0.9</td>
</tr>
<tr>
<td>Day 0/Day 28</td>
<td>12</td>
<td>9.5/11.0</td>
<td>9.2/10.4</td>
<td>1.2/1.3</td>
</tr>
<tr>
<td>Day 7/Day 28</td>
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<td>9.7/11.1</td>
<td>8.9/10.4</td>
<td>0.8/1.4</td>
</tr>
<tr>
<td><strong>AL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0/Day 7</td>
<td>16</td>
<td>9.3/10.0</td>
<td>9.6/10.3</td>
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<td>16</td>
<td>10.0/11.6</td>
<td>10.35/11.7</td>
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</tbody>
</table>

Ω- statistically significant after comparing days of treatment
CHAPTER FIVE

5.0 DISCUSSION

5.1 Summary

This was a secondary analysis of data originally collected in a trial to compare antimalarial efficacy of four antimalarials among children under 5 years with uncomplicated malaria. The original study was conducted in Navrongo and Hohoe in 2003 to support the National Malaria Control Programme in its review of the antimalarial drug treatment policy in Ghana. This was at a time the effect on Chloroquine on parasitological cure rate had markedly declined from 91% (Afari et al 1992) to 38.2% (Koram et al 2005). The study did not however look at the sex differences in haemoglobin and treatment efficacy which this study seeks to explore. This secondary analysis was however limited to variables (age, sex, Hb and treatment failures) collected from the original study. Incomplete variables also accounted for about 34% of the data.

5.2 Sex differences in antimalarial efficacy

The current spread of parasite resistance to frequently used antimalarials is posing a great challenge to the treatment and control of malaria in Africa and other parts of the world. Its is believed that, knowledge on the sex differences in efficacy of antimalarials and Hb levels will help in the better diagnosis and management of the disease. Response to these antimalarials based on the sex differences were compared between the different antimalarials (monotherapies and ACT’s) and day 14 and day 28 clinical assessment.

This present study had monotherapy cure rates/ACPR in females was generally lower than males after day 14 and 28 follow up.
The mean age at baseline less in female 24.8 months, \((SD 16.7)\) than males 28.1 months \((SD 10.81)\), making them more vulnerable to the disease. Females in both monotherapies (CQ and SP) were burdened with higher geometric mean parasite density (Table1) respectively than males and the other groups which further compromised their ability to recover. This could be attributed to the inability of the monotherapies to effectively lower the parasite density.

The ACT’s cure rates were highest in the female AL group (72.2%) and the lowest cure rates were in the males of the same group (27.8%) at day 14 and also at day 28(69.23% for females and 30.8% for males). This could also be attributed to the fact that parasite density at baseline was highest in the AL males (95%CI) 39670.56 (16730.36 - 94065.68) giving them the least cure rate among the ACT’s. Also, AL female group were older than the other groups with mean age of 39.7 months (SD9.0) and could be the reason why they had better cure rates than the other age groups. They were mostly between the ages of 25 to 28 months group.

In the ART/AMQ group, despite the highest parasite density at baseline among females it still had a better cure rate at both day 14/28 assessment i.e. 53.33% and 53.85% respectively.

There were better cure rates for males than females using mono therapies while there were better cure rates for females using ACT’s than males. The superiority of ACT’s over monotherapies have been supported by results from this study even though it is evident that efficacies are reduced across board when taking sex differences into account.

Notwithstanding the differences observed, there was no statistically significant difference observed between sexes or treatments in any of the clinical assessment days.
5.3 Prevalence of anaemia in study population

The overview of Hb levels by sex reiterates the fact that 39% of children younger than 59 months in developing countries are anaemic and 75% of children in sun Saharan Africa are anaemic (WHO 2001). Prevalence of anaemia in the present study according to the WHO standard (<11g/dl) was 88.3%, 88.5 and 42.9 before during and after treatment respectively with antimalarial. This was consistent with other findings from Kenya by Obonyo C.O et al 2003 where 80% were found to be anaemic becomes a public health problem when its occurrence of low Hb in a population is greater than 5% (WHO 2001).

Most children before during and after treatment with antimalarial were all anaemic which cast fears about the reliability of some of these reference values in different populations as suggested by Dosoo and colleagues and Songül and colleagues. The International Federation for Clinical Chemistry (IFCC) recommends that each laboratory establish reference values using the population it intends to serve (Dosoo et al 2010; DeMaeyer et al 1985). This implies that diagnostic criteria for anaemia is usually poorly defined in males and females under 5years and the high prevalence of anaemia calls for a reevaluation of anaemia for different population as suggested by the WHO. Using reference values from central Ghana by Dosoo at al 2010 defined the cut off for males as 8.1g/dl and 7.8 g/dl for females (FIG1) under five years, which rather showed that before during and after treatment, very few Ghanaian children were really anaemic and their Hb became better after antimalarial treatment irrespective of type of antimalarial (See Figure1).
5.4 Sex differences haemoglobin levels before, during and after antimalarial treatment

AL group by far, proved to be the best in terms of improvement in Hb levels by day 28 despite the fact that they had a high parasite density at baseline. The high parasite density could have hindered the ability of Hb to improve to as high as 11.7g/dl especially within females, using the three permutated comparison of days 0, 7 and 28. All comparison was statistically significant for males and females in AL except males in the day 7 and 28 comparison probably due to the fact that they were few in numbers and parasite density was very high in the males (39670.66/uL) Table1.

In the ART/AMQ group, day 0 and day 7 comparisons did not indicate much difference in Hb levels and was not even statistically significant in both males and females. But there was significant improvement in haematological recovery after day 28 which is consistent with findings in Ghana that showed improvement in Hb which was attributed to parasite clearance(Koram et al 2008) This relieved pressure on the red blood cells and the bone marrow due to malaria infection( Helleberg et al 2005) Comparing it to AL it was slower in response to hematological recovery in the first week of treatment even though it is as effective as AL in parasite clearance. There is no doubt that ACT’s hold a tremendous future in terms of malaria treatment and control but few data exit about sex difference in efficacy, dosing, acceptability and tolerability thus more should be done to study these in larger populations.

Among monotherapies CQ was not statistically significant in any of the day comparison (Table 3) except females compared between day 7 and 28 which suggest that the hematological recoveries recorded were probably due to the fact that there were fewer females and most of them experience ACPR than males.
SP was rather very much effective in Hb recovery on day 7 and 28 with a statistical significance than CQ in both males and females but the differences in male were more than female. This evidence confirms the superiority of SP over CQ as a monotherapy (Oduro et al 2005).
CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

There was no significant sex difference in efficacy of any of the antimalarials; Amodiaquine-Artesunate (AMQ/ART), Sulphadoxine-Pyrimethamine (SP), Artemether-Lumefantrine (AL) and Chloroquine (CQ), for the treatment of malaria in Ghanaian children in this study. The ACT’s appeared to show some level of better treatment outcomes especially in cure rate of females compared to the monotherapies where a lot of treatment failures occurred mostly among males. Notwithstanding, none of the treatment groups were statistically significant either at day 14 or 28 classification.

Most of the children were still anaemic according to WHO (<11g/dL) after treatment with antimalarial even though there was improvement in Hb levels compared to before treatment. AL proved to be the most effective antimalarial with respect to haematological recovery while CQ was the least. AL showed a significant difference in haematological recovery for both male and female in all the days compared except for males on day 7 and 28 comparison.
6.2 Recommendations

In response to the fact that malaria and anaemia are major causes of morbidity and mortality in children, the need for regular efficacy monitoring of recommended antimalarial is required to detect cases of resistance.

Chloroquine has been out of use since 2005 till date and this study further demonstrates how this treatment could exacerbate the burden of malaria in children thus more education should be done to prevent people from patronizing the product since it may still be in the hands of some private operators in the country.

Furthermore the use of local haematological reference values is encouraged for various parts of the country to promote better evaluation of treatment outcomes.
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