

**SCHOOL OF PUBLIC HEALTH
COLLEGE OF HEALTH SCIENCES
UNIVERSITY OF GHANA**

**A COMPARATIVE STUDY TO ASSESS THE EFFECT OF
ANTIMALARIALS ON THE HEMOGLOBIN LEVELS OF CHILDREN
IN THE KASSENA NANKANA DISTRICT OF GHANA**



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DECLARATION

I, Shamima Gbepena declare that except for the other people's work which I have duly acknowledged in this dissertation proposal. This dissertation is the result of my own original research carried out for the award of a Master of Science (Clinical Trials) degree. This dissertation has not been presented elsewhere either in whole or in part for another degree.

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Date



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Prof. Kwadwo Ansah Koram

Academic Supervisor

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Date

DEDICATION

This piece of work is dedicated to the almighty GOD for his protection and blessing throughout my program. I also dedicate this work to my mom and sister, Princess Roselyn Anamolga.



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Unceasing thanks go to the almighty GOD for his steadfast love and blessing throughout this program; your grace is indeed sufficient.

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LIST OF ACRONYMS

ACT	Artemisinin based Combination Therapy
AQ	Amodiaquine
°C	Degree Celsius
CM	Cerebral Malaria
CQ	Chloroquine
HIV	Human Immunodeficiency Virus
IPT	Intermittent Preventive Treatment
Hb	Hemoglobin
KND	Kassena Nankana District
RBC	Red Blood Cells
SP	Sulphadoxine-Pyrimethamine
µl	Microlitre
WHO	World Health Organisation

ABSTRACT

Background: Malaria associated anemia is a major problem in malaria endemic areas, especially among children five years and below. Studies have shown that treating children with uncomplicated malaria with efficacious antimalarial drugs clears parasites, which prevents the depletion of red blood cells and thereby improving the Hb concentration levels. No study has been conducted in the Kassena-Nankana District of northern Ghana to determine the effect of antimalarial on the Hb of children which is a malaria endemic area.

Method: The study is secondary data analysis of a comparative open label efficacy study which was conducted at a time that chloroquine was failing in terms of parasitological cure. 351 children aged five and below were randomized into the primary study with AQ (116), CQ (120) and SP (114). This current study used paired t-test and unpaired t-test to compare mean Hbs in the various treatment groups. The primary objective of this study was to determine the effect of treating children with uncomplicated malaria with antimalarial drugs on their Hbs.

Results: Generally mean Hbs in the various treatment groups declined on day 7 as compared to day 0 and also improved on day 28 as compared to day 0. Mean Hb level increased significantly on day 28 for AQ (0.65g/dl) with p-value 0.006 and SP (0.8g/dl) with p-value 0.001, but did not significantly improve for CQ (0.38g/dl). Males performed better in terms of improvement in mean Hb than females, with SP group (0.82g/dl) recording the highest improvement as compared to CQ (0.66g/dl) and AQ (0.18g/dl). Age group 13-36 months generally had the highest improvement in mean Hb with SP (0.82g/dl) group recording the highest in that age group as compared to AQ (0.52g/dl) and CQ (0.44g/dl).

Conclusion: It is clear that prompt and effective treatment of malaria with effective fast-acting antimalarial drugs rapidly reduces symptomatic parasitemia and this allows red blood cells numbers to be restored thereby improving the hemoglobin level and consequently preventing anemia.

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Malaria remains an important health problem and anemia, which is an indication of reduction in hemoglobin level, is a common and a serious complication of *Plasmodium falciparum* infection. Anemia is a frequent complication of malaria in many parts of the world particularly in malaria endemic areas, and chronic anemia negatively affects physical and cognitive development (Ojukwu et al., 2010). *Plasmodium falciparum* infection depletes red blood cells (RBCs) as the parasite reproduces in the body with consequent destruction of RBCs with each sporogonic cycle. Malaria-related anemia (hemoglobin level < 11 g/dL) affects an estimated 1.5 to 6 million African children especially children less than five years, with a case fatality rate of 15% (Murphy and Breman, 2001). In areas of high malaria transmission like KND, young children bear the burden of malaria and in these settings one of the commonest presentations of malaria is severe anemia. Malarial anemia is considered to develop through increased destruction or reduced production of red blood cells or a combination of both processes causing reduction in hemoglobin level. However, the principal pathogenic mechanism is incompletely understood (Von seidlein et al., 1998).

A study of malaria associated anemia in the Kassena Nankana District of Ghana of young children 6–24 months old revealed that 22% of those sampled at the end of the wet season (November 1996), a time corresponding to agricultural and nutritional abundance, had hemoglobin (Hb) concentrations < 6.0 g/dL. In contrast, a survey of the same age cohort 6 months later at the end of the dry season, and at a time of dwindling food supply, found that only 1% of the children fell into this category of severe anemia (Hb < 6.0 g/dL). (Koram *et*

al., 2000) With entomological inoculation rates in non-irrigated and irrigated sectors estimated to be, respectively, 72 and 800 infective bites per person-year (Koram et al., 2003), and a clear pattern of malaria deaths that reflected rainfall, it was reasoned that anemia trends in this vulnerable age group were primarily influenced by the intensity of malaria transmission and that dramatic troughs and peaks of severe anemia are regular seasonal events. This indicates that more than half of all the anemia cases in the KND are malaria related; therefore anemia could be prevented in this area by early treatment of malaria with efficacious antimalarials.

Also, studies in east Africa have shown that *P. falciparum* malaria and iron deficiency account for much of the anemia seen in young children (Menendez et al., 1997) and (Amukoye et al., 1997). One randomized study revealed that approximately 60% of anemia in infancy could be prevented by antimalarial chemoprophylaxis, illustrating the importance of malaria as a cause of anemia in this setting (Menendez et al., 1997). The same study also found that iron supplementation reduced the incidence of anemia by about 30%. Therefore the main strategy for reduction of malaria-related anemia in Africa especially in malaria endemic communities is early diagnosis and institution of effective treatment (WHO, 2001). Several studies have reported the association of malaria and anemia and the beneficial effect of preventing anemia with antimalarial drugs by early treatment of malaria with efficacious drugs. However no randomized studies have been done to really ascertain the effect of treating uncomplicated malaria with antimalarials on the hemoglobin levels of children living in malaria endemic areas such as the KND of northern Ghana. The objective of this study was to determine the effect of treating children under five in the KND with antimalarials (chloroquine, amodiaquine and sulphadoxine pyrimethamine) on their Hb levels. It was hypothesized that effectively treating children with complicated malaria will stop red blood

cells destruction thereby improving the hemoglobin levels of the children. Therefore there will be a higher increase in Hb levels of the children taking the most efficacious antimalarial.

1.2 STATEMENT OF THE PROBLEM

Anemia (hemoglobin levels < 11g/dl) remains one of the most important public health problems in malaria endemic areas of sub-Saharan Africa. In Ghana severe anemia (haemoglobin level < 6 g/dl) is the primary cause of malaria deaths in areas of intense malaria transmission such as the Kassena- Nankana District of Northern Ghana (Koram et al., 2000). In this setting malaria associated anemia is the leading cause of pediatric admission and impatient pediatric deaths, even though blood transfusions are available. A study conducted in 2000 in the KND revealed that severe anemia, defined as Hb <6.0 g/dL, was 22.1% at the end of the high transmission season compared to 1.4% at the end of the low transmission season, confirming the association of malaria and anemia (Koram et al., 2000). There is therefore no doubt that there is a high level of malaria associated anemia in the KND.

The escalating prevalence of malaria-associated anemia and mortality in African children is attributed partly to the rise in antimalarial drug resistance (Premji et al., 1993, Slutsker et al., 1994, Trape et al., 1998, Bjorkman et al., 2002). WHO defines drug resistance as “the ability of a parasite strain to reproduce or to live in the presence of concentrations of a drug that normally demolishes parasites of the same species or stop their reproduction” (WHO, 2002a). One of the consequences of drug resistance is poor hematological recovery causing reduction in Hb (Ekvall et al., 1998). Failed treatment contributes to malarial anemia by persistent destruction of red blood cells by parasites which could lead to severe anemia and even death. Also where efficacious antimalarial drugs are not available to prevent depletion of red blood

cells, blood infusion may be required which may expose these children to HIV infection. (Zucker et al., 1996).

Studies conducted in Tanzania, Gambia and Liberia have shown that prompt treatment of malaria of malaria infection with effective, fast-acting antimalarial drugs rapidly reduces symptomatic high density parasitemia and clears parasites from blood, allowing red blood cells numbers to be restored, improving the hemoglobin levels and preventing the risk of anemia (Crawley et al., 2004, Niagia 2004, Schellenberg et al., 2003, Menendez et al., 1997). This study is analyzing data collected from a primary efficacy study of three antimalarial drugs at a time that chloroquine was failing to support the hypothesis that there will be higher improvement in the Hb levels in the group of children treated with the most efficacious drug among children in KND.

1.3 JUSTIFICATION

Malaria associated anemia, destruction of red blood cell by the malaria parasite, is an important problem in Ghana and in sub-Saharan Africa as a whole in which children under five years are mostly affected (Chandranmohan et al., 2005). Therefore effective treatment of uncomplicated malaria and intermittent preventive treatment of children under five using efficacious antimalarials may improve hemoglobin level by clearing parasites from the blood thus enabling erythrocytes numbers to be restored and preventing anemia (Koram et al., 2000). This is because chronic anemia adversely affects physical and cognitive development affecting school performance in preschool children. Repeated episodes of malaria, causes frequent depletion of the red blood cell there by reducing the Hb level which can lead to severe, life-threatening anemia. Blood transfusions, which may be life-saving in these circumstances, can expose the children to the risk of infection with human immunodeficiency

virus (HIV) and other blood-borne agents. The management of malaria associated anemia with the concurrent administration of antimalarials has demonstrated marked improvement in the hematological status of young children. Therefore malaria prevention and treatment has been the best method to prevent malaria associated anemia (Schellenberg et al., 2004., Menedez et al., 1997). Malaria associated anemia is a major problem among under five children. Studies in east Africa have demonstrated the beneficial effect of using antimalarial drugs to prevent malaria associated anemia. There is therefore the need to gather local data to inform national antimalarial drug policy in Ghana and other similar epidemiological situations.

1.3.1 JUSTIFICATION FOR USING MONOTHERAPY

The use of monotherapy (treatment of malaria or any condition with a single drug as opposed to combination therapy that uses two or more active compounds against the parasite), is based on the primary efficacy study which was conducted in 2005 by Oduro and colleagues in Navrongo (Oduro et al 2005.,). The study was conducted using AQ, CQ and SP at the time chloroquine was failing in terms of efficacy and also at the time that ACTs had not yet been approved for use. There was therefore the need for a study to be conducted to support the need to use more efficacious drugs. Using data from the primary study, this study seeks to demonstrate that antimalarial drugs improve the Hb levels of children after treatment for uncomplicated malaria, with the hypothesis that the greatest improvement will occur among the group that was treated with the most efficacious drug by looking at those three monotherapy antimalarial drugs.

1.4 STUDY OBJECTIVES

1.4.1 GENERAL OBJECTIVE

To determine the effect of treating children under five with uncomplicated malaria using Chloroquine (CQ), Amodiaquine (AQ) or Sulphadoxine-pyrimethamine (SP) on their hemoglobin levels.

1.4.2 SPECIFIC OBJECTIVES:

1. To determine the hemoglobin levels in children with uncomplicated malaria before, during and after the treatment with CQ, AQ or SP in the KND of Ghana.
2. To compare the mean hemoglobin levels of children under five treated for complicated malaria with CQ, AQ or SP in the KND distribution.
3. To compare the mean hemoglobin levels of females and males children under five treated with CQ, SP and AQ in Ghana on days 0 and post treatment.

1.4.3 HYPOTHESIS

Null Hypothesis (H_0)

H_0 ; There is no effect on mean hemoglobin level in children under five treated for uncomplicated malaria with CQ, AQ and SP in KND

Alternate Hypothesis (H_1)

H_1 ; There is effect on mean hemoglobin levels in children treated for complicated malaria with CQ, AQ and SP in KND

CHAPTER TWO

2.0 LITERATURE REVIEW

Malaria is a serious infectious disease caused by protozoa that are transmitted to humans by the bites of infected mosquitoes and has complications such as anemia and death. Antimalarial drugs are prescribed as a preventive measure against infection with malaria and also as treatment if the disease develops. There are various types of antimalarial drugs. Some are suitable only for treatment of the infection, while others are used for both prevention and treatment. CQ, SP and AQ used to be very effective antimalarial drugs and first line of treatment for malaria until in the 1980's that studies reported parasite resistance to these drugs and suggested that combination therapy offers better treatment to malaria and its complications such as anemia. (Gasasira et al., 2003). Since combination therapy was adopted by many countries these drugs were redrawn as first line of treatment in most African countries. However these drugs are still useful since they are used in combination with the artemisinin derivatives. For example first line of treatment for malaria in Ghana is Artesunate –Amodiaquine (MOH, 2007).

Sulphadoxine-pyrimethamine (SP) efficacy was assessed in 2002 in five different sites in Benin with varying intensity of malaria transmission (Program National de lutte contre le paludisme, 2002). It had an inconsistent distribution with an overall treatment failure at day 28 found to be 22.8%, (range 3.3% to 45.9%). In 2005 it was recommended by WHO with advice from a drug treatment force set up by the National Malaria Control Program to adopt SP as an intermittent preventive treatment (IPT) in pregnant women. Ghana and other African countries adopted SP as (IPT) between 1993 and 2007; Ghana however adopted SP as (IPT) in 2003. SP is currently used as (IPT) in pregnant women and in children in Ghana.

Anemia (hemoglobin level < 11 g/dL) remains one of the most stubborn public health problems in malaria-endemic countries of Africa. It affects more than half of all pregnant women and children less than five years old, (Demaeyer et al., 1985) and has serious consequences since severe anemia (hemoglobin level < 6 g/dL) is associated with an increased risk of death, (Bradin et al., 2001) impair cognitive and motor development, (Lozoff et al., 2000) growth, immune function, (Oppenheimer et al., 2001) and physical work capacity (Barennes et al., 2004). The serpentine nature of its presentation means, however, that mild-to-moderate degrees of anemia frequently remain undetected and untreated by health care workers and in the community, (Driessen et al., 2003). This untreated anemia can cause numerous complications such as fatigue, heart problems and even death. In severe anemia cases, blood transfusion may be prescribed on the basis of inaccurate hemoglobin measurement, (Bates et al., 2001) thus exposing the patient unnecessarily to the risk of infection with human immunodeficiency virus (HIV) and other blood-borne pathogens. (Lackritz et al., 1998). Prevention is clearly of critical importance, yet current coverage with anti-malarial interventions and micronutrient supplementation is poor in many African countries (WHO, 2003). In the Kassena Nankana District of Ghana which is endemic with malaria and common with anemia, ACTs which are recommended for malaria treatment and may prevent the depletion of red blood cells, thus preventing anemia, are not available at all times. Therefore malaria anemia continues to be a problem in this setting.

In sub-Saharan Africa, over 103 million children less than five are anemic (Kwadwo et al 2005). A number of anemia studies reported that severe anemia (hemoglobin \leq 5g/dl) in children less than five, living in malaria endemic areas, is caused by malaria. (Andrea et al., 2002, Schellenberg et al., 2004). In the Kassena Nankana District of Ghana more than half of the anemia cases are malaria related (Agyei et al., 2002). The relationship between anemia and malaria is revealed by increased numbers of anemia hospitalization in the high

transmission period of malaria and decreased levels of anemia or improvement in hemoglobin levels after antimalarial therapy (Alonso et al., 1993). A randomized study conducted in Tanzania also reported that treating children with severe malarial anemia with iron was beneficial but was more effective using iron in combination with antimalarial drugs (Schellenberg et al. 2004). A trial in The Gambia showed that children given chloroquine weekly from birth until age two years had fewer episodes of malaria, better growth, and higher hemoglobin levels than the control group (Mcgregor et al., 1956). In Liberia, chloroquine was given to children 2–9 years old monthly and number of clinical malaria episodes were reduced by 50% and was associated with a significant improvement in hemoglobin levels (Bjorkrman et al., 1986).

Although nutritional deficiencies, hookworm infection, and HIV all predispose to anemia in children, evidence suggests that, in endemic countries, malaria is one of the most important factors (Roll Back Malaria 2001-2010). Therefore anemia could be prevented by antimalarial regimens which rapidly reduces symptomatic high density parasitemia and clears parasites from the blood, allowing red blood cells numbers to be restored and reducing the risk of anemia (Crawley et al., 2004).). A randomized study carried out in Tanzania also indicated that approximately 60% of anemia in children living in malaria endemic areas can be prevented by antimalarial chemoprophylaxis confirming the importance of malaria as a cause of anemia in endemic areas (Menedez et al., 1997, Schellenberg et al., 2004, Crawley, 2004).

However, the recent antimalarial drug resistance has worsened the situation, by increasing the proportion of children who fail to adequately clear parasitaemia after treatment, and who consequently remain anemic thereby increasing malaria mortality (WHO 2002b).

CHAPTER THREE

METHODOLOGY

3.1 TYPE OF STUDY

This is a secondary data analysis. However the primary study employed an open-labelled, randomized efficacy design with three treatment arms: CQ, AQ and SP. The randomisation list was computer generated and in blocks of nine for the whole sample size.

3.2 STUDY AREA

This study is a secondary data analysis which analysed data from a randomised comparative efficacy study of CQ, AQ and SP conducted at the Navrongo War Memorial Hospital in the Kassena-Nankana District (KND) of the Upper East region of northern Ghana. This is a savannah region where the people are mainly subsistence farmers. There are two main seasons, a dry season from about October to April and wet season from approximately May to September. Malaria transmission and anemia occur throughout the year with distinct patterns during the two seasons, very high in the wet season and low in the dry season. The estimated malaria attack rate is approximately 3.5 attacks per child per year (Oduro et al., 2005). Low haemoglobin levels are recorded more during the wet season when malaria transmission is high indicating possible association with malaria and anemia. The Navrongo War Memorial Hospital in KND is served by six health centers and also in collaboration with the Navrongo Health Research Centre which has a demographic surveillance system. The demographic and malariometric characteristics of this guinea savannah vegetation have been well detailed in a study conducted in the Navrongo Health Research Center in 1999 (Binka et al., 1999).

3.3 STUDY POPULATION

The primary study that yielded data for this analysis included all children aged 5 years and below with confirmed uncomplicated falciparum malaria presenting at the War memorial hospital for treatment during the study period in 2005 in the Kassena Nankana District of Ghana.

3.4 SAMPLE SIZE

The sample size used depended on the primary study; all participants that were randomized into the primary study was used in the secondary analysis. 372 participants were randomized into the primary study however 350 participants were analyzed due to drop out and missing data. However there were instances where less than 350 children were used for the analyses again due to missing data. The primary study was calculated with a power of 80% and sample ratio of 1:1 with approximately 100 cases per arm with a dropout rate of 25% (Oduro et al., 2005).

3.4.1 SAMPLING METHOD

The primary study used a block randomization method. Mothers whose children were presenting with acute febrile illness were invited to join the study. Study criteria followed the WHO (2002a) protocol for in vivo 14 day tests in areas of high transmission. Inclusion criteria were parental informed consent, and uncomplicated malaria thus, axillary temperature of $\pm 37.5^{\circ}\text{C}$, and *P. falciparum* mono-infection with asexual stage parasite density of at least 2000/ μl . Participants were excluded if they had evidence of severe or complicated malaria, or other febrile infections. A recent history of antimalarial drug use was not considered an exclusion criterion. Participants were consecutively recruited and randomly assigned to one

of the three treatments during drug administration by a block randomization of nine (Oduro et al., 2005).

3.5 DATA COLLECTION AND ANALYSIS

In the primary study, children were followed up on days 1, 2, 3, 7 and 14 following treatment of the primary malaria episode, to determine the well-being of study participants. Axillary temperature was taken and recorded on follow up days 3, 7 and 14, and anytime symptoms occurred peripheral blood smears were taken and examined microscopically for parasitemia, and blood haemoglobin levels estimated using a haemacue photometer. Data was recorded on structured case report forms. This secondary data analysis study was analyzed using STATA version 11 (STATA Corp 2009). Mean haemoglobin levels of children between the three treatment groups were compared using ANOVA and paired t-test. Simple proportions, mean/median, standard deviations and confidence intervals were used to estimate the haemoglobin levels of children.

The baseline data that were analyzed include age (months), sex, hemoglobin levels, parasite counts and temperature. Comparisons of means and mean differences were done where it applied stating p values and confidence intervals. Statistical significance level was set at alpha 0.05 ($p < 0.05$). Significant improvement of hemoglobin was expected to be at least 0.5g/dl on the 28 of follow up.

3.5.1 Data Description and Extraction

The original data which was in SPSS software was transferred to STATA 11.0 software for analysis. Children's demographic characteristics were explored in the dataset using simple descriptive methods such as proportions and frequency distributions.

All variables used were identified and described. The main variables used were clinical response, Hb at days 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.

3.5.2 OUTCOME MEASURES

In analysis of the dataset, the target was to determine the effect of antimalarial of the Hbs on children treatment for uncomplicated malaria with antimalarial drugs. The effect of these antimalarial drugs were further analyzed by sex, follow up day and also age groups. A multiple regression analysis between day 0 and day 28 on sex, age group and treatment group was also done to adjust for occurrence of multiple testing effects.

3.6 ETHICAL CLEARANCE

Written informed consent was obtained from all parents and ethical clearance was obtained from the Navrongo Health Research Centre Institutional Review Board and the Ghana health service ethical review board before the start of the primary study. This study also sought approval from the Ghana Health Service ethics review committee and from the Navrongo Health Research Centre Institutional Review Board where the primary study took place.

CHAPTER FOUR

RESULTS

4.1 DEMOGRAPHIC CHARACTERISTICS OF STUDY SUBJECTS.

This study is a secondary data analysis of a dataset that was used for a comparative study on the efficacy of antimalarials in children under five years in the Kassena-Nankana District of Ghana at a time that chloroquine had failed markedly in parasitological cure rate to 31% (Koram et al., 2005). The primary study did not address the effects the drugs had on the hemoglobin levels of the children treated with those antimalarials. Using data from the primary study, this study therefore examined the effect of treatment with the three antimalarial drugs (AQ, CQ and SP) on the hemoglobin levels of children with malaria in the Kassena-Nankana District of Ghana.

A total of 351 children were originally randomized into the three treatment groups as follows; AQ(116), CQ (120) and SP (114). However, due to missing data, less than 351 children were used for this analysis. The number of children analysed ranged from a minimum of 39 to a maximum of 350. Missing data as a proportion of the total data set (351) was between 0.3% to 11.1%

Table 1 Baseline characteristics of study children by treatment group

BASELINE CHARACTERISTICS	TREATMENT GROUPS (350)		
	AQ (116)	CQ (120)	SP (114)
Sex number (%) males	57 (49.1%)	62 (51.7%)	48 (42.1%)
Mean age in months (SD)	28.2 (14.9)	27.8 (15.5)	27.2 (14.6)
Mean weight in kg (SD)	10.7 (2.7)	11.6 (2.7)	11.7 (5.2)
Mean axillary temperature at presentation °C (SD)	38.1 (0.6)	38.1 (0.6)	38.0 (0.6)
Hb0 (SD) {g/dl}	8.8 (1.5)	8.1 (1.7)	9.0 (1.7)
Geometric Mean Parasite Density at presentation (95% CI) {count/ul}	530.1 (393.2-714.4)	558.1 (428.9-726.3)	536.1 (400.4-717.7)

AQ- Amodiaquine, CQ- Chloroquine , SP-Sulphadoxine pyrimethamine, Hb0- hemoglobin concentration at day 0, SD- Standard Deviation, 95% CI-95 percent confidence interval

Table 1 shows the details of base line characteristics. Base line characteristics were approximately the same for all treatment groups, with mean age, mean weight, mean axillary temperature, mean Hb at base line (day 0) and mean geometric parasite count at day 0 approximately the same in all the treatment groups. The numbers of females who were in AQ and SP groups were slightly higher than males except in the CQ group which had more males than females. The proportions of males in AQ, CQ and SP are 49.1%, 51.7% and 42.1% respectively. The children were divided into three age groups, thus 0-12months, 13-36months and 37+ months, the details are shown in table 4. Age group 13-36months had the greatest number of children among the three age groups. Number of children in age group 13-36months was 59 in each treatment group. AQ and SP had 20 children each in age group 0-12months while CQ had 21 children in that age group. AQ and CQ also had 29 children each in age group 37months or older whiles the SP group had 24 children.

Table: 2 Mean Hbs of treatment groups on follow up days.

Mean Hb conc (g/dl)	Treatment		
	AQ	CQ	SP
Mean Hb (95%CI) day 0	8.9 (8.5-9.1) (n=112)	8.9(8.6-9.3) (n=120)	8.9 (8.6-9.2) (n=114)
Mean Hb (95%CI) day 7	8.1 (7.6-8.6) (n=42)	8.4 (8.0-8.7) (n=52)	8.5 (8.1-8.9) (n=62)
Mean Hb (95%CI) day28	9.4 (9.1-9.8) (n=108)	9.2 (8.8-9.6) (n=82)	9.8 (9.5-10.1) (n=84)

95% CI-95% Confidence Interval, Hb-hemoglobin, n=number of observations, day 0= day drug was taken by participant, day 7= seven days after drug was taken by participant, day 28= 28 days after drug was taken

4.2 COMPARISON OF MEAN HEMOGLOBIN LEVELS AMONG TREATMENT GROUPS ON FOLLOW UP DAYS.

Due to missing data the following numbers of children were available for assessing mean Hb on days 0, 7 and 28 in the three treatments groups respectively. Tables 2 show the details of the number of participant that were used to analyse the mean Hbs on the follow up days for the three treatment groups. Mean Hbs for day 14 were completely missing from the data set. The mean Hb for day 0 in all the treatment groups was approximately 8.9 g/dl. There was no significant difference between the treatment groups p -value=0.740. Mean Hbs for day 7 declined in all treatment groups as compared to day 0. The AQ (8.1g/dl) group recorded the highest decline in mean Hbs as compared to CQ (8.4g/dl) and SP (8.5g/dl). However the decline in mean Hbs across groups was not significant, ($p = 0.447$). Mean Hbs increased on day 28 in all treatment groups, with SP (9.8 g/dl) recording the highest and CQ (9.2 g/dl) is recording the lowest. The p -value across treatment groups on day 28 was 0.071 which was statistically not significant; therefore further test (Bonferroni test) was not done. Table 2

shows the details of the analysis of mean Hbs among the treatment groups on the various days.

The analysis was further done by paired t-test and the trend was the same as in the unpaired analysis however there were instances where the p-values were significant for the paired t-test analysis unlike the unpaired analysis. Mean Hbs at day 7 for all treatment groups declined as compared to mean Hbs day 0 and all p-values were less than 0.05 therefore statistically significant. Mean Hbs day 0, for the three treatments groups were 8.8g/dl (AQ), 8.8g/dl (CQ) and 9.0 (SP). Mean Hbs day 7 for AQ, CQ and SP were 8.3g/dl, 8.4g/dl and 8.8 respectively as shown in figure 1. When day 0 was compared to day 28 the mean Hbs concentrations for day 28 were found to have increased significantly for the AQ and SP groups but not significant for CQ. Increase in mean Hb for both AQ and SP was approximately 1.0g/dL at day 28. The mean Hbs at day 0, day 28 and p- values for the groups are as follows; (AQ) 8.8 g/dl, 9.5g/dl and 0.001, (CQ) 9.1 g/dl, 9.2g/dl and 0.700 and (SP) 8.8 g/dl, 9.8 g/dl and 0.001. Figure 1 shows the trend in change of the mean Hbs for the various treatment groups

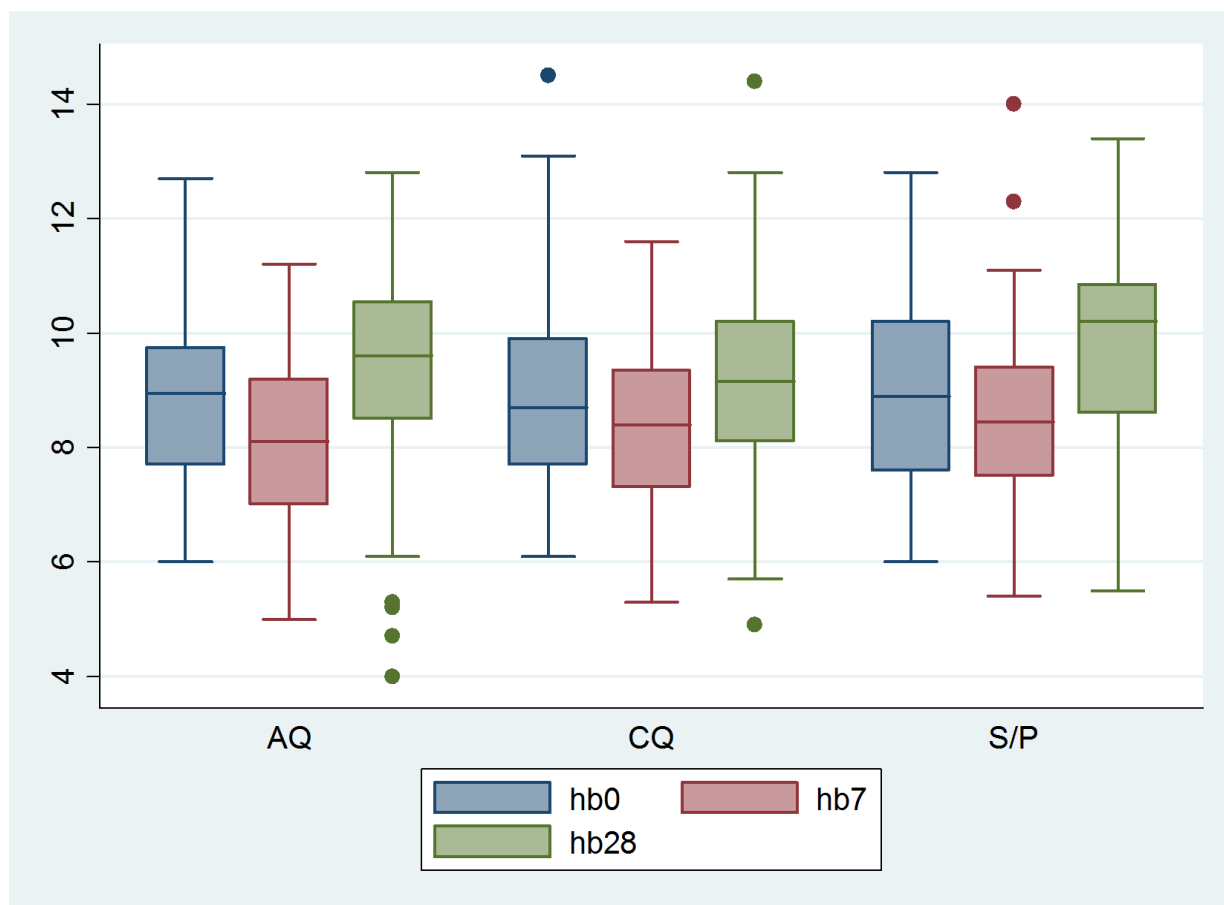


Figure 1: Changes in Hb concentrations after treatment

Hb0=Hb taken the on the first day drug was taken, Hh7 – seven days after drug was taken, Hb twenty- eight days after drug was taken,

Table 3: Mean Hbs by sex in the various treatment groups

Mean Hb con (g/dl) 95% IC	Sex					
	Male			Female		
	n	Mean Hb (95% CI)	(95% CI)	n	Mean Hb (95% CI)	(95% CI)
AQ						
Day 0	54	8.9	(8.6-9.3)	58	8.4	(8.0-8.8)
Day 7	18	8.2	(7.4-9.1)	24	7.7	(7.1-8.5)
Day 28	51	9.3	(8.8-9.8)	57	9.2	(8.6-9.7)
CQ						
Day 0	62	8.6	(8.3-9.2)	58	9.0	(8.6-9.4)
Day 7	27	8.0	(7.5-8.5)	25	8.5	(8.0-9.1)
Day 28	40	9.1	(8.5-9.7)	42	9.0	(8.5-9.5)
SP						
Day 0	47	8.7	(8.3-9.3)	66	8.8	(8.4-9.2)
Day 7	25	7.9	(7.2-8.6)	37	8.7	(8.2-9.2)
Day 28	38	9.7	(9.3-10.3)	45	9.6	(9.1-10.1)

Day 0- day drug was taken, day 7 – seven days after drug was taken, days 28- twenty eight days after drug was taken, n= number, 95% CI- 95 percent confidence interval

4.3 COMPARISON OF MEAN HEMOGLOBIN BY SEX

The trend was not different when analysis was done by sex among all the treatment groups. Mean Hb on day 0 for males (M) and females (F) in the treatment groups are as follows AQ (M= 8.9 g/dl, F=8.4 g/dl) CQ (M=8.6 g/dl, F=9.0 g/dl) and SP (M=8.7 g/dl, F= 8.8 g/dl). Mean Hbs for females were slightly higher than males in CQ and SP groups, but was different for the AQ group with males having higher mean Hb than females at day 0. Mean Hbs again declined for both males and females in all treatment groups on day 7 of follow up as compared to day 0. Interestingly mean Hb concentrations dropped by 0.7 g/dl in both male and females in the AQ group. The highest drop in mean Hb was 0.8g/dl which was observed among males in the SP group and the lowest drop in mean Hb level was also witnessed among females in the same treatment group.

Mean Hbs levels increased again among both males and females in all treatment groups on day 28 compared to day 0 and day 7 of follow up. SP group recorded the highest improvement of mean Hbs on day 28 of follow up as 1.0 g/dl and 0.8 g/dl for males and females respectively as compared to day 0 of follow up. The least improvement of mean Hbs was recorded among males in the AQ group when mean Hb day 0 was compared to mean Hbs day 28. Table 3 illustrates mean Hbs for day 0, day 7 and day 28 for both sexes in all the three treatment groups.

Paired t-test analysis was also done by sex for all treatment groups and the trend in mean Hbs day 7 was not different from the previous analysis witnessed. However males had slightly higher mean Hbs than females in the AQ and SP groups but this was different in the CQ groups where females had slightly higher Hbs than males. Mean Hb declined by 0.5g/dl on day 7 of follow up as compared to day 0 among males in the AQ treatment group. However, Hbs improved by 0.4g/dl on day 28 of follow up as compared to day 0 among males in the in the same treatment (AQ). Mean Hb for females in the AQ group also declined by 0.6 on day 7 of follow up as compared to day 0. On day 28 of follow up mean Hb increased significantly by 0.8g/dl among females in the AQ treatment group with a border line p-value of 0.05. In the CQ group mean Hb declined by 0.5 in both sexes on day 7 of follow up as compared to day 0. There was no significant improvement of mean Hb among both sexes on day 28 of follow up as compared to day 0 in the CQ treatment group. Mean Hb increased by 0.3g/dl among males and 0.1 among females in the CQ treatment group. For the SP group mean Hb declined by 1.0g/dl on day 7 of follow up with p-value of 0.012 and improved by 1.0g/dl on day 28 of follow up as compared to day 0 among males. Among females in the SP treatment group, mean Hb declined on day 7 by 0.2g/dl and improved significantly on day 28 by 0.9g/dl.

Table 4: A table showing mean Hb by age groups in the various treatment groups

Mean Hb Conc (95%CI) g/dl	Age Groups					
	0-12 months		13-36months		37+ months	
	n	(95%CI)	n	(95%CI)	n	(95%CI)
AQ						
day 0	20	8.2 (7.7-8.7)	55	8.5 (8.1-8.9)	29	9.2 (8.6-9.8)
day 7	6	6.8 (5.4-8.5)	24	7.6 (7.0-8.2)	9	9.6(8.8-10.4)
day 28	18	8.0 (7.3-8.8)	54	9.0 (8.4-9.5)	28	10.5 (10.0-11.0)
CQ						
Day 0	21	9.1 (8.5-9.8)	59	7.9 (7.6-8.1)	29	9.6 (8.9-10.2)
Day 7	10	7.6 (6.9-8.6)	23	7.7 (7.2-8.2)	16	9.2 (8.5-10.0)
Day 28	13	9.1 (8.5-9.8)	37	8.2 (7.8-8.8)	22	9.7 (8.9-10.4)
SP						
Day 0	20	7.9 (7.3-8.6)	59	8.6 (8.2-9.0)	24	9.3 (8.6-10.1)
Day 7	10	6.9 (6.0-8.0)	26	8.1 (7.6-8.7)	19	9.1 (8.4-9.9)
Day 28	14	9.1 (8.1-10.2)	46	9.4 (9.0-9.9)	17	10.3 (9.5-11.3)

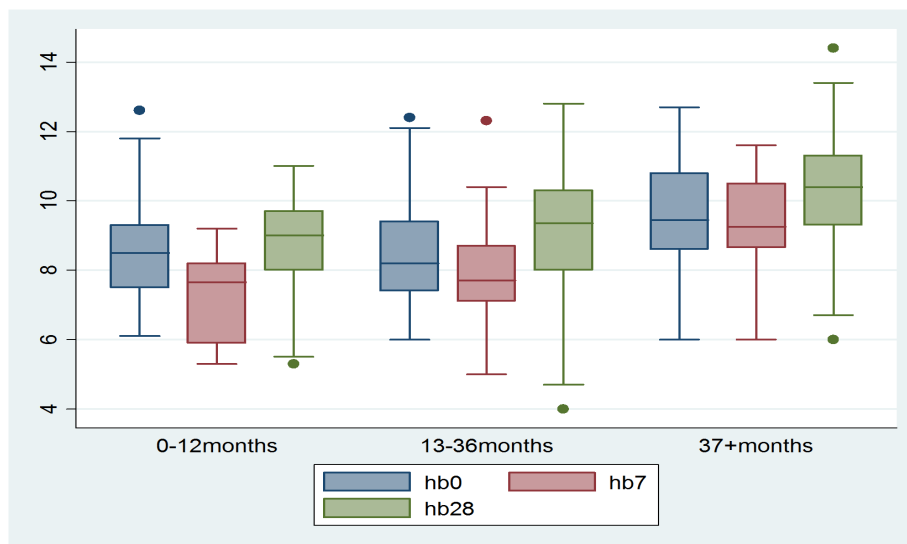
0-12months- children aged between zero to twelve years old, 13-36 months- children aged between thirteen and thirty six years old, 37+ -children age thirty seven and above, n-number, 95%CI- 95 percent confidence interval, mean Hb conc- mean haemoglobin concentration.

4.4 COMPARISON OF MEAN HB ACCORDING TO AGE GROUPS

The children (age 0-5years) were stratified into three age groups thus 0-12 months, 13-36 months and 37+ months and analyses done according to the various treatment groups on follow up day 0, day 7 and day 28. The overall trend for the various days did not change for all the three age groups, it was the same as reported earlier in all treatment groups with Hbs dropping on day 7 and rising again on day 28. After the stratification approximately equal numbers of children were in all the three treatment groups with age group 13-36 having the highest number of children across all the treatment groups. AQ and SP treatment groups contained 20 children each in age group 0-12 whiles CQ treatment group had 21 children in the same age group. Age group 13-36 had 59 children each in all the three treatment groups.

For age group +37 AQ and CQ treatment groups contained 29 children each while SP group 24 child. The number of children that were finally available for the secondary data analysis due to missing data is presented in table 4 with mean Hbs for the various treatment groups. Age group 37+ recorded the highest mean Hbs in all the treatment. Figure 2 shows the trend in the mean Hb concentration for the various age groups.

Figure 2: Changes in mean Hb by age group and follow up days.



Hb0=Hb taken the on the first day drug was taken, Hh7 – seven days after drug was taken, Hb twenty eight days after drug was taken, 0-12 months- children aged between zero to twelve years old, 13-36months- children aged between thirteen to thirty six years old, 37+ months- children aged thirty seven years and above.

The analysis was also done by paired t-test for the age groups comparing mean Hb on day 0 to that of day 7 and day 28. Mean Hbs declined in all the age groups on day 7. The following are the amount Hbs declined by on day 7 as compared to day 0 in all the three age groups with their p –values. 0-12 months (1.2 g/dl and 0.002), 13- 36 months (0.5g/dl and 0.001) and 37+ months (0.1g/dl and 0.809). Also, mean Hbs concentrations increased for all age groups on day 28 of follow up. The following are the amounts mean Hbs improved on day 28 as

compared to day 0 for the various age groups and their p-values. 0-12months (0.4g/dl and 0.145), 13-36 months (0.7g/dl 0.001) and 37+ months (0.8g/dl and 0.001).

The trend was slightly different from the usual trend of mean Hb's declining on day 7 and improving on day 28 as compared to day 0 when mean Hb of each of the treatment groups (AQ, CQ and SP) was compared to the follow up days. For AQ group mean Hb concentration dropped on day 7 as compared to day 0 by 1.2 g/dl (p-value = 0.001) for age group 0-12months, and 0.9g/dl (p-value 0.002) for age group 13-36 months. However, mean Hb concentration improved on day 7 by 0.4 for age group +37 which differs from the usual trend of mean Hbs declining on day 7.

In the same treatment group (AQ) mean Hbs for day 28 as compared to day 0 improved significantly for age group 13-36 months and 37+ months by 0.6g/dl and 1.2g/dl respectively with p-values 0.049 and 0.005 respectively. Again the story was slightly different when mean Hb declined by 0.2 for age group 0-12 months on day 28 as compared to day 0 in the AQ treatment group. The usual trend witnessed is that mean Hbs improved on day 28 as compared to day 0 but this was not the case for the 0-12 months in the AQ treatment group.

Unlike the AQ group, mean Hb concentration for all the three age groups declined on day 7 following the usual trend in the CQ treatment group, with statistically significant drop of 1.3 g/dl among age group 0-12 months with p-value 0.001. Mean Hbs declined by 0.1g/dl and 0.3g/dl respectively for age groups 13-36 months and 37+ months. Comparing day 0 to day 28, mean Hb level only improved among 13-36 months age group by 0.55g/dl with a statistically significant border line p-value of 0.054. Mean Hbs declined slightly on day 28 for age groups 1-12 months and 37+ months. This again did not follow the usual trend where mean Hbs improved on day 28.

The result for the SP group followed the general behaviour for mean Hb on day 7 and day 28. Mean Hbs for all treatment groups decline on day 7 with the 0-12 months age group declining significantly by 1 .1g/dl with p-value 0.032. The drop in mean Hbs for age group 13-36 months and 37+ months was statistically not significant. Mean Hbs improved significantly in all age groups in the SP treatment group on day 28.

Table 5: Regression of age group, sex and treatment group.

Day 28-day 0	Difference		
	Coef	95% CI	P-value
0-12 months	-	-	-
13-36 months	0.26	-0.35-0.86	0.404
≥37 months	0.43	-0.25-1.10	0.212
Male	-	-	-
Female	-0.01	-0.46-0.44	0.964
AQ	-	-	-
CQ	-0.37	-0.92-0.17	0.179
SP	0.39	-0.14-0.93	0.150
Cons	0.36	-0.29-1.00	0.265

Coef-Coefficient, Cons- Constant, 95% CI- 95 percent confidence interval, 0-12 months- children aged between zero to twelve years old, 13-36months- children aged between thirteen to thirty six years old, ≥37 months- children aged thirty seven years and above, day 0- day drug was taken, day 28-twenty-eight days after drug was taken.

4.5 MULTIPLE REGRESSION ANALYSIS

In order to adjust for the occurrence of multiple testing, a multiple variant linear regression of difference in mean Hbs between day 28 and day 0 on age group, sex and treatment group was done. Table 6 shows the result of the regression. Children in the SP group had their mean Hbs increased by 61% which was the highest improvement among all the three treatment groups

just as reported in the paired and unpaired analysis. However, none of the p-values were statistically significant. All 95% confidence intervals overlap indicating no statistical significance.

CHAPTER FIVE

DISCUSSION

5.1 SUMMARY

Earlier detection and prompt treatment of malaria remains the core strategy for preventing and treating malaria associated anaemia worldwide (Green, 2004 and Oduro et al., 2005) except that the current spread of parasite resistance is posing the greatest challenge to this effort. In this study of Ghanaian children aged 0-5years the effect of three antimalarials (AQ, CQ and SP) on the hemoglobin levels after the treatment of uncomplicated malaria is reported. It was hypothesized that children treated with the most efficacious drug in the three treatment groups will have the greatest improvement of mean Hb concentration level after treatment (on day 28 of follow up). Of the 351 uncomplicated malaria patients treated, CQ (46.7%) showed the least favourable treatment outcome in terms of adequate clinical and parasitological cure rates compared with AQ (86.1%) and SP (77.6%) (Oduro et al., 2005). For both paired and unpaired analysis children in the SP group had the greatest improvement of mean hemoglobin level on day 28 of follow up as compared to children in AQ and CQ group. The results for both paired and unpaired analysis were approximately the same. The figures are as follows for the paired t- test analysis SP (1.0 g/dl), AQ (0.6 g/dl) and CQ (0.1g/dl), and for the unpaired analysis we have 0.9 g/dl for SP, AQ (0.5 g/dl) and CQ (0.3g/dl). It was hypothesised that the children who took the most efficacious drug will have the highest improvement of mean Hb on day 28 of follow up. However, AQ was the most efficacious drug and yet children in the SP group showed the highest improvement of mean Hb level than children in the AQ group. This may be as a result of AQ having more tendency of hemolytic anaemia effect on children than SP and CQ (Ernest et al., 2007). It was not surprising that CQ which was the least efficacious drug also showed the least improvement of

mean Hb level after treatment in both paired and the unpaired analysis. This result confirms previous findings where treatment with ineffective antimalarial drugs was associated with an increased frequency of anemia and poor hematological recovery (Ekvall et al 1998). Other consequences of ineffective antimalarial therapy include increased hospitalization rates, severe anemia, case fatality rate and blood transfusion rates (Greenwood, 2004., WHO 2002b).

Children were stratified into three age groups thus 0-12 months, 13-36 months and 37+ months. Children in age group 0-12 months old showed the least improvement of mean Hb after day 28 of follow up. This finding indicates that drug related hemolysis decreases as one grows. Though this study could not pin down the effect of antimalarial on the mean Hb of either males or females, generally males mean Hb increased slightly better than females.

5.2 EFFECT OF ANTIMALARIAL ON MEAN HB OF CHILDREN ON FOLLOW UP DAYS.

Though early treatment of malaria infections with effective, fast-acting antimalarial drugs promptly reduces symptomatic high density parasitemia and clears parasites from the blood, allowing erythrocyte numbers to be restored (Ekvall H 2003, Bjorkman 2002, Crawley 2004) and reducing the risk of anemia. However studies have shown that hemolytic anemia may occur during the first few day of treatment among most drugs, thus between 1 to 7 days after taking drug (Beuler 2006, Ernest et al., 2007), and begins to disappear after the seventh day of treatment.

The results of our study were not different from the findings of other studies. On day 7 of follow up, mean Hb decline for all treatment groups for both paired t-test and unpaired

analysis with the greatest decline in mean Hb occurring among children treated with AQ. For paired t- test, mean Hbs declined on day 7 of follow up by 0.6 g/dl for the AQ as compared to CQ (0.5g/dl) and SP (0.5). For the unpaired analysis, mean Hb declined on day 7 of follow up in the three treatment groups by AQ (0.8 g/dl), CQ (0.5 g/dl) and SP (0.4g/dl). This finding is consistent with other studies that showed that antimalarial drugs have more hemolytic effect during the first few days of treatments (Braden et al 2002 and Ernest et al., 2007). The time course of hemolysis is different for different drugs and also for drug dose. For instance hemolysis caused by primaquine is detectable between 1 and 3 days after drug administration (Ernest et al., 2007). This result further suggests that AQ has the greatest hemolytic effect as compared to SP and CQ.

However mean Hbs improved dramatically among all treatment groups on day 28 of follow up with the SP group showing the highest improvement of mean Hb while CQ group showing the least improvement of mean Hb. This clearly shows the relationship between malaria and anemia and if malaria is treated promptly and effectively it will prevent anemia by destroying parasites and preventing the depletion of red blood cells. A study conducted in a malaria endemic area in south Tanzania demonstrated a 60% reduction in clinical episodes of malaria and anemia in children given weekly primethamine plus dapson between ages of 2 and 10 months old (Crawley 2004), thereby confirming the finding of this study.

5.3 EFFECT OF ANTIMALARIAL ON THE MEAN HB OF CHILDREN BY AGE GROUP

The children were further stratified into three age groups, and decline in mean Hb level on day 7 was significantly related to age group 0-12 month old. For paired t- test mean Hbs declined in ascending order of age group. Unexpected trend in Hb behaviour occurred among AQ and CQ group when analysis was done according to treatment groups and age groupings.

Instead of all mean Hbs declining on day 7 among all age groups as witnessed in the general trend in mean Hb levels, there was an increase in mean Hb level in the AQ group among age group 37+ months. There could have been two explanations to this change, the first being that hemolytic anaemia due to drugs decreases as one ages, and the second being as a result of G6PD deficient patient being in age group 0-12 months than the other two age groups. However, G6PD deficient patients were excluded from the primary study so the later reason is ruled out. In the CQ group instead of mean Hbs increasing on day 28 for all age groups as expected, mean Hbs levels for age group 0-12 months and 37+ months decreased. This could be as a result of CQ no longer being effective in the treatment of malaria and consequently increasing the frequency of anaemia and poor hematological recovery.

Nevertheless, mean Hb declined more among children aged 0-12 months years old, confirming the finding of a study that was conducted in 1999 among age group 1 to five years old in Tanzania which indicated that anemia was prevalent among children aged 1-11 months old (Schellenberg et al., 1999).

5.4 EFFECT OF ANTIMALARIAL ON MEAN HB OF CHILDREN BY SEX

Generally mean Hb levels improved better on day 28 among males than females for both paired t-test and unpaired analysis, except in the SP group in which mean Hb level increased significantly among females than males for the paired t-test analysis. Also females had higher mean Hb on day 28 in the CQ group for the unpaired analysis. It is difficult to pinned down this findings to gender since mean Hb levels improved better among female than males in one treatment group and improved dramatically among males than females in another treatment group (Pasricha et al., 2010, Nitin et al., 2005).

Mean Hbs declined significantly on day 7 of follow up among females in the AQ group and among males in the SP treatment group for both paired t-test and unpaired analysis. However, mean Hb levels declined more among males in the SP group as compared to females in the same group on day 7. Again this behaviour in mean Hbs could not be completely linked to gender because for one drug mean Hbs declined significantly among males than females and another drug mean Hbs levels declined significantly among females than males on day 7 of follow up. It was also difficult to pin down drug related hemolysis to gender for the some reasons.

5.5 MULTIPLE REGRESSION ANALYSIS ON AGE, SEX AND TREATMENT

The multiple regression of the difference in mean Hbs between day 0 and day 28 on age sex and treatment groups did not show any statistical significant result among the groups. This analysis had to be done to avoid effect of multiple testing. This result was also in line with both the unpaired and paired analysis result that was discussed where children in the SP treatment group had the greatest improvement of mean Hbs. CQ which was reported to have the least parasite clearance rate also recorded the least improvement in the regression analysis which confirmed the unpaired and paired analysis result.

5.6 LIMITATIONS

This study may suffer the limitations associated with missing data since the study used secondary data for the analysis. For instance Hb measured on day 14 was not available which could have made a greater impact on the study. Also another limitation this study suffers as secondary data analysis is that, the result cannot be inferred on ACT's which are the current line of treatment for uncomplicated malaria in Ghana and other malaria endemic countries. This is because the study relied on data set from a study that was conducted in 2005 when

monotherapy was the first line of treatment for uncomplicated. Therefore these results are based on data set from a study that used monothrepy drugs which are no longer recommended for the treatment of uncomplicated malaria. However, the study showed that effective clearance of parasitaemia using an efficacious treatment leads to improved haematological recovery. Therefore the analysis may support the use of the current first line drugs, ACTs, which are known to clear parasitaemia rapidly from the blood (Koram et al 2005). Thus, the use of ACTs is likely to prevent malaria associated anaemia because of its effectiveness in treating malaria. It will however be more appropriate to conduct a study in this area using ACT's which are the current line of treatment for uncomplicated malaria.

CHAPTER SIX

CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

It is clear that prompt, effective treatment of malaria with effective fast-acting antimalarial drugs rapidly reduces symptomatic high density parasitemia and clears parasites from blood allowing red blood cells numbers to be restored (Ekvall et al., 2003) and thereby improving the hemoglobin level and consequently preventing anemia. Also the effect of antimalarial on mean Hbs of children with uncomplicated malaria is associated with age, as children in age group 0-12 months had the least improvement in mean Hb on day 28 of follow while children in age group 36+ had the greatest improvement in mean Hb. This indicates that haemolytic anemia due to drugs decreases as one ages. Furthermore, the effect on these drugs on the mean Hbs of children cannot be pinned down to gender since mean Hb improved significantly among males in one treatment group and among females in another treatment group.

6.2 RECOMMENDATION

From the findings of the study, the following recommendations will therefore be necessary.

- Malaria should be treated promptly with effective fast – acting antimalarial drugs to prevent malaria associated anemia which is currently a burden in malaria endemic areas in Africa and other complications associated with malaria such as cerebral malaria (CM), respiratory distress and even death.
- Other means of preventing malaria such as bed net usage and residual spraying should be employed to prevent malaria which consequently leads to anemia.

- A primary study should be conducted in this area using ACT's which are the current line of treatment for uncomplicated malaria.
- Last but not the least, support from policy makers, stake holders, research institutions and non-governmental agencies is essential to help combat malaria associated anemia. All these bodies especially the minister of health should understand that malaria control is important and cost effective treatment and yields substantial health benefits since it prevents malaria associated complications such as anemia, respiratory disorders mental retardation in children and even death

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