THE EFFECT OF VITAMIN A AND ZINC OR VITAMIN A, ZINC & MULTIVITAMIN SUPPLEMENTATION ON MORBIDITY DUE TO MALARIA

BY

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CERTIFICATION

I hereby declare that this submission is my own work towards the MPhil and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for award of any other degree in the University. I have undertaken the study reported herein under the supervision of Dr. Patricia Brown, Dr. Harry Tagbor and Prof. Ibok Oduro and that except portions that are duly cited this dissertation is the outcome of my research work

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ABSTRACT

Interventions with vitamin A or zinc have been shown in various studies to reduce incidences of malaria and other illness. However the effect of supplementing with vitamin A, Zinc and multivitamins has not been studied. We measured the effect of combining vitamin A, zinc and multivitamins on malaria morbidity. A randomized, controlled trial was conducted in children in the *Ejusu-Juaben* Municipality of Ghana. Children (n=542) aged between 6 to 60 months were randomly assigned to 1 of 3 intervention groups; group 1, control - vitamin A (single dose 200 000 IU), group 2-vitamin A (single dose 200 000 IU) & zinc (10 mg daily), group 3-vitamin A (single dose 200 000 IU) with multivitamin (according to age) and zinc (10mg daily). Malaria episodes were detected by surveillance or cases self-reported to a community health worker. Cross-sectional surveys were conducted at the beginning and the end of the study period. The primary outcome was an episode of malaria (temperature ≥37.5°C) which was confirmed by microscopy and testing with a rapid test kit for malaria antigen (HRP2) of plasmodium *falciparium*. The risk of malaria infection among the children who received vitamin A, zinc & multivitamin during the study period was reduced to 62% (RR = 0.62, p = 0.018) of the risk in children who received vitamin A alone. The risk of children who received vitamin A & zinc was 81% though this decrease was not significant (RR = 0.81, p = 0.109).The children in the vitamin A alone group had the highest geometric mean parasite density the end of the study. Amongst the groups, it took those in the vitamin A, zinc & multivitamin group a longer time (112 days) to develop the first episode of malaria compared to the vitamin A alone group (93days, p = 0.004); differences in time to develop malaria between the other groups were not significant.; vitamin A & zinc; 94 days and vitamin A; 93 days. The results suggest that combined supplementation with vitamin A, zinc and multivitamins reduces the risk of malaria infection appreciably.

CHAPTER ONE

1.1 BACKGROUND

Essential micronutrients are nutrients required by humans and other living things throughout life in small quantities (micrograms and milligrams). They are needed to orchestrate a whole range of physiological functions, which the organism itself cannot produce (WHO, 2011). Micronutrient deficiencies are estimated to be responsible for 21% of worldwide deaths in children under 5 years in low- and middle-income countries every year (Onis de and Blössner, 2009). Most of the diseases that cause these deaths are infectious diseases such as malaria, pneumonia, diarrhoea, and measles (Pelletier and Frongillo, 2003). This disease burden is mostly due to deficiencies in zinc and vitamin A, and is highest in Asia and sub-Saharan Africa (Black *et al*., 2008).

Studies have indicated that macronutrient and certain forms of micronutrient malnutrition exacerbate malaria morbidity and mortality (Shankar, 2000). A high prevalence of several micronutrient deficiencies has been found among 6 to 60-month-old Ghanaian infants (Lartey *et al.*, 2000). Deficiencies in vitamin A, B_1, B_2, C, E and zinc have also been associated with susceptibility to malaria infection (Black *et al.*, 2008). Deficiencies of thiamin, folate, and antioxidants including vitamin E have been noted in patients with acute malaria (Metzger *et al.*, 2001). There are a lot of trials (Allard *et al.*, 1998; Akompong *et al.*, 2000b; Banajeh, 2003; Wrenger *et al.*, 2006 ; Brown *et al.*, 2010) that measure the effect of vitamin A and zinc independently on malaria infection. However, the results from these trials are inconsistent; some suggest protective effects while others are exacerbative.

For example, in vitro studies with human monocyte cell lines suggests that vitamin A may facilitate the breaking up of red blood cells infected with malaria parasites and thus may reduce the severity of malaria (Serghides and Kain, 2002). Studies in humans indicated that vitamin A supplementation reduced the frequency of *P. falciparum* malaria episodes among pre-school children (Shankar *et al.*, 1999a; Cox *et al.*, 2005) . In contrast, a vitamin A supplementation trial in preschool children in Northern Ghana reported no statistically significant effects of vitamin A on *P. falciparum* morbidity or mortality (Binka *et al.*, 1995).

Zinc is essential for the production of immune proteins like immunoglobin G (IgG), interferon-γ (IFN-γ), and tumour necrosis factor –α, implicated to help in resistance to malaria (Good *et al.*, 1998; Fischer-Walker and Black, 2004). A trial of zinc supplementation in preschool children in Papua New Guinea (Shankar *et al.*, 2000) documented a 38% reduction in health center attendance owing to *P. falciparum* malaria. However, a subsequent trial of daily zinc supplementation of preschool children in Burkina Faso indicated no protective effect on *P. falciparum* (Muller *et al.*, 2001).

The discrepancies in the results may be because the response to these supplementations are suppressed in children who are also deficient in other nutrients known to be essential for immunity, or in nutrients that impair absorption or utilization of other nutrients (Maggini *et al.*, 2007) . For example, zinc is involved in the conversion of β-carotene to vitamin A and it is required in mobilizing vitamin A within cells and from the liver (Dijkhuizen *et al.*, 2004).

Also, vitamin A deficiency may reduce absorption and lymphatic transport of zinc by altering synthesis of a zinc dependent binding protein; vitamin E is generally recognized as necessary for optimal utilization of vitamin A. Riboflavin depletion impairs absorption and increases the rate of gastrointestinal loss of endogenous iron and possibly other minerals (Powers, 1998).

1.2 Problem Statement

Malaria is also a burden worldwide. In Ghana and the *Ejisu-Juaben* municipality, 40% and 60% of outpatient cases are due to malaria respectively (MOH, 2010). Also, high prevalence of several micronutrient deficiencies have been found among 6 to 60-month-old Ghanaian children (Lartey *et al.*, 2000). Literature suggests that certain forms of micronutrient deficiencies exacerbate malaria morbidity and mortality. Deficiencies in vitamin A, B_1, B_2, C, E and zinc have also been associated with susceptibility to malaria infections (Black *et al.*, 2008). Deficiencies of thiamin, folate, and antioxidants including vitamin E have been noted in patients with acute malaria (Black *et al.*, 2008). Hence, supplementation programs have been used over the years to correct vitamin and mineral deficiencies in children and even the elderly.

Vitamin A supplementation has been used as a possible strategy to improve the nutrition of infants at high risk of vitamin A deficiency, and thus potentially reduce their mortality and morbidity. This is because vitamin A is central to normal immune function, and supplementation has been shown to lower the morbidity of some infectious diseases.

The effect of vitamin A supplementation in preventing malaria has been studied, some studies suggest a protective effect while others suggest an exacerbative effect. Other reviews suggest that these results are discordant because the individuals may have been deficient in other nutrients which help the bioavailability of vitamin A. One such nutrient is zinc. Zinc is known to interact with vitamin A and deficiency in either nutrient may affect the bioavailability of each other. Coincidentally, zinc has also been tried in some studies as a prophylactic in malaria prevention but the results in these studies are also discordant (Keen and Gershwin, 1990; Fraker *et al.*, 2000; Cui *et al.*, 2003).

In addition to the problem above, the WHO in collaboration with the government of Ghana undertake vitamin A supplementation twice a year the country. These supplementations are done from the fact that vitamin A supplementation corrects vitamin A deficiency, and if the vitamin A nutriture of the children is improved then they can be better protected from common infections like malaria. But malaria is still the highest outpatient case in Ghana and specifically in the Ejisu-Juaben municipality. It is possible that, the vitamin A supplementation may not be effective in correcting the deficiency especially in children who are also deficient in other nutrients especially zinc.

It is assumed that children who may not respond as well to the vitamin A supplementation are those located in the middle and upper belt of Ghana. This is because these children may be lacking zinc in their diet because known good sources of zinc in the diet are sea foods particularly oysters and mollusks.

Some of these foods are known to be scarce in the geographical location (*Ejisu-Juaben* Municipality in the *Ashanti* Region) of our study population. The *Ashanti Region* is located in the middle belt of Ghana, which is far from the coastline, making sea foods scarce in this part of the country. These foods may be lacking in the diet of the research population hence making them deficient in this nutrient.

Additionally, if zinc is deficient, vitamin A bioavailability may also be impeded. It can be proposed then that the children may also be deficient in other nutrients known to be essential for immunity. If so, then zinc and other micronutrients would act synergistically, and simultaneous supplementation with other nutrients might be required to overcome the lack of effect that may occur when zinc or vitamin A is given alone

To compound the problem, the consumption of fruits and vegetables is known to provide the body with the needed vitamins and minerals whose deficiency has been linked with malaria infection like B vitamins and vitamin C. This practice is known to be very low in Ghanaian children under 5years. Low fruit and vegetable consumption prevalence ranged from 36.6% (Ghana) to 99.2% (Pakistan) for men and from 38.0% (Ghana) to 99.3% (Pakistan) for women (Hall *et al*., 2009). This may also predispose them to common infections like malaria. A daily multivitamin and mineral supplement is known to reduce the number of infections (Barringer *et al*., 2003),.

1.3 Justification

This study is timely because, it can be an approach that can be used by policy makers as part of preventive measures for the control of infections from *P. falciparum.* Other benefits may also be gained; for example, nutrient supplementation may mitigate the delay in acquired immunity associated with bed nets and chemoprophylaxis.

The result of the study also has the potential of contributing to the realization of the Millennium Development Goal 4 which is reduction of childhood mortality.

Secondly, patients will respond better to treatment and length of treatment will be reduced. This will lead to less cost of treatment per patient. The increase response to treatment will translate into more children recovering from the disease and reduce mortality associated with it.

Also, this study seeks to investigate the relationship malnutrition and malaria. The two share certain consequences, including stunting, wasting, cognitive impairment and decreased school performance. If malnutrition and malaria rates are reduced, children will grow well and will also grow into intelligent and productive adults.

Additionally, since vitamin A and zinc protects the body against night blindness, stunting and other common infections like cough and diarrhoea, children will benefit health wise. The multivitamin and mineral supplement will also protect them from common infections.

Moreover, the country will also benefit socio-economically since the time spent by parents off the job at the hospital will be used for productive work. And children will spend less time away from school resulting in a better educated population.

Lastly, findings from this work will be disseminated worldwide through publications and presentations at conferences to expand general knowledge on nutrition and malaria, specifically, vitamin A, Zinc and multivitamins. If this study shows a positive benefit, a more sustainable method of supplementation will be developed. This will be either fortification of complementary foods or development of a complementary food from local foodstuffs rich in these nutrients

1.4 Main Objectives

To determine the effect of multivitamin and zinc supplementation on malaria infection and morbidity in children under 5 years in the Ejisu-Juabin Municipality of Ashanti Region in Ghana

1.5 Specific Objectives

1. To supplement children aged between 6months and 5years with zinc and multivitamin supplements for 5 months
2. To determine the prevalence of malaria and the parasite density in participants before and after the trial.
3. To determine the incidence of malaria episodes among study children
4. To determine the incidence of other morbid episodes among study children
5. To assess the various foods eaten by our study population

1.6 Study Hypothesis

Based on the known effects of zinc and vitamin A (Zeba *et al*.,2008; Shankar *et al*.,2008) It is hypothesized that the risk of developing malaria will be lowered by 50% in children given a single dose of vitamin A (200,000 IU) and daily doses of either Zinc (10mg) or multivitamin syrup (1-5ml per body weight) together with daily doses of zinc (10mg) compared to those given vitamin A alone.

CHAPTER TWO

LITERATURE REVIEW

2.0 Vitamin A and malaria

Vitamin A is a family of compounds with similar structures called retinoids. In plant-based foods, vitamin A is found in the form of provitamin A, principally beta-carotene (Solomons, 2006). The recommended intake of vitamin A in males and females for age 6months to 8years is between 13,33IU and 16,66IU per day. A dosing schedules for universal distribution of vitamin A for infants 6-11months is 100,000IU every 4-6months and for children aged between 12-59months, the intake is 200,000IU every 4-6months (Marks, 1975). Rich sources (more than 2000 µg retinol-equivalents/100g edible portion) of vitamin A include carrots and liver. Other moderate sources 100-500retinol – equivalents/100g edible portion) include spinach, cheese, cereals and fish (Ames, 1969).

Vitamin A is essential in the development and function of virtually all cells. Vitamin A deficiency has been associated with reduced numbers and activity of natural killer cells and eosinophils (Erickson *et al.*, 2000; Stephenson, 2001). In adaptive immune response vitamin A appears to maintain the normal antibody-mediated immune response (Long and Santos, 1999; Stephenson, 2001). In vitro studies showed that addition of free retinol to *P. falciparum* cultures reduced parasite replication in two studies (Davis *et al.*, 1998; Hamzah *et al.*, 2003), although this was not seen in another (Samba *et al.*, 1992).

Meta-analyses of findings from intervention trials have shown that, in areas of endemic vitamin A deficiency, all-cause preschool child mortality can be reduced, on average, by 23% to 34% by vitamin A interventions. Vitamin A lowered the risk of fatality from severe *Plasmodium falciparum* malaria, based on findings from a trial in Papua New Guinea (Shankar *et al.*, 1999a).

2.1 Zinc and malaria

Zinc is a trace mineral that is essential for all forms of life, including plants, animals, and microorganisms. In human subjects growth and development is strictly dependent on Zinc (Brown and Wuehler, 2000). The recommended intake of infant and children is between 5-12mg per day. Meat and animal products rich in zinc include oysters, liver, pork and calf. Vegetable and plant sources include whole meal flour, carrot and potato (FAO/WHO, 2001). Zinc is involved in a variety of cellular functions including membrane stabilization, free radical defense, signal transduction, transcription, and cell replication (Food and Nutrition Board, 2001). Given the multiple biological roles of zinc, deficiency of this element has immunological consequences. Classical signs of zinc deficiency include diarrhea and dermatitis (Keen and Gershwin, 1990; Fraker *et al.*, 2000; Cui *et al.*, 2003).

Zinc has a particularly important role in the control of blood stages of Plasmodium spp. Zinc is essential for the production of immune proteins like immunoglobin G (IgG), interferon-γ (IFN-γ), and tumour necrosis factor α (TNF-α) implicated to help in resistance to malaria (Fischer-Walker and Black, 2004).

In Papua New Guinean children, daily zinc supplementation led to a reduction of the number of fevers attributable to malaria due to *P. falciparum* by 38% (Shankar *et al.*, 2000). In contrast, in a supplementation trial in Burkina Faso, zinc provided no or only little protection against malaria (Muller *et al.*, 2001) despite evidence that the children studied were zinc deficient.

Table 2.1. Overview of some published trials to assess effects of preventive zinc supplementation in sub-Saharan African children

Country	Population Studied	Design	Main findings
Ghana (Zlotkin *et al.*, 2003)	Rural anemic children, 6–18 months (n=304)	Zinc (10 mg as gluconate) plus iron (80 mg as ferrous fumarate) versus iron alone, daily for 2 months 1	No evidence of improved zinc status or catch-up growth
South-Africa (Bobat *et al.*, 2005)	HIV-infected children, not receiving antiretroviral therapy; 6–60 months (n=96)	Zinc (10 mg as sulphate) versus placebo, daily for 6 months	No effect of zinc on plasma viral load or CD4 counts. Overall odds of diarrhoea (all surveys combined) lower in zinc group (p=0.001
(Walker *et al.*, 2007)	Infants aged 1–5 months with acute diarrhoea (n=163) (multi-country study also including children in India and Pakistan)	Zinc (10 mg as sulphate) versus placebo, daily for 2 weeks	No apparent benefit
Pemba, Tanzania (Olney *et al.*, 2006; Sazawal *et al.*, 2004; Kordas *et al.*, 2009)	Children (without severe malnutrition), 1–35 months (n=42,546)	Zinc (5–10 mg as sulphate) versus placebo, daily until children reached the age of 48 months	Zinc resulted in reduction in all-cause mortality by 7% (–19% to 6%). Effect seemed more pronounced among children aged > 12 m (18% [0–32%] reduction in all cause mortality). Zinc also resulted in longer sleep duration, increased hemoglobin concentration and decreased ZPP:H ratio
South Africa (Luabeya *et al.*, 2007; Chhagan *et al.*, 2009)	HIV-positive and HIV-negative children, 4–6 months (n=36 and 341)	Zinc (10 mg as gluconate) plus multi-nutrients plus vitamin A versus zinc plus vitamin A versus vitamin A alone, for 18 months. 21%–23% of children in all groups received therapeutic iron during the study (dose/ duration not specified)	2007: No evidence that zinc, or zinc plus multi-nutrients reduce the prevalence of diarrhoea and respiratory tract infections. No difference in effect between subgroups. 2009:Improved growth and increase in hemoglobin concentration due to multi-nutrients, as compared to zn+vit A, or vit A alone

2.3. Other micronutrients and malaria

There have also been studies to elucidate the role of other micronutrients in malaria. Poor thiamine (vitamin B_1) status is associated with greater risk of severe malaria and simple clinical malaria (Krishna *et al.*, 1999). Also, high doses of riboflavin (vitamin B_2) suppress parasite growth by preventing the oxidation of hemoglobin needed by the malaria parasites (Akompong *et al.*, 2000a). Thus, high-dose riboflavin therapy could possibly be of benefit. No evidence of the role of niacin (Vitamin B_3), pyridoxine (vitamin B_6), cobalamin (vitamin B_{12}), vitamin D on malaria have been found (Rall and Meydani, 1993). Experiments in monkeys has indicated that vitamin C deficiency exacerbated malaria (McKee and Geiman, 1946). In general, data is lacking on the effects of these nutrients on malaria morbidity, pathology, and mortality in humans. Additional studies in this area are clearly warranted.

2.4 Multiple micronutrient supplementation and malaria

Literature suggests a potential interaction between Vitamin A and zinc (Smith *et al.*, 1973; Christian and West, 1998). In children with severe protein energy malnutrition, zinc supplementation improved serum retinol binding protein and retinol concentration (Rahman *et al.*, 2001a). Subsequently, a combined Zinc and vitamin A supplementation reduced malaria morbidity by 38% in rural Burkinabee children aged 6months- 6yrs (Zeba *et al.*, 2008).

Only one study was found to have examined the role of zinc and multiple micronutrient supplements in malarial outcomes in children less than five years of age. In this study it was found that preschool children in Tanzania showed no evidence that multi-nutrients influenced the effect of zinc (or vice versa). Neither zinc nor multi-nutrients influenced malaria rates respectively. This clearly indicates that more research is needed in this area.

2.5 Anthropometry

Anthropometric measures include physical measurements of weight, height, head circumference, mid upper arm circumference, and skin fold thickness that are compared to reference values. A single measurement generally indicates cumulative growth, while repeated measurements show whether growth is proceeding normally. Head and brain growth is maximal during the first two years of life, after which growth is very slow. Mid upper arm circumference measurements (MUAC) reflect the amount of subcutaneous fat and muscle, and changes correlate positively with changes in weight. A decrease in MUAC indicates a reduction in one or both of these tissues (Lee and Nieman, 1996).

2.6 Significance of weight-for-age, weight-for-height, height-for-age

The weight or height of an individual is compared to a known reference of the same age or height. The most widely used reference is that of the US National Centre for Health Statistics (CDC/NCHS/WHO). Anthropometric indices are reported using three different systems namely Z-scores, percentiles, or percentage of the median.

The z-score or standard deviation (SD) unit is given by the calculation below:

$$\text{Z-score} = \frac{\text{(observed value for an individual)} - \text{(median of the reference population)}}{\text{SD of the reference population.}}$$

The advantage of this index is that the curves are normally distributed and a fixed Z-score interval corresponds to a fixed weight or height difference for children of a given age (Onis de and Blössner, 2009).

Weight-for-age: Low weight-for-age index identifies the condition of being underweight, for a specific age. The advantages of this index are that it may reflect both past (chronic) and/or present (acute) undernutrition (although it is unable to distinguish between the two)

Height-for-age: This index is an indicator of past undernutrition or chronic malnutrition. It cannot measure short term changes in malnutrition. For children below 2 years of age, the measurement used is length-for-age; above 2 years of age, the index is referred to as height-for-age. Deficits in length-for-age or height-forage are signs of stunting.

Weight-for-height: This index helps to identify children suffering from current or acute undernutrition or wasting and is useful when exact ages are difficult to determine. Weight-for-length (in children under 2 years of age) or weight for- height (in children over 2 years of age) is appropriate for examining short-term effects such as seasonal changes in food supply or short-term nutritional stress brought about by illness. The three indices are used to identify three nutritional conditions: underweight, stunting and wasting (De Onis *et al.*, 1997).

2.7 Assessing nutritional status

Nutritional status can be determined using a 24-h dietary recall and a food frequency questionnaire. In a 24-h recall the respondent recalls and provides a detailed description of all food and drink consumed, including cooking methods and brand names (where possible), on the previous day. Food quantities are measured using household measures or food models. The food frequency questionnaire asks about the frequency (daily, weekly, monthly, or yearly) of consumption of major foods. Food consumption data are converted into nutrient intake using food composition tables and reported as percentage of the recommended daily allowances (Lee and Nieman, 1996).

CHAPTER THREE

METHODOLOGY

3.1. Study site and recruitment

The study was conducted between November 2011 and April 212, in areas in the *Ejusu-Juaben municipality,* Ghana. These were *Achinakrom, Sarpeh, Onwe, Abenase, Donyina*. These communities were selected because of the rural setting and the fact that only one (*Onwe*) has a health center, making access to health information and care very low. Due to this the treatment of malaria is not properly handled. The malaria infection rate is 60% of outpatient cases in the municipality (MOH, 2010). Announcements were made at the various information centers in the various communities to encourage parents with children in the age group to make them available for the study

3.2 Ethical Issues

The study was reviewed and approved by the Committee on Human Research, Publications and Ethics, Kwame Nkrumah University of Science And Technology, School of Medical Sciences & Komfo Anokye Teaching Hospital Kumasi, Ghana. The study was explained explicitly to parents in their local language for them to completely understand what the study involved. Consent was obtained from parents enrolling each child into the study either orally, in writing or by use of thumb.

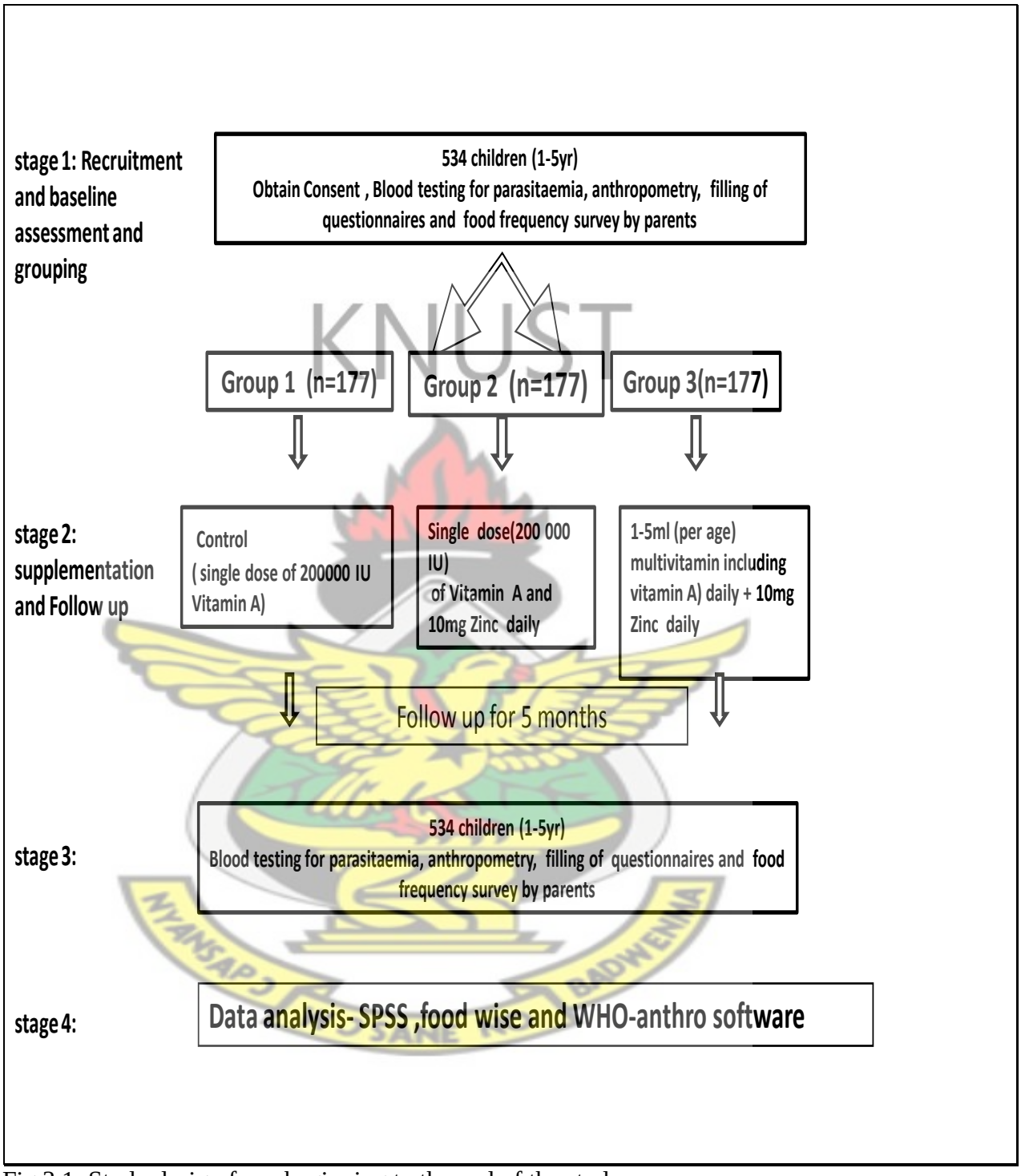

Fig 3.1: Study design from beginning to the end of the study

3.3 Sample Size

Assuming a prevalence rate of 35% of malaria episodes in the age group with 90% power and $\alpha = 0.05$, it is hypothesized that combined vitamin A and zinc or vitamin A zinc and multivitamin supplementation will reduce the prevalence rate by 50% (see page 7), assumption that 10% of participants would be lost to follow up. From this premise the sample size was calculated as n =177 for each group making a total of 531 children.

3.4. Randomization and Micronutrients Distribution

Children aged 6 months to 5 years who had received vitamin A (200,000 IU) supplements as part of a national supplementation were enrolled into the study. The vitamin A supplement had been given two weeks before the study. Confirmation of intake was done by checking their health record cards, the presence of an indelible mark on their small finger and oral confirmation from their care givers. They were included if 1) they showed no signs of malaria infection or other illness; 2) there was parental consent for the child's participation. 3) they planed not to move from the locality for at least the next 6 months. Children showing signs of malaria, allergic to any of the drugs or supplements or having obvious or terminal illness e.g. cancer, HIV etc were exclude from the study. After enrolment, children were randomly sectioned into vitamin A only (control), vitamin A and zinc or multivitamin and zinc by allowing them to select group numbers from an envelope. The vitamin A group was called the control group since all the children in the study had received a single dose of vitamin A.

The vitamin A and zinc group received a capsule of zinc containing 10 mg of elemental zinc in addition to the Vitamin A, 7 days a week for a 5-month period. In the multivitamin and zinc group each child received a 1-5ml/age multivitamin syrup once a day and a tablet of 10mg elemental zinc 7 days a week for 5 months. As per national guidelines, children who tested positive to the rapid test kit for malaria but were not showing symptoms were treated with a 3 day course of Artermether (4-5mg/kg)/ Lumifantrine (10mg/kg)-(3days) in order to clear any malaria infection 7 days before the initiation of supplementation. An episode of *P. falciparium* malaria was defined as temperature ≥37.5° C, accompanied by the presence of asexual forms of the *P. falciparium* on blood smear , or a positive response to the malaria rapid test kit in children with guardian-reported fever and no other obvious cause for the illness. History of fever, cough, diarrhea, and stomach ache and the use of mosquito net on the previous night were recorded.

3.5 Cross Sectional Survey and Follow Up

Two surveys were conducted – before and after the study. During these surveys the history of fever, immunization data, physical examination encompassing height and weight. The ages of the children were recorded from birth record cards. The parents of children were interviewed using a 24 hour recall and food frequency questionnaires to get fair representation of their nutrient intake. A structured questionnaire was administered to parents to ascertain factors that may predispose them to malaria.

The primary outcome, an episode of malaria, was pre-defined as a positive response to the malaria rapid test kit in children with guardian-reported fever and any of the following confirmed fever (axillary temperature ≥ 37.5°C), separated by at least 14 days from a previous malaria episode. Community health workers who have been trained under the Home Management of Malaria Program administered supplement to participating children. The Parents were advised to bring their children to the home of the health worker as soon as the child fell sick. The health worker also visited the homes weekly to record any signs of sickness.

The health workers were trained to diagnose malaria with the malaria test kit. The health workers made regular, unannounced spot checks to ensure adherence to procedures. Supplementation and follow-up continued for all children for five months. Each child was visited by a community health worker for zinc and multivitamin administration, and for recording any sign of illness. An episode of *P. falciparum* malaria was defined as temperature ≥37.5° C, accompanied by a positive test for the malaria antigen P.*falciparium* (Histidin Rich Protein 2) detection rapid card test. Malaria episodes were treated with artemether lumefantrine and were followed up for 7 days. Forms used by the health workers to record administration of micronutrients and monitoring of malaria episodes are attached.

3.6 Laboratory Procedures

First Response malaria antigen P.*falciparium* detection rapid card test (Premier Medical Corporation Ltd, Nani-Daman, India) for the qualitative determination of malaria histidine -rich protein 2 (HRP2) in blood was used.

The test kit contains a membrane strip, which is coated with a monoclonal antibody across a test strip. The monoclonal antibody (test line) is specific to the Histidine –rich protein 2 of the plasmodium. This test has a sensitivity of 95% for samples with positive *P. falciparum* parasites and 99% for random normal human specimen (Velecha *et al.*, 2002). Blood films were prepared for all children. Children with *Plasmodium* infection were treated with artemether-lumefantrine. Thick and thin Giemsa-stained blood films were reviewed for the presence of *Plasmodium* species. Each film was examined by microscopy by two experienced laboratory technicians who were blinded to the groups. The parasite count per µl was done by counting 200 white blood cells and the number expressed on the basis of 8000 WBC per µl (Trape, 1985,).

3.7. Anthropometry

Scales were calibrated for each measurement. Child weight was measured with an electronic scale for children who could stand and a hanging scale was used for children who could not stand on their feet. In measuring the weight, the child's shoes, bulky clothing, and hair ornaments that interfere with the measurement were removed. The hanging scale was zeroed after it has been adjusted with the weighing pants and measurement taken when child was still. All measurements were taken to the nearest kilogram.

A locally made stadiometer was used to measure the height of children who can walk. The child was made to stands with head, shoulders, buttocks, heels touching a flat surface, feet flat, straight, together, and arms were at the sides, and with shoulders level. A horizontal head board was lowered firmly onto the head while the subject inhales and a reading taken at observer's eye level.

Those who couldn't stand were made to lie before their lengths were taken with a tape measure and the measurement was accurately recorded to the nearest 0.1 centimeter. The mid-upper arm circumference (MUAC**)** was measured with the subject standing with his left arm at right angles. The midpoint of the child's left upper arm was calculated by measuring the length of the tip of the shoulder to the end of the elbow and dividing by two. The arm circumference was then measured at the midpoint with the arm hanging relaxed and using a non-stretching flexible fiber glass tape held snugly around the arm.

3.8 Statistical Analysis

The analysis was done with SPSS (v 19·0 for Windows, SPSS, Chicago, IL, USA), GraphPad prism (v.5.01 for windows, Graphpad software Inc) .The analysis was based on the mean (for continuous variables) or proportion (for binary variables). Comparison of malaria incidence between the treatment groups was based on the two-sided 95% confidence interval. All analyses were by intention to treat. The risk ratio (RR) of a P.*falciparium* episode in those given vitamin A only, zinc and vitamin A and vitamin A, zinc and multivitamin was the ratio of incidence between the vitamin A (control) and the other groups. Weight, height and age data were converted to Z-scores based on the National Center for Health Statistics standard with the WHO anthropometry software (WHO).

CHAPTER FOUR

RESULTS

4.1. Demographic characteristics of children and care givers

In the current study a total of 587 children within the age groups 6months to 60 months were screened, however 45 children were eliminated from the population sample for the following reasons; irregularity of care giver's residency during the study period, ill health, unreliability of date of birth records (Fig 4.1). Five hundred and forty two (542) were randomized into the three groups; vitamin A (control n=177), vitamin A and zinc (n=189), vitamin A, zinc and multivitamin (179). The number of children belonging to the different classes were fairly representative (Table 4.1).

A total number of 347 children between the age group 6 months and 60 months completed the study which began with 542 children. The results shown in this section are therefore based on the 347 participants who completed the study or on children we had both their baseline and end of study data taken. The ratio of males to females was 45.8 to 54.2 % (Table 4.1). Out of the 347 respondents who completed the course, 82 % had parents who were married. The remaining 18% had single parents (Table 4.1). The majority of the parents had had primary/elementary education. About 80 % (Table 4.1) of the parents have either had secondary or primary education. During the study a number of factors contributed to children not completing the study (Fig 4.1)

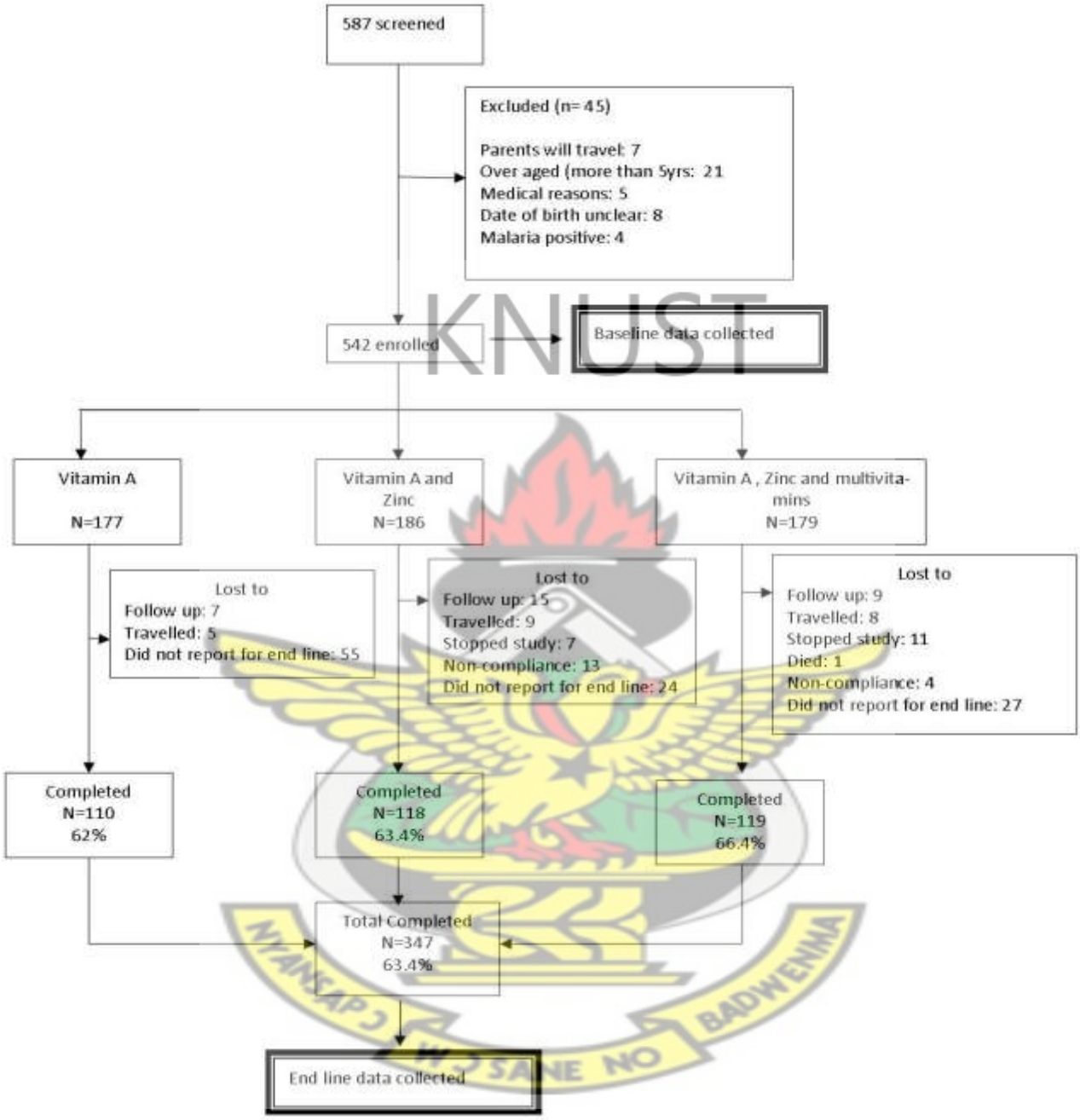

Fig 4.1: The study profile of the intervention from beginning to end of study;

Also another factor that reduced the number of children who completed the study was that fact that the study was not placebo controlled. Those in the vitamin A group felt left out and so when the end of study data was being taken at the community centers they refused to turn up (n=55). The reason we can give for those in the vitamin A & zinc and vitamin A, zinc & multivitamin groups not turning up (n=51) is the fact that the health worker did not meet them in their home to give them the information, they did not hear the public address system announcement , they had other pressing commitment or did not attach sufficient importance to participation. Other mothers (n=19) were not giving the supplements to the children as directed by the health workers and so they were withdrawn from the study.

The proportion of foods consumed which were rich in carbohydrate and protein rich foods were 51.5% and 23.7% respectively while the proportion fruits and vegetables was 24.9% (Table 4.2). All the carbohydrate rich foods are poor sources of vitamin A and zinc. The dietary patterns indicate a low intake of animal protein, zinc and vitamins such as vitamin A, and C.

Table 4.1: Socio-demographic data on children and care givers who completed the study (n=347)

	N		Percent (%)	
Age class of participants				
>1year	75		21.6	
< 1year	272		78.5	
Gender of participants				
Male	159		45.8	
Female	188		54.2	
Marital status of care givers				
Single	61		17.6	
Married	286		82.4	
Head of household of participants				
Father	310		89.3	
Mother	36		10.4	
Other	1		.3	
Monthly income (GHC) of care givers of participants				
Less than 100	62		19.5	
100-300	238		69.4	
300-600	35		9.0	
600-900	6		1.7	
1000-3000	1		.3	
Educational background of care givers				
	Women	Men	Women (%)	Men (%)
primary/elementary	249	194	72.2	55
secondary	54	86	15.7	25.3
post secondary	4	22	1.2	6.5
Tertiary	5	9	1.4	2.6
None	31	13	9	3.8
don't know	4	23	0.6	6.8

Table 4.2: Various meals/snacks eaten by all children (n= 542) based on a 24 hour recall

Meals/snacks eaten by population in 24hours	Number children eating the food	meals/snacks by population in 24hours	Number children eating the food
CARBOHYDRATES		**VEGETABLES**	
Banku	94	Beans	17
Plain rice	72	Carrot	12
Fufu	56	Nsusuaa	10
Kenkey (Fante /Ga)	51	Cabbage	5
Cooked Plantain	37	Green pepper	3
Cooked yam	31	mushrooms	1
Gari / Eba	23	**DAIRY PRODUCTS**	
Fried yam	15	Boiled eggs	22
Fried plantain	11	Condensed milk	15
Jollof Rice	11	Evaporated Milk	12
Fried Rice	10	Fried eggs	5
MEATS /FISH /SEA FOOD		**FRUITS**	
Beef	42	Orange	65
Fish	30	Banana	12
Chicken	3	Water melon	12
Goat meat	2	Avocado Pear	9
SOUPS		Apple	8
Groundnut soup	50	Pawpaw	8
Palm nut soup	41	Pineapple	6
Kontonmire soup	36		
Okro soup	24		
STEWS		**DRINKS**	
Tomato stew	47	Sweetened drinks Kalyppo	43
Okro stew	44	Minerals	9
Garden egg stew	34	Malt	5
Beans stew/ Beans & oil	17	Fruit Juices	1
BREAKFAST		**PASTRIES**	
Koko	49	Biscuits	57
Tea	42	Doughnut/ Bofrot	2
Bread (White /Brown)	37	Meat pie	2
Tom Brown	19	**OTHERS**	
Kose	17	Formula	12
Hausa koko	11	Breast milk	213
TOTAL MEALS/SNACKS CONSUMED			**1552**

4.2 Baseline characteristics of study participants who completed the study by intervention groups.

The distribution of the sexes, age groups, the use of mosquito nets and plasmodium infection at baseline according to the intervention groups is shown in table 4.3. The intervention groups were similar in terms of sex distribution (p value = 0.73), age (p value = 0.38) and bed net use (p value =0.4).

Table 4.3: baseline characteristics of study participants who completed the study by intervention groups

	Vit A alone	Vit A plus zinc	Vit A, Zinc & multivitamin	p-value
Variables	n %	n %	n%	
	110 (31.7)	118 (34)	119 (34.3)	
Sex				
Male	49 (44.5)	52 (44.1)	58 (48.7)	0.731
female	61 (55.5)	66 (55.9)	61 (51.3)	
Age class of participants				
> 1year	23 (30.7)	24 (32.0)	28 (37.3)	0.82
< 1year	87 (32.0)	94 (34.5)	91 (33.5)	
Use of mosquito nets by the participating children				
Use	69 (62.7)	75 (65.2)	68 (57.6)	0.477
Don't use	41 (37.3)	40 (34.8)	50 (42.4)	

4.3 Indicators of malaria infection among intervention groups for baseline and end of study as well as during the 5month follow up period

The risk of malaria among children who received vitamin A, zinc & multivitamin during the study period was 62% (RR = 0.62, p= 0.018)) of the risk in children who receive vitamin A alone (Table 4.4a). Also the risk of children who received vitamin A & zinc developing malaria during the study period was 81% (RR = 0.82, p= 0.32) of the risk in children who received vitamin A alone (Table 4.4a). Similarly, The risk of other illness other than malaria among children who received either vitamin A, zinc & multivitamin or vitamin A & zinc during the study period was 77% (RR = 0.77) and 83% (RR = 0.83) respectively (Table 4.4a).

There was no difference among the three groups in terms of positive plasmodium infection during the two cross sectional surveys. The parasite density for baseline was not reported due to errors in slide preparation. At the end of the study, the vitamin A and zinc group had the lowest parasite density (1608 mps/ul) compared to the other groups (see Table 4.3b). Vitamin A group had the highest number of incidences of diarrhoea, fever, rashes, vomiting and other illness (e.g. headache, convulsion etc) while the vitamin A and zinc group had the highest number of children with measles (Fig 4.2).

Table 4.4a: Comparison of episodes of malaria and other morbidity between vitamin A alone and the other groups during the study period

Groups	**Malaria episodes**			
	Cases	No cases	RR(95% Cl)	P-value
Vit A alone [n=110(%)]	39 (35.5%)	71 (64.5%)	1	
Vit A/ zinc [n=118(%)]	34 (28.8%)	84 (71.2%)	0.81(0.55-1.19)	0.3210
Vit A/ zinc /Multivite [n=119(%)]	25 (64.5%)	94 (79.0%)	0.62 (0.39-0.91)	0.018
	Illness other than malaria			
	Cases	No cases	RR(95% Cl)	P-value
Vit A alone [n=110(%)]	54 (50.9%)	56 (50.8%)	1	
Vit A/ zinc [n=118(%)]	48 (40.7%)	70 (59.3%)	0.77 (0.57-1.02)	0.109
Vit A/ zinc /Multivite [n=119(%)]	45 (37.8%)	74 (62.2%)	0.83(0.62-1.11	0.2310
	General morbidity (malaria and other illness together)			
	Cases	No cases	RR(95% Cl)	P-value
Vit A alone [n=110(%)]	72 (65.5%)	38 (34.5%)	1	
Vit A/ zinc [n=118(%)]	62 (52.5%)	56 (47.5%)	0.80(0.65-0.99	0.0594
Vit A/ zinc /Multivite [n=119(%)]	54 (46.6%)	62 (53.4))	0.71 (0.56-0.90)	0.005

*RR- Risk ratio of vit A/zinc and vit A or vita A/zinc/multivite and vit A

Table 4.4b: Comparison of indicators of malaria infection between vitamin A alone group and other groups during cross sectional survey at baseline and end of study

	Positive malaria rapid test kit[a] result by intervention groups during cross-sectional surveys			
Groups	Baseline	endline	RR((95%Cl)	P-value
Vit A alone [n=110(%)]	50 (45.5%)	33 (30%)	1	
Vit A/ zinc [n=118(%)]	44 (37.2%)	35 (29.5%)	0.92(0.7-1.2)	0.63
Vit A/ zinc /Multivite [n=119(%)]	40 (33.6%)	34 (28.5%)	0.9(0.62-0.18)	0.52
	Endline geometric mean parasite density[b] among intervention groups during cross-sectional surveys			
	Mps/ul		**P-value between groups**	
Vit A alone [n=110(%)]	6620		p =0.139	
Vit A/ zinc [n=118(%)]	536			
Vit A/ zinc /Multivite [n=119(%)]	1608			

*p-values are the overall group comparison using Pearson-Chi square test for significance (p< 0.05)

a. First Response malaria antigen P.falciparium detection rapid card test for qualitative determination of malaria histidine -rich protein 2 (HRP2) in blood.

b. counting 200 white blood cells and the number expressed on the basis of 8000 WBC per µl.

*RR- Risk ratio of vit A/zinc and vit A or vita A/zinc/multivite and vit

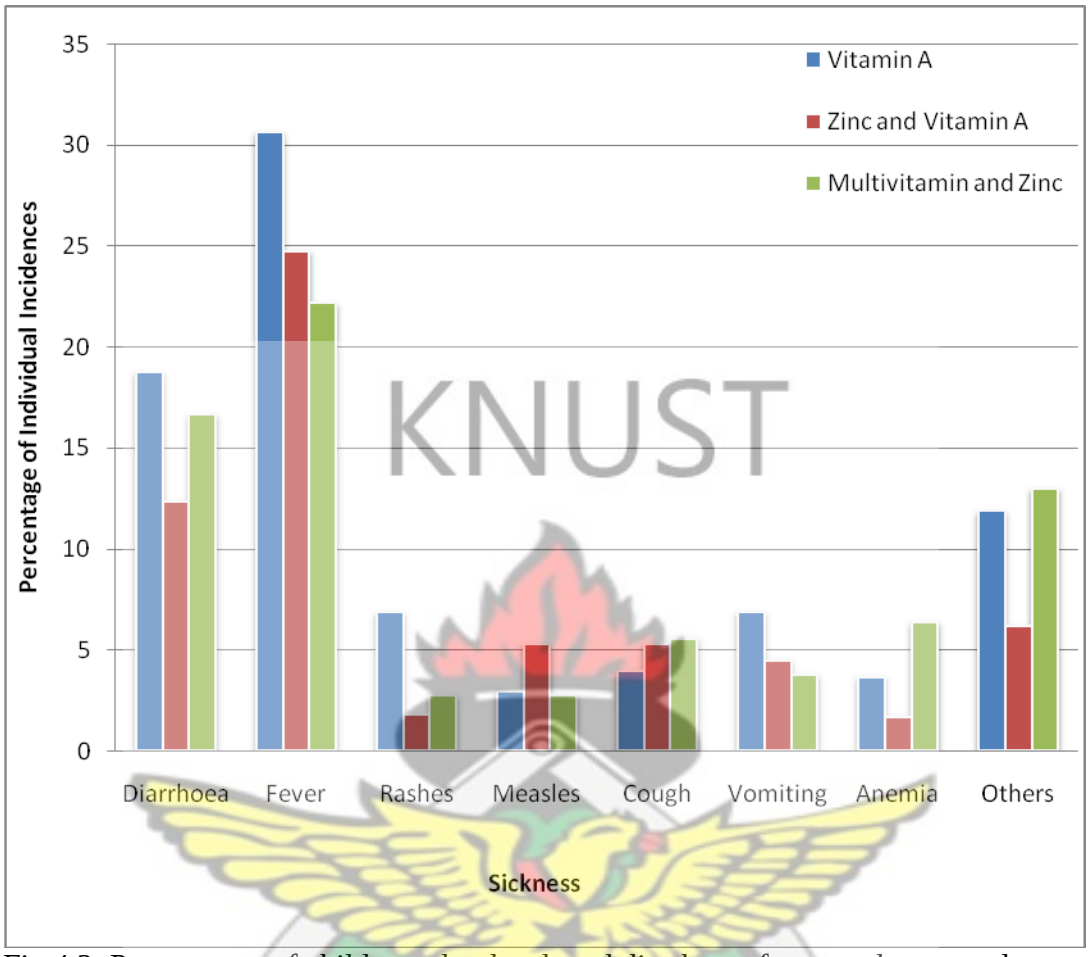

Fig 4.2: Percentages of children who developed diarrhoea, fever, rashes, measles, cough, anemia, vomiting and other illness (e.g. headache, convulsion etc.) among the intervention groups during the five month follow up period.

4.4 Mean days to first infection of illness in the intervention groups during study period

Amongst the groups it took those in the multivitamin and Zinc group a longer time (average of 112 days) to get malaria than the others groups; vitamin A (93days) and vitamin A and Zinc (94 days) groups (Table 4.5). The vitamin A and zinc group recorded an average of 106 days to develop any other illness apart from malaria than the other two groups. When the two variables were put together (general illness), the multivitamin and zinc group took a longer time (104 days) as compared to 99 days and 98 days for vitamin A and vitamin A and Zinc groups respectively.

Table 4.5: Mean days to first malaria episode, other morbidity and general illness between intervention groups during the study

Treatment	Factor	Mean (days)	Range[c]	Standard Dev
Vitamin A	Malaria	93	12--161	50.8
	Other Morbidity[a]	103	8--168	50.6
	General Illness[b]	99	8--168	50.8
vitamin A and Zinc	Malaria	94	6--167	49.2
	Other Morbidity	106	6--167	50.8
	General Illness	98	6--167	52.9
Vitamin A, zinc & multivitamin	Malaria	112	24--162	47.5
	Other Morbidity	103	9-167	49.5
	General Illness	104	9-167	48.4

a. any other illness apart from malaria e.g. diarrhoea, fever, rashes, measles, cough, anemia, vomiting

b. malaria and other illness together

c. Number of days to first infction in the group and the highest number of days in the group to develop an illness

4.5. Anthropometric indices

The summary of the z-score values and the standard deviation for weight-for-age, height for age, weight for height factor is given in the table 4.6. The anthropometric indices improved (higher z-scores at end of study) across all the three indices (weight for age, length for age, weight for height).

Table 4.6: z-score values for weight for age, length for age, weight for height in various intervention groups at baseline and end of study for children who completed the study

Treatment	Baseline		Endline		Sig.
	Mean	Stand. Dev	Mean	Stand. Dev	
Weight-for-age					
Vitamin A	-0.38	1.56	-1.22	1.5	0.0000
Zinc and Vitamin A	-0.76	1.51	-1.17	1.36	0.0089
Multivitamin and Zinc	-0.36	1.69	-1.23	1.4	0.0000
Overall	-0.5	1.59	-1.21	1.42	0.0000
Length/height-for-age					
Vitamin A	-0.2	1.58	-1.83	1.49	0.0000
Zinc and Vitamin A	-0.07	1.66	-1.53	1.57	0.0000
Multivitamin and Zinc	-0.08	1.72	-1.79	1.35	0.0000
Overall	-0.12	1.65	-1.71	1.48	0.0000
Weight-for-height/length					
Vitamin A	-0.39	1.7	-0.31	1.66	0.6600
Zinc and Vitamin A	-0.91	1.82	-0.45	1.72	0.7200
Multivitamin and Zinc	-0.54	1.61	-0.36	1.66	0.6600
Overall	-0.62	1.72	-0.38	1.68	0.6800

a. z-score ± Standard deviation

p-values are the overall group comparison using Pearson-Chi square test for significance ($p < 0.05$)

The summary for the weight-for-age factor is given in the table above for the different treatments. It shows an overall significant difference between the baseline and endline measurements. There is significant difference in all treatments at a level of significance of 0.05 with the Zinc and Vitamin A group registering a relatively extreme mean of -0.76.

The length-for-age factor also shows a significant difference between the baseline and endline overall results. This difference is due to the fact that at a significance level of 0.05, all treatments were significantly different with a common mean of -1.71. The Vitamin A group recorded a high in magnitude mean of -1.83.

The weight-for-height/length factor on the other hand has an overall significance of 0.6800 , it implies that there is no significant difference in the mean measurements with the groups (i.e. Vitamin A group, Zinc and Vitamin A group and Multivitamin and Zinc group) by comparing the endline and baseline statistics.

CHAPTER FIVE

DISCUSSION

In this study, there was evidence the risk of malaria infection in children who received vitamin A, zinc & multivitamin was significantly reduced to 62% of the risk of those who received Vitamin A alone (100%). In children who received vitamin A & zinc the risk was 81%, though this decrease was not significant. This means that vitamin A, zinc & multivitamin protected the children better than giving the children vitamin A alone or vitamin A & zinc. It is of interest that the effects of vitamin A, zinc & multivitamin on malaria were not reflected in cross-sectional malaria test kit results, suggesting that zinc primarily affects immunological or pathological processes associated with clinical episodes. However, vitamin A, zinc & multivitamin decreased end of study geometric mean parasite density as compared to supplementing with vitamin A alone

This indicates that there is a synergistic effect of zinc, vitamin A and multivitamins on malaria rates. More vitamin A is stored in the liver when the diet contains vitamin E and zinc than when the diet is deficient in vitamin E and zinc. Hence, concurrent ingestion of several nutrients may result in synergistic, or threshold effects as compared to a single nutrient (Ames, 1969). In this study, it was found that vitamin A, zinc & multivitamin increased the time to first malaria and decreased the episodes of malaria, is very noteworthy. This is because there are a few studies (Ramakrishnan and Huffman, 2001; Barringer *et al.*, 2003; Luabeya *et al.*, 2007) that examine the interaction between vitamin A, zinc, multivitamins and as it relates to morbidity.

Barringer *et al.*, (2003), reports in a study in North Caroline that patients taking placebo pill reported more infections and more days missed from work due to infection than did

patients taking the vitamin and mineral pill. Subsequently, a study in Tanzania suggests a protective effect of multivitamin supplementation on malaria. In that study (Villamor *et al.*, 2007) , daily multivitamin supplementation of HIV-infected women during pregnancy and the lactation period decreased the incidence of malaria outcomes among their children during the first 2 years of life. A combination of vitamins B-complex, C, and E significantly decreased the incidence of clinical malaria by 71%; a protective effect was also suggested on high parasitemia, although it did not reach statistical significance. The same can be said of this current study, since the parasitemia levels were lower in the zinc and multivitamin group than the vitamin A group, but it was not significant (p=0.139). Albeit, in another study in children aged 6–60 months there was no evidence that preventive zinc supplementation, alone or with multinutrients, reduced rates of febrile attacks of malaria.

Furthermore, there was no evidence that multi-nutrients influenced malaria rates and multi-nutrient supplementation may have increased the incidence of first malaria episodes by approximately 30% (Veenemans *et al.*, 2011). The results from Veenemans and colleagues could have been exacerbative because the multinutrients they administered included iron. Iron has been speculated to enhanced parasite proliferation specifically in children with iron deficiency (Oppenheimer *et al.*, 1986). This is because iron absorption in iron deficient children is more efficient and thus may lead to transient production of non-transferrin bound iron (Hutchinson *et al.*, 2004; Baron *et al.*, 2008).

This may act as a nutritional source and favour the proliferation of *Plasmodium* parasites (WHO, 2007). A randomized trial among children aged 1–35 months in Pemba, Tanzania showed that daily supplementation with iron (12.5 mg as ferrous sulphate) and folic acid

increased rates of hospital admission and all-cause mortality (combined endpoint) by 12% (Sazawal *et al.*, 2006). This report reinforced earlier concerns that iron interventions can increase the incidence of malaria and infectious disease, even in individuals without iron overload (Oppenheimer 2001, 2002).

The multivitamin used in our study however, did not include iron hence enhancing the protective effects of the multivitamin. Nevertheless, it is not possible to determine to what extent the apparent benefits of multivitamins (B_1, B2, B_6, B_{12}, C, D and E) could have contributed to the actions of individual nutrients. In our study; the potential mechanisms that mediate the vitamins' effects on clinical P. *falciparum* malaria are speculative.

As mentioned, despite the lowering of P. *falciparum* episodes in children given vitamin A, zinc & multivitamins, consistent effects were not observed in cross-sectional malaria test kit results. Indeed, the percentage decrease in P. *falciparum* prevalence at the end-of-study survey was higher in the vitamin A group compared to the vitamin A & zinc /multivitamins group. It is, however, noteworthy that differences in parasite density did not follow the same pattern. One possibility for this observation may be that there may have been greater rates of clinic attendance due to malaria or other infections in the vitamin A group.

This could have led to higher consumption of anti-malarial drugs or immune boosters, possibly resulting in the observed differences in cross-sectional prevalence. However, the frequency of their infection could have contributed to their high geometric mean parasite densities. Alternatively, given that zinc is a known antioxidant and a potent inhibitor of

apoptosis (Brown *et al.*, 2009c), children given zinc may better endure the immunopathologies associated with a P. *falciparum* episode and appear less ill to their parents, resulting in fewer clinic visits.

Considering the effect of the combination of vitamin A and zinc on malaria, it has been earlier proven by a study in Bangladesh (Rahman *et al.*, 2001b) that zinc helps improves vitamin A status. In that study, although >90% of the children had received a vitamin A capsule (200,000 IU) as part of the National (India) Vitamin A Week campaign 4–6 mo before enrollment, 38% of these children were still vitamin A deficient. After receiving another large dose of vitamin A (200,000 IU) during the study, a significant number of children in all groups except the Zinc and vitamin A group remained vitamin A deficient. Thus, vitamin A status improved significantly in children who received both zinc and vitamin A, but not in those who received vitamin A alone.

This can be based on well documented evidence that zinc deficiency decreases plasma vitamin A levels, and zinc deficiency impair hepatic Retinol Binding Protein synthesis (Smith *et al.*, 1976). This protein helps in the hepatic mobilization of vitamin A. Zinc is also for essential for the production of immune proteins like immunoglobin G (IgG), interferon-γ (IFN-γ), and tumour necrosis factor α (TNF-α) implicated to help in resistance to malaria (Fischer-Walker and Black, 2004).

Based on these findings and the role of vitamin A in reducing childhood morbidity and mortality, Zeba et al., (2008) studied the effect of a combination of vitamin A and Zinc on malaria morbidity.

This was from the backdrop that vitamin A and zinc independently ((Shankar *et al.*, 1999a; Shankar *et al.*, 2000) reduced malaria rates by 30% and 38% respectively. The findings of Zeba and others were consistent with our findings since in their work, the combination reduced plasmodium infection by 38%, although in our case the reduction was not statistically significant (p=0.052).

The mean parasite densities counted on the blood films between groups showed that the vitamin A group, had a high mean parasite density of 6620[280-12,960]parasites/µL at end of study .The mean parasite density was lowest in the vitamin A & zinc group; 536 [240-440]parasites/µL at end of study. This is consistent with the vitamin A and zinc trial in Burkina Faso (Zeba *et al.*, 2008). In that study, the combination of vitamin A and zinc reduced the parasitemia from 1589 [1026–2459] to 1011 [647– 1579], and there was a significant increase in the placebo group from 1444 [923–2259] to 1945 [1155–3275] (p = 0.023). In the current study the baseline parasitemia levels could not be presented due to errors at the preparation of slides. The slides could not be prepared again because blood samples were not collected for storage. In spite of this the level of parasitemia in the vitamin A and zinc group is worth commenting on and can be said to be comparable to the previous study in Burkina Faso (Zeba *et al.*, 2008). Lastly, a trial in Ghana reported that addition of zinc to the routine intervention package of malaria chemoprophylaxis, iron and folic acid for pregnant women in Ghana was associated with reduced densities of malaria parasites (Saaka *et al.*, 2009).

Similarly in our case, there was a reduction in parasite densities in the groups which took the additional nutrients in addition to vitamin A. Overall, the mean number of days (112 days) to develop the first malaria episode and other illness including malaria (104 days) was longer in the vitamin A, zinc & multivitamin group than in the other groups. Zinc appears to have an effect beyond an impact on malaria alone as many studies have shown that zinc reduces morbidity due to numerous infectious diseases (Jacob *et al.*, 1978; Moran and Lewis, 1985; Fraker *et al.*, 1987; Sazawal *et al.*, 1998; Dutta *et al.*, 2000). This is shown in the vitamin A and zinc group having a higher mean number of days [106 days] to develop other illness as compared to the other groups. The incidence of confirmed malaria was lowest (25 cases) in the multivitamin group with the vitamin A group having the highest number (39 cases) of malaria incidence. Reports from a study in South Africa (Chhagan *et al.*, 2009) indicates that supplementing HIV-infected and non-infected children with multivitamins resulted in an increase in haemoglobin levels, although the haemoglobin levels of our population was not checked, the multivitamins may have contributed to the children having an improved immune status or the mothers took good care of their children.

Across groups the vitamin A, multivitamin and zinc groups recorded the highest number of sickness-free children either from malaria or from other illness (p=0.015). This finding is in contrast to the finding of a study in Tanzania (Veenemans *et al.*, 2011) which found no evidence that supplementing with multivitamins and zinc reduced malaria incidences although multiple micronutrient supplementation has been associated with improved immune function and delayed disease progression in HIV/AIDS patients, but there is a recommendation for more research into the area (Buys *et al.*, 2002).

The number of fever episodes was significantly lower in children who received additional supplements in addition to vitamin A. This confirms the findings of a Papua New Guinea study in which there was no effect of vitamin A alone on the number of fever episodes (Shankar *et al.*, 1999b) . It has been demonstrated that free retinol has a pharmacological effect against malaria parasites (Davis *et al.*, 1994). Nevertheless the very low concentrations of free retinol in the serum make its hypothetical effect inconclusive given the lack of association between serum retinol concentration and malaria morbidity found in Papua New Guinea (Shankar *et al.*, 1999a).

The serum retinol concentrations were not determined in this study, but the levels ingested by the children (single dose of 200000IU) for the five month period may have been inadequate to protect them from morbidity. An earlier study in Ghana (Binka *et al.*, 1995) found supplementing children with single dose of 200000IU of vitamin A for six months to be non-protective. Also the number of episodes of other illness (Fig 12) was higher in the vitamin A group except for the incidences of cough and measles which were more prevalent in the zinc and vitamin A group. Comparably Women who received daily pre natal multiple vitamins had significantly higher CD3+, CD4+, and CD8+ counts, as well as improved infant outcomes compared with the control group who received iron-folate supplements that is the standard of care (Fawzi *et al.*, 1998). This means that the multivitamins improved the immune status of the children.

The 24-hour survey suggested that the children were receiving low amounts of zinc in their diet since zinc rich foods like oysters and mollucks were absent from their diet. This can be one reason why the children responded well to the supplementation.

Although the weights of food consumed were not recorded, protein rich foods and fruits and vegetables did not form a high percentage of the foods consumed. Protein rich foods and fruits and vegetables are an important source of micronutrients. This suggests that it is unlikely that children in this study were taking high levels of these micronutrients and any effects seen cannot be attributable to a high intake by a specific group.

It is worth commenting that there was a high dropout rate and one major factor was parents concern about length of time their children consumed the supplements. A larger sample size could have improved the power of the study and allowed the detection of smaller effects of vitamin A, zinc & multivitamin supplementation on malaria episodes.

CHAPTER SIX

6.0 CONCLUSION

The prevalence of malaria in the study population was significantly lower (p=0.006) at end of study (29.4%) than at baseline (36.6%).The incidence of malaria was significantly lower (0.018) in the group supplemented with Vitamin A, Zinc and multivitamin group (21%, RR= 0.62) compared to the group that received Vitamin A alone (35.5%). General morbidity was lowest in the Vitamin A, Zinc & multivitamin group (46.6%) and highest in the Vitamin A alone group (65.5%). The 24-hour recall suggested that the children were receiving low amounts of protein rich foods in their diet.

6.1. LIMITATIONS

In this study, we did not determine the levels of the various vitamins and minerals in the children before and after the study. This makes it uncertain whether the benefits of the vitamin and mineral supplement were due to its effects on nutritional status.

6.2. RECOMMENDATIONS

A placebo controlled trial would be recommended for a larger study with more participants to give more statistical power to the study as well as reduce the dropout rate. Furthermore, immunological assays could have given us a better understanding of what was going on at the cellular level before and after the study. A more sustainable food-based approach such as fortification, improving dietary quality, and education to improve micronutrient intakes of young children must be also pursued.

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APPENDICES

APPENDIX I- SUPPLEMENTS USED IN THE VARIOUS GROUPS AND THEIR NUTRIENT COMPOSITION

Table 1.1: intervention groups and their doses of the various supplements given to them.

Group 1	A single dose of vitamin A (200,000 IU or (60000µg)-control
Group 2	A single dose of vitamin A (200,000 IU or (60000µg) followed by daily 10mg of elemental zinc
Group 3	A single dose of vitamin A (200,000 IU or (60000µg and Daily doses of a 1-5ml(per age) of multivitamin (with vitamin A) supplement and daily doses of 10mg of elemental zinc

Table 1.2: nutrient composition of the various supplements, the RDA for age group used

	Quantity	RDA (6months-8yrs)
multivitamin syrup		
Vitamin A	300ug(1000 IU)	400* µg(1333 IU)
Vitamin B1	1.07mg	0.6 -2mg
Vitamin B2	0.4mg	0.2-8mg
Vitamin B3	8mg	2-8mg
Vitamin B6	0.4mg	0.1-0.6mg
Vitamin B12	1mg	0.4-1.2mg
Vitamin C	50mg	40-25 mg
Vitamin D	10ug	5ug
Vitamin E	5mg (7 IU)	4-7mg
Others		
Zinc tablets	10mg of zinc sulphate monohydrate and Sweet orange powder	2-10 mg
Vitamin A capsules	200,000 IU for six months	

APPENDIX II -PARTICIPANT INFORMATION SHEET

Title of research: The Relationship between Vitamin A, Zinc and Multivitamin Supplementation And Morbidity Due To Malaria

Name(s) and affiliation(s) of researcher(s) : Wilhelmina Annie Mensah[1](Bsc),Patricia Brown [1](PhD.), Harry Tagbor [2](MB CHB, DrPH), Adabie Appiah(MB CHB)[3], Karen Duca[1](PhD) ,Ibok Oduro[1] (PhD), 1.Department of Biochemistry and Biotechnology, KNUST- Kumasi , 2. School of Medical Sciences ,KNUST- Kumasi, 3.Komfo Anokye Teaching Hospital-Kumasi

Purpose of Research: The purpose of this research is to find out if the intake of vitamin A (already received) and Zinc (essential food supplement like vitamin A) or multivitamin and mineral syrup by children (6months-5yrs) can protect them from getting malaria and **not to test a new drug or product.** Your child has been chosen to take part because she/ he received Vitamin A during the national supplementation.

Procedure of the Research: If you agree for your child to participate, you will then be invited to the community center to help us fill a simple questionnaire (your child's food intake and socio-economic status, medicines she/he is taking) **on a set date.** We will then take measurements of your child: Age, weight, height, circumference of the middle of upper arm, thickness of their skin with tapes and finger prick blood draw for malaria testing. If he/she is found to be positive she/he will be treated with the standard malaria treatment (Arthemeter/lumefantrine or Artesunate/amodiaquine) . After that he /she will be put in a group to receive either zinc (important food substance) daily or multivitamin syrup (multiple food substances) daily or neither of the two **for five months**. After that, the body measurements and testing will be done again to find the effect of the zinc or multivitamin syrup on how they get malaria.

Duration of study: Your child will be in the study for 5 months and during this time whenever your child shows signs of sickness, we have to be called to have him/her tested for malaria and if it is positive your child will be treated.

Cost: You are **NOT** required to pay anything to participate in this study

Compensation: your child will be given snack during sample taking

Risks: Apart from discomfort during finger pricking all other procedures are routine. If allergic reactions to supplements/ drugs develop your child will be taken out of the study

Benefits

- Children who will be found to be positive for malaria at the start of study and during the study will be treated with the standard malaria treatment at the cost of study team
- The results of the measurement and laboratory test will be given to the parents. The measurements will also tell if your child is growing well or not.
- Since vitamin A, Zinc, multivitamin and mineral supplement protects the body against night blindness and other common infections like cough and diarrhoea, subjects will benefit health wise.

- The results of the study will help increase knowledge of the role nutrition plays in the development of malaria. The study has the potential to provide a means to reduce susceptibility to malaria

Confidentiality: All information obtained from your child will be coded and this will ensure confidentiality of any information obtained from your child. Values obtained from the analysis will be documented and the samples disposed off. As part of our responsibility to conduct the research properly, the ethics committee may access to these records and give an approval.
Voluntariness: You are in no way obliged to let your child participate in this research and you can stop at any time. Your participation is entirely by your own volition.
Alternatives to participant: If you choose not to let your child participate, this will not affect you in any way.
Withdrawal from research: You can also choose to withdraw your child from the research at any time within the duration of the study. However, please note that some of the information that that might have been already obtained about your child may have been modified or used for publications. This information cannot be removed anymore. Also the researchers promise to make the effort to comply with your wishes as much as practicable.
Contact: if you have any questions concerning this study, please do not hesitate to contact Mina -0272884596, Michael- 0244026352 or William-0243740404
If you have any concern about the conduct of this study (your welfare or your rights) as a research participant, you may contact:
The Chairman
Committee on Human Research and Publications Ethics
Kumasi
Tel: 03220 63248 and 020 5453785

APPENDIX III -PARENTAL CONSENT -For Child's Participation

Statement of person obtaining informed consent:
I have fully explained this research to the parent(s) of
_____ (name of child)
And have given sufficient information, including risks and benefits, to make an informed decision.
NAME: _____ (name of personnel)
SIGNATURE / THUMPRINT_____ DATE: _____
Statement of parent giving the consent:
I have read the description of the research or have had it translated into languages I understand. I have also talked it over with the interviewer to my satisfaction. I understand that my child's participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to judge that I want my child to take part in it. I understand that my child may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet for myself.
(Note: Information given is very confidential)
Date: _____ Guardian Signature_____
Guardian Name**:** _____
Guardian Phone Number(S)**:** _____
Witness Signature (Applicable if guardian cannot read and write):_____
Witness Name: _____
Witness Contact Number: _____
Residential Address (**Area, house number and simple direction; name of a popular place around house……to help us find you when we are visiting)**
_____
_____
_____
Date Of Birth Of Child: _____Day_____Month_____Year (e.g. 25th May,2011)

APPENDIX IV -CHILD ASSENT FORM

(Please don't fill this section)
Statement of person obtaining assent:
I have fully explained this research to
Name of child: _____
I have given sufficient information, including risks and benefits, to make an informed decision. I have translated the procedures into languages that he/she understands. He/she understands that participation is voluntary. He/she understand that he /she may freely stop being part of this study at any time. I testify that he/she has given his/her full assent to this study.
NAME: _____ (name of personnel)

SIGNATURE / THUMPRINT_____ DATE: _____

*****The study participants are between the ages of 6months-5yrs hence oral assent was sought which was written down by personnel.

APPENDIX V -DATA CAPTURING SHEET

FIX PHOTO HERE

A. Personal data code

1. Name of Child:_____
2. Date of interview _____ DATE__ __/__ _/_ __
3. Interviewer ID INTERID
4. Child ID:_____ CHILDID
5. Date of birth of Child:_____ DATE__ __/_ _/___
6. Age of Child:_____ AGECH
7. Sex of Child: 1=Male 2=Female SECHD
8. Contact number :_____
9. Residential Address:

_____

_____

B. ANTHROPOMETRIC DATA

STANDING OR RECUMBENT

HEIGHT (cm):
WEIGHT (Kg):
MID-UPPER ARM CIRCUMFERENCE(mm)
HEAD CIRCUMFERENCE(cm
TRICEPS SKINFOLD THICKNESS(mm)
SUBSCAPULAR SKINFOLD THICKNESS(mm)

C. LABORATORY DATA

Parasitaemia 1= Positive 2=Negative
Parasite density ……

D. **PHYSICAL EXAMINATION**

(for each trait specify: 0=normal, 1+=mild, 2+=moderate, 3+=severe)

a. Oedema ☐

b. Paleness(lips, tongue, palms, mouth , skin) ☐

c. dry, dull hair ☐

d. glossitis (the tongue is swollen and changes colorR ☐

E. ADDITIONAL INFORMATION AND NOTES

F. WITHDRAWAL INFORMATION(to be filled by personnel in case of withdrawal from study)

a. Date of withdrawal _____

b. Reasons for withdrawal

APPENDIX VI -QUESTIONNAIRES FOR PARENT

PERSONAL DATA CODE

10. Nickname of father_____

11. Nickname of Mother_____

12. Respondents Relation to child :_____

13. Marital status: 1=Single 2=Married ☐

MASTA

SOCIODEMOGRAPHIC INFORMATION

14. Head of household 1=father 2=mother 3= other (specify) HEHOS) ☐

15. Highest Educational level of mother/Guardian(female) HEMOT ☐

1=primary/elementary 2=secondary 3=post secondary 4=tertiary 5=none 6= don't know

7=other (specify)…….

16. Highest Educational level of father/Guardian(male) HEFAT ☐

1=primary/elementary 2=secondary 3=post secondary

4=tertiary 5=none 6= don't know 7=other (specify)…….

17. Occupation of mother /Guardian OCMOT ☐

1=artisan(carpenter, hairdresser, seamstress etc)

2=professionals(teacher, lawyer, accountant)

3=office worker(secretary) 4=trading 5= not employed 6= Don't know

18. Occupation of father /Guardian OCFAT ☐

1=artisan(carpenter, hairdresser, seamstress etc)

2=professionals(teacher, lawyer, accountant)

3=office worker(secretary) 4=trading 5= not employed 6= Don't know

19. Residential status RESTA ☐

1=own house 2=family house 3= rented house

4=company/mission house 5=government house 6=caretakers

20. How many people are in your household HHSIZE ☐

21. How many children have you given NOCHD ☐

22. On the average, how much income comes into the house pr month in GHC)

MOTIN ☐

1=< GHC 100 2= GHC 100-300

3= GHC 300-600 4= GHC 600-900

5= GHC 1000-3000 6=> GHC 3000

23. Ethnic grouping – please state …….ETGR . ☐

QUESTIONS ABOUT CHILD HEALTH

24. Dietary Intake (relative to you're your childs intake): DEINT ☐

1=no change 2=change: duration = _____weeks

25. Status of GI Tract today: 1= intact 2= Loose bowel SATGI ☐

26. Swallowing difficulties today: 1= Yes 2=No SWADI ☐

27. Medicines being taken by child: 1= Yes 2=No MEDTA ☐

(if yes state ……..

28. Vitamin or mineral supplementation: 1= Yes 2=No VITTA ☐

(if yes state ……

29. Recent illness apart from malaria? 1=yes 2=No REILL ☐

(if yes state …….

30. Recent malaria episode. REMAL ☐

1= 1-5days ago 2=a week ago 3=2 weeks ago

4=more than 2 weeks 5=none

31. Treatment given TREGIV

1=malaria drug given at the hospital upon testing

2= malaria drug given at the hospital without testing

3= malaria medication bought from pharmacy

4=self medication

5=herbal preparation

6=none

32. Use of mosquito nets.1= Yes 2=No USEMOS ☐

33. Does your child take regular anti-malaria drugs including herbal medicine

1= Yes 2=No(if yes state …… USEMED ☐

34. Does your child have sickle cell anemia 1= Yes 2=No CHSICL ☐

(if yes state group……

35. Do you take any other precaution to prevent your child from getting malaria?

1= Yes 2=No(if yes state …… MALPRV ☐

36. Do your child get tired easily1= Yes 2=No ESTIRE ☐

FOOD FREQUENCY QUESTIONNAIRE						
Code	Foods	Notes	Portion Size	Past 24hrs 1=Yes 2=No	Past OneWeek 1=Yes 2=No	No Times Per Week
	CARBOHYDRATES					
BNK	Banku	Balls=				
KNK	Kenkey (Fante /Ga)	Balls=				
JFR	Jollof Rice	Plate=				
FDR	Fried Rice	Plate=				
SPG	Spaghetti	Tablespoon=				
FFU	Fufu	Bowl=				
CDY	Cooked yam	Slices=				
FDY	Fried yam	Slices=				
OMT	Omutuo	Ball=				
GRI	Gari / Eba	Ball=				
FDP	Fried plantain	Slices=				
RTP	Roasted Plantain	Fingers=				
CDP	Cooked Plantain	Fingers=				
	MEATS /FISH /SEA FOOD	1= Fried 2= steamed 3= grilled				
CHK	Chicken					
FSH	Fish					
BEF	Beef					
GMT	Goat meat					
OYS	Oysters					
PRK	Pork					
CBS	Crabs					
SMP	Shrimps					
SSG	Sausage					
	SOUPS	**Ladles**				
LTS	Light soup					
PNS	Palm nut soup					
GNS	Groundnut soup					
OKS	Okro soup					
KMS	Kontonmire soup					
	STEWS					
GES	Garden egg stew					
VES	Vegetable Stew					
KES	Kontomire stew					
OKS	Okro stew					
BNS	Beans stew/ Beans & oil					
	BREAKFAST					
TEA	Tea					
KOK	Koko					

TMB	Tom Brown					
HSK	Hausa koko					
CCD	Cocoa drink					
KSE	Kose					
BRD	Bread (White /Brown)	Slices=				
MGB	Margarine / Butter					
OTS	Oats					
	VEGETABLES					
CRT	Carrot					
CAB	Cabbage					
BNS	Beans					
LTT	Lettuce					
NSU	Nsusuaa					
CCB	Cucumber					
GPP	Green pepper					
GEG	Garden eggs					
OKR	Okro					
	DAIRY PRODUCTS					
FEG	Fried eggs					
CDM	Condensed milk	Tablespoon=				
EVM	Evaporated Milk	Tablespoon=				
BEG	Boiled eggs					
	FRUITS					
APP	Apple					
ORG	Orange					
PNP	Pineapple					
BNA	Banana					
PWP	Pawpaw					
AVP	Avocado Pear					
WTM	Water melon					
MGO	Mango					
	DRINKS					
MLT	Malt					
MNS	Minerals					
STD	Sweetened drinks Kalyppo					
FJS	Fruit Juices					
	PASTRIES					
DGT	Doughnut/ Bofrot					
MTP	Meat pie					
CPS	Chips					
BCT	Biscuits					
	OTHERS					

Appendix VIII -MEDICAL ASSESSMENT FORMS

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [___]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION:[____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY: [_____
LOCATION: [_____] AXILLARY TEMPERATURE: [_____^{0}C]

A. Symptoms presented by caregiver	Yes	No	Duration (Days)
1. Fever			
2. Vomiting			
3. Diarrhoea			
4. Refusal of feeds			
5. Chills			
6. Headache			
7. Abdominal pain			
8. General weakness			
9. Cough			
10. Runny nose			
11. Fast breathing/difficulty in breathing/noisy breathing			
12. Pallor			
13. Convulsion			
14. Jaundice			
15. Dark urine			
16. Other……			

B. Ask these questions:	Yes	No
1. Does the child vomit everything?		
2. Is the child unable to drink/breastfeed?		
3. Has the child had a convulsion with this illness?		
4. Does the child have bloody diarrhoea?		

C. Check for these signs	Yes	No
1. Severe palmer pallor		
2. Sunken eyes/reduced skin elasticity		
3. Lethargy/ Unconsciousness		
4. Fast breathing/difficulty in breathing/noisy breathing		
5. Neck stiffness		
6. Ear discharge		

*****If any of **B** or **C** ticked **Yes**, refer immediately to the nearest health facility.

MANAGEMENT PLAN

HOME MANAGEMENT with RDT		REFERRED TO CLINIC/HOSPITAL	

Health worker's Name: [_____] Signature: [_____] Date: [____/_____/_____

HEALTH WORKER MALARIA FOLLOW-UP FORM

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY:

[_____]

		E. IF NOT IMPROVED, WHAT HAS BEEN DONE FOR THE CHILD?	
A. VISIT No		Child sent to a clinic/hospital	
B. TREATMENT/POST-REFERRAL DAY		Child given herbal medication/sent to spiritualist/pastor	
C. AXILLARY TEMP		Medication bought at the drug store	
		Medication continued	
D. **CHILD'S CONDITION**		Nothing done about it yet	
Improved		**F. ACTION TAKEN BY HEALTH WORKER**	
Not Improved		Child referred to nearest health facility	
Not At Home		Care-giver advised to heed referral to health facility	
		Care-giver advised to continue treatment at home	

Signature: [_____] Date: [____/_____/_____

EFFECT OF VIT A AND ZINC OR MULTIVITAMIN AND ZINC SUPPLEMENTATION OF MALARIA MORBIDITY
HEALTH WORKER MALARIA FOLLOW-UP FORM

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY:

[_____]

		E. IF NOT IMPROVED, WHAT HAS BEEN DONE FOR THE CHILD?	
A. VISIT No		Child sent to a clinic/hospital	
B. TREATMENT/POST-REFERRAL DAY		Child given herbal medication/sent to spiritualist/pastor	
C. AXILLARY TEMP		Medication bought at the drug store	
		Medication continued	
D. **CHILD'S CONDITION**		Nothing done about it yet	
Improved		**F. ACTION TAKEN BY HEALTH WORKER**	
Not Improved		Child referred to nearest health facility	
Not At Home		Care-giver advised to heed referral to health facility	
		Care-giver advised to continue treatment at home	

Signature: [_____] Date: [____/_____/_____

VIT A & ZINC , ZINC AND MULTI GROUPS CHILD PROGRESS SHEET

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION:
[____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY: [_____]

	Date	**ASSESSMENT TYPE** Supplement Dosing Supplement Follow Up Medical Assessment(**use form)** RDT Test Treatment Follow Up Referral feedback Follow up on referral Post referral assessment Withdrawal from study	Supplement compliance				RDT results after assessment		Treatment follow up		Referral diagnosis	Referral follow up		RDT results after assessment	
			taken weekly dose	Yes	No	Withdrawal date	+	-	improved	Not improved		Improved	Not improved	+	-

VITAMIN A GROUP CHILD PROGRESS SHEET

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION:
[____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY: [_____]

	Date	**ASSESSMENT TYPE** Medical Assessment RDT Test Treatment Follow Up Referral feedback Follow up on referral Post referral assessment Withdrawal from study	SYMPTOMS PRESENTED BY CARE GIVER															RDT results after assessment		Treatment follow up		Referral diagnosis	Referral follow up		RDT results after assessment	
			fever	vomiting	diarrhoea	refusal of feeds c	chills	headaches	abdominal pain	general weakness	cough	running nose	breathing problems	pallor	convulsion	dark urine	jaundice	other	+	-	improved	Not improved		Improved	Not improved	+	-

SUPPLEMENTATION COMPLIANCE/ FOLLOW-UP LOGBOOK(MID-WEEK)

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____] GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____ NAME OF HEALTH WORKER: [_____] COMMUNITY: [_____]

	Date	Taking The Required Dose		If NO **WHY** Reasons given	Discontinued Study		IF YES WHY	Stopped study		IF YES WHY
		Yes	No		YES	NO		Yes	No	

HEALTH WORKER REFERRAL FORMS

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY:

[_____]

AXILLARY TEMPERATURE: [_____^{0}C]
The Medical Officer in charge
…….
…….
Dear Sir/Madam,
REASON FOR REFERRAL

Sign	Yes	Duration (Days)
1. Fever of 7 days or more		
2. Cough of 14 days or more		
3. Diarrhoea present continuously for 7 days or more		
4. Bloody diarrhoea		
5. Severe palmer pallor		
6. Jaundice		
7. Vomiting everything		
8. Unable to drink/breastfeed		
9. Sunken eyes and/reduced skin elasticity		
10. Dark urine (coke-like urine)		
11. Lethargy/prostration		
12. Unconsciousness		
13. Difficulty in breathing/fast breathing/noisy breathing		
14. History of convulsion with present illness		
15. Ear discharge		
16. Neck stiffness		
17. Rapid diagnostic test for malaria is negative		
18. Not getting better with ACT		
19. Not better after ACT completed		

Pre-referral treatment given: Paracetamol [____] ORS [____] ACT [____]
I would be very grateful for your further assessment and management.
Thank you.
CDD's Name: [_____] Signature: [_____] Date: [____/_____/20_____

CHILD RDT RESULTS SHEET

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____] GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____ NAME OF HEALTH WORKER: [_____] COMMUNITY: [_____]

	Date	Temp	RDT resultt		Management	
			+	-	Treated	Referred

FEEDBACK FORM

CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]

GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____

NAME OF HEALTH WORKER: [_____] COMMUNITY:

[_____]

Child admitted: Yes [_____] No [_____]

Child referred out: Yes [_____] No [_____]

LABORATORY INVESTIGATIONS **RESULTS**

Blood film for malaria parasites POSITIVE [_____] NEGATIVE [_____]

Haemoglobin level _____g/dl

White blood cell count _____$\times 10^9$/L

Urine routine examination suggestive of UTI YES [_____] NO [_____]

CHEST EXAMINATION

Suggestive of pneumonia YES [_____] NO [_____]

DIAGNOSIS:

[_____]

DATE: _____/_____/ 20_____

HEALTH INSTITUTION:

[_____]

FOLLOW-UP AFTER TREATMENT/REFERRAL ON DAY 7

CHILD'S CHILD ID [_____] NAME OF CHILD[_____] SEX (M/ F): [_____]AGE: [_____]
GROUP [_____] DATE OF START OF SUPPLEMENTATION: [____/_____/_____
NAME OF HEALTH WORKER: [_____] COMMUNITY:

[_____] ____]

SECTION A-POST TREATMENT ASSESSMENT

1. Did your child complete the medication as prescribed by the CHW? Yes [____] ***Answer Q2, 3***
   No [____] ***Answer Q3, 4***

   Ask caregiver to see the pack.
2. Is the pack empty? Yes [____] No [____]
3. Indicate the number of tablets left if pack not empty [____]
4. Why did your child not complete the medicine?
   a. Child was vomiting the medicine [____]
   b. Child was refusing to take the medicine [____]
   c. I was advised by family to seek alternative treatment [____]
   d. Medicine got lost [____]
   e. I forgot to give the medicine regularly [____]
   f. I sent the child to the hospital/health centre [____]
   g. Child reacted to the medicine [____]

SECTION B- ADVERSE EVENTS ASSESSMENT

Ask the caregiver to know if the child experienced any of the following symptoms after taking the medication.

Symptom	Yes	No
1. Nausea		
2. Vomiting		
3. Sleeplessness		
4. Headache		
5. Itching		
6. General weakness		
7. Jaundice		
8. Dark urine		
9. Skin rash		
10. Sore mouth		
11. Dizziness		
12. Pallor		
13. Palpitation		

If yes to any of the above, what was done for the child?

a. Child sent to a clinic/hospital/health centre [____]
b. Child given herbal medication/sent to spiritualist/pastor [____]
c. Medication continued [____]

Name: [_____] Signature: [_____] Date: [____/_____/20_____

SECTION C- POST REFERRAL ASSESSMENT

1. Was the child sent to the nearest hospital as was requested by CHW? Yes [____] No [____]
2. If no, why was the child not sent to the nearest health facility?

Reason	
a. I did not have money to travel to the health facility	
b. My child is not insured by NHIS	
c. I preferred to visit the drug store	
d. I was advised to see the herbalist/spiritualist/pastor	
e. I did not see the need to go	
f. Other……	
g. Other……	
h. Other……	

3. Condition of child: IMPROVED [____] NOT IMPROVED [____]

If child's condition not improved, reassess the child using the assessment form.

4. Action taken by field worker
   Child referred immediately to nearest health facility [____]
   RDT repeated [____]

5. RDT results: positive [_____] negative [____]
   Child treated with ACT [____]
   Child referred to nearest health facility [____]

Name: [_____] Signature: [_____] Date: [____/_____/20___