CHARACTERIZATION OF SEVERE MALARIA AND TREATMENT-RELATED ADVERSE DRUG REACTIONS AMONG HOSPITALISED CHILDREN, AT THE KNUST HOSPITAL, KUMASI, GHANA.

BY

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DECLARATION

I hereby declare that this submission is my own work towards the MPhil Clinical Pharmacy and that to the best of my knowledge, it contains no material previously published by another person or material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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Student name Signature Date

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Supervisor Signature Date

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Head of Dept. Signature Date

DEDICATION

TO MY MOTHER, GLADYS AYA GHUNNEY.

YOU ARE MY ROCK.

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ABSTRACT

BACKGROUND: Malaria remains one of the most important parasitic causes of mortality among humans, accounting for nearly three million annual deaths globally. Morbidity pattern is thought to vary according to such factors as age, geographic location, non-malaria co-morbidity and level of transmission. A comprehensive picture of the local clinical and epidemiological spectrum of severe malaria would aid early recognition, diagnosis and treatment of the disease. The introduction of the Artemisinin-based Combination Therapy (ACT) policy in Ghana has come with reports of associated adverse drug reactions. In spite of monitoring exercises, data regarding adverse antimalarial treatment-related reactions among hospitalized Ghanaian children remains sketchy.

OBJECTIVES: To document the demography of paediatric admissions due to severe malaria, presentation and determinants of clinical symptoms, as well as treatment and treatment-related adverse reactions.

METHOD: A prospective observational study examining the clinical manifestations and laboratory features of severe malaria was conducted at the Kwame Nkrumah University of Science and Technology Hospital in Kumasi, Ghana over a one-month period. Children aged between 0 and 144 months with confirmed *Plasmodium falciparum* infection and expressing at least one sign of severe malaria as defined by the World Health Organization were recruited. Evaluation of data was done for patient demographics, reaction characteristics and outcome of reactions. Assessment of causality severity and risk factors was also done.

RESULTS: Of 96 paediatric admissions, there were 82 (85%) malaria cases. Severe falciparum malaria as defined by the World Health Organization accounted for 69 (84%) of all malaria cases. The proportion of males was significantly higher (62.3%, p=0.002) than females. Children under 2 years accounted for 30 (43.5%) of severe malaria cases. The main presentations were anaemia of moderate to severe form (56/69, 81%); fever (52/69, 75%); convulsions (23/69, 33%); impaired consciousness (2/69, 2.9%); impaired consciousness and

convulsions (1/69, 1.45%). Prostration was observed in all cases. Children under 5 years of age were associated with anaemia [p=0.018] and neurological symptoms (convulsions, impaired consciousness) [p=0.003]. Parasitaemia was associated with fever [p=0.01]. Clinical presentation of severe malaria was found to be independent of sex. No deaths were recorded in all patients. Quinine was used as treatment in 17(24.6%) of cases; monotherapy with artemisinin derivatives in 37.7% cases and artemisinin-amodiaquine combinations in 27.5% of the cases. The prevalence of treatment-related ADRs was 15.9% and was independent of sex. Incidence of ADRs was significantly higher in older children [p=0.024]. No significant difference was seen between overall incidence of ADRs in males and females. Majority of ADRs were type A, mild, had an unlikely drug cause and resolved fully without any intervention. Multiple concurrent drug therapy was a risk factor for ADRs.

CONCLUSION: Prostration, anaemia, fever and convulsions make up the clinical spectrum of severe paediatric malaria, in the study area. Incidence of adverse drug reactions increased significantly with age. Multiple concurrent drug therapy predisposed patients to adverse drug reactions.

CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND

Of the 350-550 million malaria cases reported globally every year (World malaria report, 2005), an estimated one to two percent are severe or life threatening (Snow *et al*, 2005). This proportion largely accounts for the 2.7 million annual deaths attributable to malaria, especially in sub-Saharan Africa, where about 90% of all falciparum malaria-attributable deaths occur (Breman, 2001; Newton *et al*, 1998). Pregnant women and children under 5 years are most vulnerable to the pathological effects of malaria. In Africa, it is reported that 75% of deaths in children under the age of five years are attributable to malaria (Breman, 2001). Malaria-related effects on pregnant women, their foetuses, and newborns comprise an extremely large and often hidden burden. The manifestations of these effects are maternal anaemia, low birth weight, and consequent infant mortality.

It is estimated that between 75,000 and 400,000 infant deaths per year are associated with malaria infections during pregnancy. In Africa, there may be up to one million malaria-associated low birth weight babies born each year and approximately 400,000 of these children will die (Steketee *et al*, 2001). In Ghana, malaria remains the major cause of morbidity, accounting for more than 44% of all reported outpatient cases and an estimated 22% of under-5 mortality (Ghana Health Service Annual Report, 2007). In children, the complications of malaria include metabolic acidosis (often caused by hypovolaemia), hypoglycaemia, hyperlacticacidaemia, severe anaemia, seizures and raised intracranial pressure. In adults, renal failure and pulmonary oedema are more common causes of death (Njuguna and Newton, 2004).

The disease pattern of severe malaria may change according to a number of factors. These include the genetic characteristics of the population, malaria epidemiology, health-seeking behaviour and non-malaria co-morbidity (Marsh *et al*, 1995). Other determinants are age, geographic location and different levels of transmission (Genton *et al*, 1997; Imbert *et al*, 1997; WHO, 2000).

In a study of 1,921 children in the Kassena-Nankena district of northern Ghana, Oduro *et al* (2007) reported severe anaemia (36.5%), followed by respiratory distress (24.4%), prolonged or multiple convulsions (21.6%) and cerebral malaria (5.4%), as the predominant manifestations of severe malaria. The frequency of severe anaemia was significantly higher in children aged 6-24 months than in children of 25-60 months of age. Another study in northern Ghana (Tamale) showed severe anaemia in more than half of the patients, followed by prostration, respiratory distress, multiple convulsions and impaired consciousness. The frequency of anaemia was shown to decrease with age. Conversely, the neurological symptoms (convulsions and impaired consciousness) were more frequent in older children (Mockenhaupt *et al*, 2004). Similar findings have been gathered in Gabon (Libreville), where over 60% of cases presented with anaemia, followed by respiratory distress and cerebral involvement. Anaemia was found to be more common in children under 18 months, while cerebral malaria usually occurred in older children (Dzeing-Ella *et al*, 2005).

In the Manhica district of southern Mozambique, prostration was reported as the predominant sign of severe disease, followed by respiratory distress and severe anaemia (Bassat *et al*, 2008). In rural Burkina Faso, noted for high falciparum transmission rates, severe anaemia was found to significantly predominate, followed by prostration and neurological symptoms (convulsions and coma). However, in the urban subsample (Ouagadougou), with lower transmission rates, more than half of all reported cases had coma, followed by neurological features and anaemia (Modiano *et al*, 1998). Al-Taiar *et al* (2006) reported that in Yemen, prostration was the commonest indicator of severe malaria, followed by respiratory distress, severe anaemia and cerebral malaria. These examples clearly underscore the diversity in manifestations of severe malaria.

The importance of studying the disease pattern and subsequently carrying out a site-specific characterization of severe malaria in Kumasi is relevant to the development of adequate guidelines for malaria management and public health interventions. Although standard criteria have been prescribed by the World Health Organization (WHO 1990; revised in 2000), these are often not wholly applicable to our setting. A comprehensive

picture of the local clinical and epidemiological spectrum of severe malaria would aid early recognition, diagnosis and treatment of the disease.

Effective malaria treatment is a key element of the Roll Back Malaria Partnership toward achieving the 2015 malaria-related Millenium Development Goals (UNICEF, 2003). Introduction of the new Artemisinin-based Combination Therapy (ACT) policy in Ghana has been accompanied by reports of unpleasant treatment-related effects. Some adverse reaction reporting exercises have been undertaken by the National Centre for Pharmacovigilance (NCPV) of the Centre for Tropical Pharmacology and Therapeutics at the University of Ghana. However, it remains unclear whether or not there is data on adverse antimalarial treatment-related reactions among hospitalized Ghanaian children.
Studies carried out in this direction would therefore be instrumental in providing valuable information regarding potential problems of antimalarial drug usage. Through these efforts, anticipated problems could be prevented and actual problems identified and resolved, resulting in continuous improvement in patient care.
Periodic evaluation of adverse antimalarial-related drug reactions reported at the KNUST hospital would help in characterizing the pattern of such adverse reactions, ultimately facilitating the design of steps to improve the safety of drug use.

1.2 HYPOTHESIS

Studies undertaken previously in different malaria endemic regions of Africa and the Middle East have postulated that the manifestations of severe malaria differ with such factors as age, sex, intercurrent illness, previous exposure and genetic characteristics. Consequently, the expression of varying levels in prevalence and severity, of different symptoms of severe malaria were expected to be observed.

1.3 RESEARCH QUESTIONS

- What proportion of paediatric admissions at the KNUST Hospital are due to severe malaria?
- What is the gender distribution of cases of severe malaria and are any differences significant?

- Which age groups carry the highest severe malaria burden?
- What are the most commonly expressed manifestations of severe malaria?
- Is there any significant relationship between age and sex, and the expression of these symptoms?
- Is there any association between the level of parasitaemia and the number and nature of symptoms expressed?
- How is severe malaria managed at the KNUST hospital?
- Are there any malaria treatment-related adverse reactions at the KNUST hospital?
- What is the pattern of these reactions, if there are any?

1.4 AIM

This study set out primarily to characterize cases of severe malaria and treatment-related adverse reactions, among hospitalized children at the KNUST Hospital.

1.5 SPECIFIC OBJECTIVES

Specific objectives outlined for this study were:

- to determine the proportion of paediatric admissions at the KNUST Hospital that were due to severe malaria
- to assess demographic characteristics of patients on admission from severe malaria
- to determine clinical features that identified those children most severely ill with malaria
- to examine cases of antimalarial treatment-related adverse reactions

1.6 POTENTIAL BENEFITS

It is envisaged that findings from this study would be of relevance to:

- health promotion and malaria prevention advocacy
- prompt diagnosis and effective management of severe malaria
- the provision of useful guidelines to ensure patient safety

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 MALARIA

Malaria in humans is transmitted through the bite of the female anopheles mosquito that is infected with one of the four species of *Plasmodium*: *falciparum, malariae, ovale or vivax. P. falciparum* infections are the most dangerous in terms of mortality rates, and are the most common in Ghana. A lack of the duffy blood antigen in West Africans confers an apparent resistance against *vivax* malaria (Tournamille *et al*, 1995).

Severe *falciparum* malaria annually causes at least one million deaths, most of which occur in African children less than 5 years of age (Sachs and Malaney, 2002).

In parts of the world where endemicity of *falciparum* malaria is stable, severe malaria is mainly a disease of children from the first few months of life to the age of 5 years. It is less common in older children and adults, because of the acquisition of partial immunity. In areas of lower endemicity, however, severe malaria occurs in both adults and children. Non-immune travellers and migrant workers are also vulnerable to severe malaria.

Babies born to mothers who have malaria during pregnancy are at risk of having a lower birth weight than the community average, usually as a result of intrauterine growth retardation. Low birth weight is associated with increased mortality from all causes in infancy. Congenital malaria is however quite rare, due to passive immunity offered by maternal antibodies (Smith *et al*, 1994).

2.1.1 Detection of severe *falciparum* malaria

It is important to note that malaria has multi-organ system involvement and the clinical presentation in children can mimic a variety of conditions. Delay in diagnosis and treatment culminate in complications and ultimately, death.

In a patient with asexual *P. falciparum* parasitaemia and no other confirmed non-malarious cause for their symptoms, the presence of one or more of the following clinical

or laboratory features classifies that patient as suffering from severe malaria (WHO,2000):

Prostration

This is the inability to sit unassisted in a child who is normally able to do so. In children not old enough to sit up it is defined as the inability to feed. Prostration is recorded directly and not based on history. Many children who are pyrexial and feel unwell prefer to lie or be carried but are capable of sitting if gently encouraged to do so. In adults prostration is usually manifested as extreme weakness.

Severe anaemia

This is determined by haemoglobin measurements. As an alternative, packed cell volume may also be measured. Severe anaemia is defined as haemoglobin <5 g/dL or haematocrit <15%. It should be specified whether results are from a finger prick or venous sample. Finger prick samples may underestimate the haemoglobin concentration by a gram or more if the finger is squeezed during collection.

Impaired consciousness

This is defined as a Blantyre coma score of ≤4. This coma scale (Molyneux *et al*, 1989) is modified from the widely used Glasgow coma scale to be applicable to children, including those who have not learned to speak. Total score can range from 0 to 5. A score of 2 or less indicates 'unrousable coma' and is reserved for cerebral malaria.

Table 1.1: Blantyre coma scale for children

Parameter	Score
(a) Best motor response	
Localizes painful stimulus(rub knuckles on patient's sternum)	2
Withdraws limb from pain (firm pressure on thumbnail bed with horizontal pencil)	1
Non-specific or absent response	0

(b) Verbal response	
Appropriate cry	2
Moan or inappropriate cry	1
None	0
(c) Eye movements	
Directed (e.g., follows mother's face)	1
Not directed	0

Multiple convulsions

This is defined as a respective history within the preceding 24 hours, plus one directly observed convulsion. The length, nature and number of convulsions should be recorded. Many convulsions associated with malaria are focal and care should be taken to detect minor manifestations such as twitching of a digit, repetitive jerky eye movements with deviation, increased salivation or abnormal respiratory patterns.

Respiratory distress

This refers to sustained nasal flaring, subcostal recession or Kussmaul breathing. Respiratory rate and pattern can be assessed only in a child who is not crying or otherwise disturbed.

Hypoglycaemia

This is defined as a whole blood glucose concentration of less than 2.2 mmol/L (less than 40 mg/dL).

Acidosis

This is specified as a plasma bicarbonate concentration (<15 mmol/L) or base excess (>-l0). The acidaemia which may accompany acidosis is defined as pH <7.35 measured in capillary or arterial blood.

Circulatory collapse

It is difficult to provide exact definitions for small children, not least because children who become shocked with malaria often deteriorate very rapidly. However, a systolic blood pressure <60 and <80 mm of Hg in children≤ 5and >5 years of age, respectively, plus cool limbs or weak or absent peripheral pulses, are adequately indicative of circulatory collapse in children.

Pulmonary oedema

Pulmonary oedema appears to be a rare manifestation of malaria in children. Diagnosis is often difficult and requires a chest X-ray.

Abnormal bleeding

This is rare in children with severe malaria. A check should be made for bleeding from gums, nose, gastrointestinal tract or venepuncture sites.

Jaundice

This is detected clinically by examining the sclera and/or mucosal surfaces of the mouth.

Haemoglobinuria

When the urine is dark red or black, and the urinanalysis dipstick test is positive for haemoglobin/myoglobin, the absence of microscopic haematuria suggests either haemoglobinuria or myoglobinuria.

Hyperlactataemia

The normal range for plasma lactate is up to 2 mmol/L. A level >5 mmol/L is an indication of severe malaria (Krishna *et al*, 1994).

Hyperparasitaemia

The relation of parasitaemia to severity of illness is different in different populations and age groups. In non-immune children in areas of unstable endemicity, a peripheral parasitaemia of 4% or more carries an increased risk of death and should be considered a

sign of severe malaria (Luxemburger *et al.*, 1994). In areas of stable endemicity, threshold levels are derived from local experience but, in the absence of data, a parasitaemia >20% is considered to indicate severe malaria.

Renal impairment

Renal failure is rare in children. It is defined as a urine output of less than 12 mL/kg/24 h or a plasma creatinine concentration above the age-related normal range, persisting after rehydration.

2.1.2 Classification of severe paediatric malaria

Over 90% of all cases of life-threatening malaria are in African children. In many places the resources for systematic detection is lacking. A classification based on both need for treatment and prognosis is therefore provided by the World Health Organisation (WHO, 2000) as follows:

Group 1

Children at immediate increased risk of dying who require parenteral antimalarial drugs and supportive therapy.

a) ***Prostrated children***

Three subgroups of increasing severity are distinguished:

(i) Prostrate but fully conscious

(ii) Prostrate with impaired consciousness but not in deep coma

(iii) Coma (the inability to localize a painful stimulus).

b) ***Respiratory distress*** (acidotic breathing):

(i) Mild - sustained nasal flaring and or mild intercostal indrawing (recession)

(ii) Severe - the presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing.

Group 2

Children who, though able to be treated with oral antimalarial drugs require supervised management because of the risk of clinical deterioration but who show none of the features of group 1 (above):

(a) Children with a haemoglobin level ~5 g/dL or a haematocrit < 15%

(b) Children with 2 or more convulsions within a 24 h period.

Group 3

Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of groups 1 or 2 (above).

2.1.3 Treatment of malaria

At the time of this study, the national recommended treatment for severe malaria was Quinine (10mg/kg body weight of dihydrochloride salt, maximum 600mg, 8 hourly in 5-10ml/kg body weight of 4.3% Dextrose in 0.18% normal saline, given intravenously over 4 hours until patient can tolerate oral quinine to complete a full 7-day course. In previously untreated patients, a loading dose of 20mg/kg body weight is given. Alternatively, intramuscular injections of 10mg/kg of quinine dihydrochloride may be given 8 hourly until oral therapy can be tolerated).

Artemisinin derivatives are also useful (artemether - 3.2 mg/kg body weight intramuscularly on the first day, followed by 1.6 mg/kg body weight daily for a minimum of 3 days until the patient can take oral treatment or another effective antimalarial; artesunate – 2.4 mg/kg body weight on the first day, followed by 1.2 mg/kg body weight daily for a minimum of 3 days until the patient can take oral treatment or another effective antimalarial) (Standard Treatment Guidelines, 2004).

2.2 ADVERSE DRUG REACTIONS

2.2.1 Definition

An adverse drug reaction is defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of a disease or for the modification of physiologic function." (Nebeker *et al*, 2004).

The terms "drug allergy," "drug hypersensitivity," and "drug reaction" are often used interchangeably. Drug reactions encompass all adverse events related to drug administration, regardless of aetiology. Drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient whereas drug allergy is restricted specifically to a reaction mediated by immunoglobin E (IgE) (Riedl and Casillas, 2003).

2.2.2 Classification of ADR's

Adverse drug reactions are either type A (pharmacological) or type B (idiosyncratic) (Pirmohamed *et al*, 1998; Rawlins and Thompson, 1991). Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose dependent and are therefore readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

Although the pharmacological classification of ADRs as type A and B reactions is useful, it is sometimes difficult or impossible to assign a reaction to one type. For example, dose-dependent (type A) nausea and vomiting due to erythromycin could also be classified as type B because it is not pharmacologically predictable. Furthermore, other types of adverse reactions are not comfortably classified by the system. For example, osteoporosis from corticosteroids depends not only on dose but also on duration of treatment. Additionally, some reactions, such as asthma from β-adrenoceptor antagonists, do not

occur in all patients. A newer three-dimensional classification-the DoTS system, is based therefore, on dose relatedness, timing and patient susceptibility (Aronson and Ferner, 2003).

Another system of classification of adverse reactions to medicines, as proposed by Wills and Brown (1999), groups ADRs as follows:

Type A: Augmented reactions

These reactions are dose-related effects of a medicine on the human body, which could have been predicted based on knowledge of the mode of action and pharmacology of the drug or excipient. Type A reactions can only occur while the subject is still receiving the preparation and improve partially or completely when the causative agent is withdrawn or the dose reduced.

Type B: Bugs reactions

These are adverse reactions that occur through promotion of growth of certain microorganisms. These type B reactions are pharmacologically predictable events, but they are not type A according to the definition used in the preceding section, since the direct and principal pharmacological action of the culprit drug is on the microorganism rather than on the human body. Examples include sugar-containing medicines promoting dental caries, antibiotics causing overgrowth of resistant bacteria species in the intestine, broad spectrum antibiotics causing oral thrush and over use of one agent stimulating the development of resistance among a specific species of microorganism rendering further use of the agent ineffective.

It should however be noted that an infection arising as a result of drug- induced immunosuppression would not be a type B reaction. The primary adverse event in such a case would be suppression of the human immune system, which is usually a type A reaction. Infections arising as a result of this would be a secondary event.

Type C: Chemical reactions

A number of adverse reactions depend on the chemical nature of a drug or excipient rather than pharmacological properties. They are all basically forms of chemical irritation, which makes it likely that when exposed to the preparation, most people could experience a similar reaction. The severity of a type C reaction is more a function of concentration of the offending substance than dose. Typical side-effects in this category include extravasation reactions, phlebitis, pain at the site of an injection owing to the irritant action of a drug or excipient, acid or alkali burns, contact (irritant) dermatitis and gastrointestinal mucosa damage caused by local irritant action.

These reactions are not pharmacologically predictable, but knowledge of the physicochemical characteristics of the causative agents may enable them to be foreseen.

Type D: Delivery reactions

A variety of adverse reactions occur as a specific consequence of the method of drug delivery. These reactions are not dependent on the chemical or pharmacological properties of the constituents of the preparation, but occur because of the physical nature of the formulation and/or the method of administration. These reactions will be heterogeneous. Methods of delivery vary and so the specific nature of the adverse reactions must also vary.

The unifying characteristic is that if the method of delivery is changed, the adverse reaction will cease to occur. Examples include inflammation or fibrosis around implants, particles in injections causing thrombosis or blood vessel occlusion, a tablet lodging in the throat, inhaling the 'dust cap' of an inhaler, cough after using a dry powder inhaler, infections at the site of an injection (owing to the opening of a port of entry for bacteria) and infections due to contamination of injection solution with microorganisms.

Type E: Exit reactions

These are known as withdrawal reactions, and are a manifestation of physical dependence. It is only possible for them to occur after administration of the medicine has ceased or the dose suddenly reduced. Unlike all other adverse reactions, which typically

worsen if the causative agent is continued, reintroduction of the drug will actually ameliorate symptoms. The likelihood of occurrence of a reaction is linked more to duration of administration than dose.

Type F: Familial reaction

Certain adverse drug reactions occur only in susceptible individuals with genetically determined and inherited metabolic disorders. Some of the more common familial disorders include phenyl ketonuria, glucose-6-phosphate dehydrogenase (G6PD) deficiency; esterase inhibitor deficiency, porphyria and sickle cell anaemia.

These reactions must not be confused with those that occur because of the normal variation in ability to metabolize a drug among the population. For example, up to 10% of the population of the western world are deficient in CYP 2D6. However, this does not make them liable to suffer unique adverse effects compared with the rest of the population.

Type G: Genotoxicity reactions

A number of drugs can produce genetic damage in humans. These drugs are potentially carcinogenic or genotoxic. Some, but not all, teratogenic agents damage genetic material within the foetus.

Type H: Hypersensitivity reactions

These are side-effects caused by allergy or hypersensitivity. They are probably the most common adverse reactions after Type A reactions. There are many different types, but all involve activation of an immune response.

They are not pharmacologically predictable, and neither are they dose-related according to the definition of 'dose-dependent' given above (although very small doses can sometimes be used for desensitization). Accordingly, reducing the dose does not usually lead to amelioration of symptoms; the drug must be stopped. Some examples are anaphylaxis, allergic skin rashes, Stevens–Johnson syndrome, photoallergy, acute angio-

oedema, hypersensitivity, cholestasis, and hypersensitivity-mediated blood dyscrasias.

Type U: Unclassified reactions

Some ADRs have a mechanism that is not understood and these must remain unclassified until more is known about them. This may necessitate the introduction of new adverse reaction categories in the future.

Examples include drug-induced taste disturbance, muscular adverse effects of simvastatin, and nausea and vomiting after a gaseous general anaesthetic.

Various other dimensions may be employed in the classification of adverse drug reactions:

- severity index – benign, severe or fatal
- onset/latency – acute or delayed
- causality – definite, probable, possible, doubtful or unknown
- frequency – common, likely, frequently, occasionally, rare, almost never or never.

2.2.3 Epidemiology of ADRs

Adverse drug reactions caused by immune and non-immune mechanisms are a major cause of morbidity and mortality worldwide. They are the most common iatrogenic illness, complicating 5-15% of therapeutic drug courses (Riedl and Casillas, 2003).

The incidence of ADRs varies widely, as documented in published literature. In the United States, more than 100,000 deaths are attributed annually to serious adverse drug reactions. Three to six percent of all hospital admissions are because of adverse drug reactions and 6-15% of hospitalized patients (2.2 million persons in the United States in 1994) experience a serious adverse drug reaction (Lazarou *et al,* 1998).

A French study of 2067 adults aged 20-67 years attending a health centre for check up reported that 14.7% gave reliable histories of systemic adverse reactions to one or more drugs (Vervloet and Durham, 1998). In a Swiss study of 5568 hospital inpatients, 17%

had adverse reactions to drugs. Fatal drug reactions have been reported to occur in 0.1% medical inpatients and 0.01% of surgical inpatients (Vervloet and Durham, 1998).

Chrischilles, *et al* (1992) surveyed a community-dwelling population aged 65 years and older, and reported the following:

- 10% self-reported at least one ADR within one year of survey
- 75% reported this ADR to their physician
- 7% reported that their ADR resulted in an admission to the hospital

Jick (1974) reported that in hospitalized adult patients:

- 30% of patients experienced at least one ADR during their admission
- 3% of admissions to medical services are the result of ADRs

Manasse Jr. (1989) noted that adverse drug reactions are reported to cause or occur in 0.66% to 36.4% of hospital admissions (this includes inappropriate use of drugs as well as unexpected adverse effects).

The main drugs implicated in majority of cases are antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Adverse reactions to drugs occurring during anaesthesia (muscle relaxants, general anaesthetics and opiates), although less common (1 in 6000 patients receiving anaesthesia), are life threatening, with a mortality of about 6% (Vervloet and Durham, 1998).

2.2.4 Avoidability of ADRs

Hallas, *et al* (1990) graded avoidability of ADRs as:

- ***definitely avoidable*** – the ADR is due to a drug treatment procedure inconsistent with present day knowledge of good medical practice
- ***possibly avoidable*** – the ADR could be avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice
- ***unavoidable*** – the ADR cannot be avoided by any reasonable means.

Although it is difficult to prevent type B reactions, it has been suggested that at least half of the pharmacological (type A) reactions could be prevented (McDonnell and Jacobs, 2002). Pirmohamed, *et al* (2004) in a prospective analysis of 18,820 patients on admission, found that as high as 72% of ADRs are avoidable (9% definitely avoidable, 63% possibly avoidable).

2.2.5 Causality Assessment

Assessing the causality of reported adverse drug reactions (imputation) is a dynamic process of causal inference through continuous assessment of information considered on the differential diagnosis of an adverse drug reaction (Macedo *et al*, 2003).

Available tools for assessing causality of ADRs include the Bayesian assessment, Global Introspection and several decisional/standardized algorithms.

Using a standardized list of diagnostic questions with an accompanying scoring system, Naranjo, *et al* (1981) demonstrated increased agreement among clinical pharmacologists and pharmacists when reviewing suspected cases of ADRs.

Table 2.1: Naranjo causality assessment algorithm

QUESTIONS	YES	NO	DO NOT KNOW	SCORE
Are there previous **conclusive** reports on this reaction?	+1	0	0	
Did the adverse event **appear** after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a **specific** antagonist was administered?	+1	0	0	
Did the adverse reaction **reappear** when the drug was readministered?	+2	-1	0	

Are there **alternative causes** (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction reappear when a **placebo** was given?	-1	+1	0	
Was the drug detected in the **blood** (or other fluids) in the concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in **any** previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Numerical scores are translated to qualitative scores as follows:

- Scores of 1-4 indicate possible causality
- Scores of 5-8 indicate probable causality
- Scores of 9 or more indicate definite causality

2.2.6 Severity of ADRs

Assessment of severity remains largely subjective. Although there is no universal scale for severity assessment, an algorithm proposed by Hartwig, *et al* (1992) adequately describes drug reactions as *mild, moderate or severe*, thus providing a means of assessing severity of ADRs.

Mild reactions are usually self-limiting and able to resolve over time without treatment. They are of minor significance albeit being distressful sometimes to people who

experience them. Common examples include digestive disturbances, headaches, fatigue, vague muscle aches, malaise and disturbance of sleep patterns.

Moderate adverse reactions to drugs are defined as those that prolong hospitalization by one added day and require therapeutic intervention but resolve within twenty-four hours after change in drug therapy or the introduction of specific treatment to prevent further outcome.

Reactions that are usually described as mild are considered moderate if the person experiencing them considers them distinctly annoying, distressing, or intolerable. Such reactions include skin rashes, visual disturbances, muscle tremor, difficulty in urination, any perceptible change in mood or mental function and certain changes in blood components.

Severe ADR's are those reactions that are life-threatening, produce persistent or significant disability (including birth defects) or prolong hospital stay by a minimum of four added days. They also comprise reactions that lead to hospitalization, requiring intensive medical care, or lead to the death of the patient. Such reactions are relatively rare and include liver failure and abnormal cardiac rhythms (Hartwig *et al*, 1992).

2.2.7 Susceptibility to ADRs

Factors predisposing individuals to pharmacological adverse reactions include genetic variation, age, sex, physiological variation, exogenous factors (including co-prescribed drugs and diet), concomitant host disease, dose of drug, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities and drug-drug interactions. More than one susceptibility factor may be present (Pirmohamed *et al*, 1998).

There is no consensus, however, on the relation between genetics and ethnic or racial classifications. Some have argued that ethnic and racial labels are poor biological determinants for underlying genotype but ethnic classification could still account for complex interactions between genetics, environment, society and other factors (Risch *et al*, 2002).

2.2.8 Economic implications of ADRs

Adverse drug reactions are an important consideration when prescribing and funding medicines. Not only do they affect patient compliance and the cost of treatment (as they may lead to further treatments), but serious adverse effects can lead to hospitalization, long-term disability or even death. Equally, if not more, importantly, is the fact that the overall implications of ADRs can have significant economic dimensions.

A study conducted in the UK from November 2001 to April 2002 in two NHS hospitals in Merseyside, with 18 820 patients aged over 16 years, indicated that there were 1225 admissions related to an ADR, giving a prevalence of 6.5%, with the ADR directly leading to the admission in 80% of cases. Also in this study, it was found that patients admitted with an ADR had a median stay of eight days, with the average cost per medical bed day being £466million a year (Pirmohamed *et al,* 2004).

In a report by the Agency for Healthcare Research and Quality (AHRQ), examining the health economics of ADRs, it is revealed that ADRs in the USA result in more than 770,000 injuries and deaths each year and cost up to $5.6 million per hospital, depending on size. Additionally, patients who experienced adverse drug events (ADEs) were hospitalized an average of 8 to 12 days longer than patients who did not suffer ADEs, and their hospitalisation cost $16,000 to $24,000 more (Bates *et al,* 1997).

CHAPTER THREE

3.0 METHODOLOGY

3.1 STUDY SITE

The study was conducted at the Kwame Nkrumah University of Science and Technology (KNUST) Hospital. The hospital is situated approximately eight miles to the east of Kumasi, the capital of the Ashanti region of Ghana. It is classified as a district health facility. The hospital serves a catchment area population of approximately 300,000 including the University community (with an estimated population of 150,000 as at June, 2008) and surrounding localities. The average annual attendance is estimated at 112,000 with paediatric attendance accounting for 9.8% (11,028/112,000). Approximately 4,397 admissions are made annually. Malaria, in all ages, accounts for an annual average of 45,762 attendances; which constitutes 40.9% of average annual attendances. The Children's Ward of the hospital is a 24-bed ward with annual admissions averaging 1150.

3.2 STUDY POPULATION

i. *Target* – All new paediatric admissions over the stipulated period.

ii. *Inclusion criteria* – Patients who satisfied the following criteria:

- Aged 0-144 months (inclusive)
- Positive blood film for asexual forms of *Plasmodium falciparum*
- Expression of at least one symptom suggestive of severe malaria, as defined by the WHO
- Verbal informed consent

iii. *Exclusion criteria* – Patients who were not enrolled for this study were:

- Those already on admission with either severe malaria or some

other medical condition, on commencement of the study

- Patients whose clinical presentation was due to a cause other than severe malaria

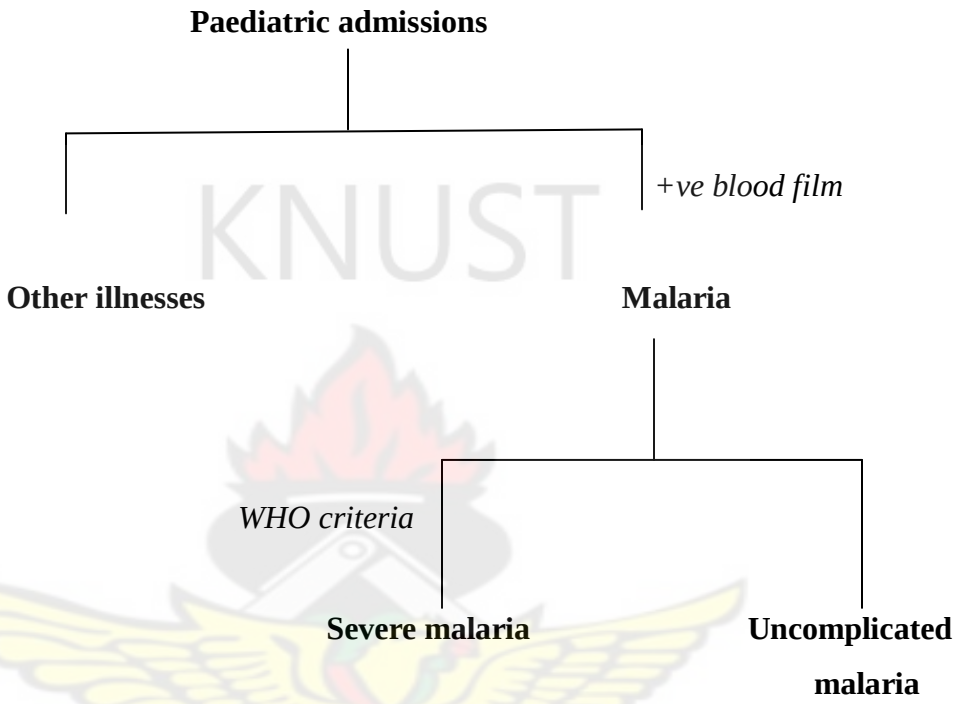

Figure 3.1: Schematic representation of screening procedure for eligible participants

3.3 STUDY DESIGN

The survey was structured as a prospective, non-randomised, observational study, spanning a one-month period (May, 2008). It incorporated cross-sectional interviews of subjects and/or their care-givers with monitoring for treatment-related adverse reactions. Spontaneous reporting of suspected ADR's was also encouraged among care-givers.

3.4 DATA COLLECTION

The *general* and *isolation* wards making up the Children's ward, were designated as *A* and *B*, respectively. Beds in each ward were then labeled '*A1, A2, A3….*' and '*B1, B2,*

B3….' respectively. This formed the basis for special identification codes for patients, to ensure confidentiality of all information obtained. Patients were identified as they were admitted and their care-givers contacted for the study. Verbal informed consent was obtained from care-givers of successfully enrolled patients. Structured interviews of patients and/or care-givers were carried out and information obtained documented on case report forms (Appendix I). Other data relevant to the study (laboratory findings, general observations, treatment details, details of adverse drug reactions) were obtained from patients' medical records. Treatment outcomes and duration of hospitalization were also recorded for each patient. Patients were seen daily while on admission.

Cases were defined as *severe* if they met WHO (2000) classification criteria for severe malaria. *Fever* was defined as an axillary temperature >37.5^{o}C. *Severe anaemia* was defined as haemoglobin <5 g/dL or haematocrit <15%, of blood from venepuncture. *Neurological symptoms* referred to cases of either impaired consciousness or convulsions, or both. *High parasitaemia* was defined by 11-100 parasites per 100 thick film fields (++), 1-10 parasites per single thick film field (+++), or >10 parasites per single thick film field (++++). *Low parasitaemia* (+) referred to 1-10 parasites per 100 thick film fields. Dosages of anti-malarial agents were deemed *incorrect* if the drug dose, frequency of administration or duration of therapy did not conform with recommended guidelines, either individually or collectively.

In cases of suspected ADR reports, information relating to associated symptoms, date of onset of suspected reaction, intervention employed and outcome, were documented. Causality relationships between suspected ADRs and corresponding drug therapy were assessed using a modification of the Naranjo probability algorithm (Appendix I). ADRs were classified according to Rawlins and Thompson's classification (Section 2.2.2), with severity being determined by Hartwig's severity scale (Section 2.2.6). Patient outcomes were reported as *fatal* (leading to death), *damaging* (life-threatening/ resulting in persistent or significant disability or incapacity), *fully recovered* (suspected ADR resolved completely during hospitalization, with or without any intervention), *ongoing* (condition improved but suspected ADR not completely resolved, at time of discharge) or

unknown (not documented after initial report).

Design of case report form (Appendix I)

Section one – Eight questions were designed to elicit the following patient details: patient identification, age, sex, weight, height, date of admission, source of patient and pre-existing medical conditions.

Section two – The questions in this section centered on the details of any previous malaria episodes encountered by the patient.

Section three – This section sought to document findings of clinical and laboratory examinations. Questions addressed parasite load, axillary temperature, haemoglobin levels and presenting signs.

Section four – Treatment details, comprising therapy information for both malaria and other concomitant conditions, were captured in this section. Dosage details such as drug name, full dosage regimen, route of administration and therapy start and stop dates were highlighted in this section.

Section five – This section captured information on treatment-related adverse reactions. The nature, date of onset, outcome and duration of reactions were documented here. This section sought information on interventions carried out in response to adverse reactions and additionally, sought to establish a causality association between drugs taken and the observed adverse reactions.

Data handling

All data captured on the structured case report forms were analysed using SPSS for Windows statistical software, version 16.

Using this software, basic statistics (proportions and means) were calculated for baseline characteristics (weight, temperature, parasitaemia and haemoglobin levels). Standard deviations were determined for means and 95% confidence intervals calculated for proportions. Prevalence of clinical and laboratory features were determined by age group and sex. Pearson's chi-square test, with Yates' continuity correction was used to determine association between the occurrence of clinical symptoms and age, sex and level of parasitaemia. Comparisons between groups were made also by chi-square. Odds ratio for the association of risk of anaemia, fever and neurological symptoms in high

parasitaemia, were determined. Statistical significance was set at $P<0.05$.

3.5 STUDY VARIABLES

Data obtained were analyzed for the following:

- Prevalence of severe malaria
- Demographic characteristics of patients on admission from severe malaria
- Commonly presented symptoms of severe malaria
- Prevalence of antimalarial treatment-related adverse reactions
- Nature and causality of such adverse drug reactions
- Outcome of adverse drug reactions
- Treatment of adverse drug reactions and outcome of such treatment

3.6 PRE-TESTING

The case report forms developed for this study were pre-tested on five (5) previously admitted children. Questions found to be ambiguous, not applicable or misleading were identified and re-constructed.

3.7 ETHICAL CLEARANCE

Ethical clearance was sought from the Committee on Human Research, Publications and Ethics (CHRPE), of the School of Medical Sciences, College of Health Sciences, KNUST.

3.8 LIMITATIONS

- Provision of details regarding previous malaria episodes depended largely on the memory of care-givers. Memory bias could therefore have led to some inaccurate estimates.

- There was difficulty in ascertaining adverse drug reactions in younger children. Thus, assessment of treatment-related adverse reactions was done only for children aged 36 months and over, who could reliably express pain or discomfort.

CHAPTER FOUR

4.0 RESULTS

4.1 PATIENTS' DEMOGRAPHICS

4.1.1 Proportion of admissions due to severe malaria

Out of 96 children admitted over the study period, 82 cases (85.4%) were as a result of malaria. Severe malaria represented 84.2% (69/82) of all malaria admissions (Figure 4.1). There was one case (1.2%) of neonatal malaria.

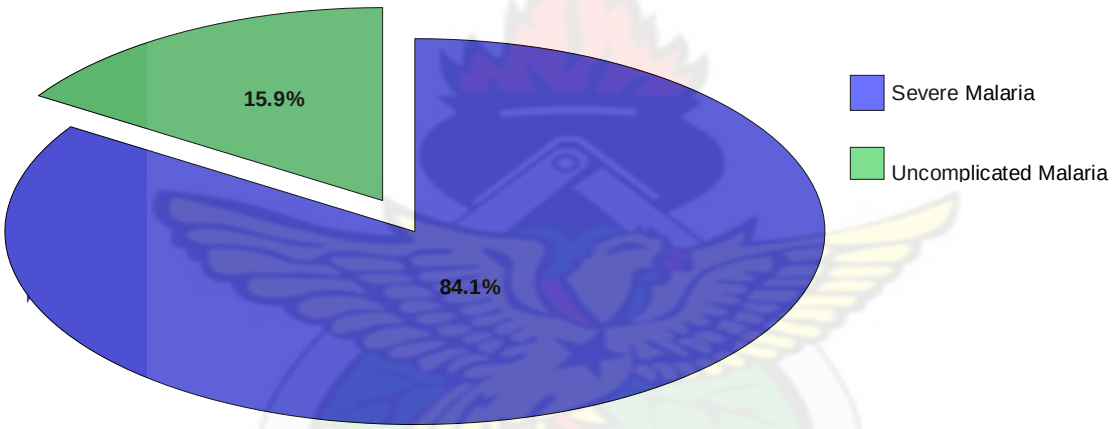

Figure 4.1: Proportion of admissions due to severe malaria

4.1.2 Patient characteristics

Males accounted for 62.3% (43/69, p = 0.002) of severe malaria admissions (Figure 4.2, 4.3).

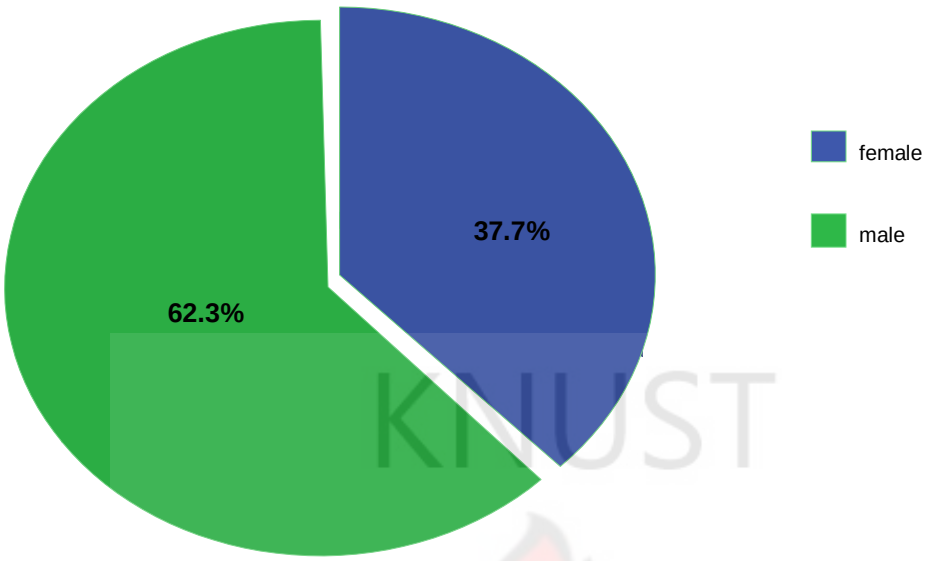

Figure 4.2: Gender distribution of severe malaria cases

The age distribution of severe malaria admissions is shown in Figure 4.3. Children under two years generally bore the highest burden of severe malaria cases (43.5%). The median age for enrollees was 36 months (Table 4.1).

Table 4.1: Median ages

Variable	Age (months)					Sex	
	0-24	25-60	61-120	121-144	All (0-144)	Male	Female
Median age [AR]*	*17.5 [0.5-24]*	*45 [36-60]*	*96 [84-120]*	*144 [132-144]*	*36 [0.5-144]*	*36 [0.5-144]*	*36 [7-144]*

**AR=Absolute range*

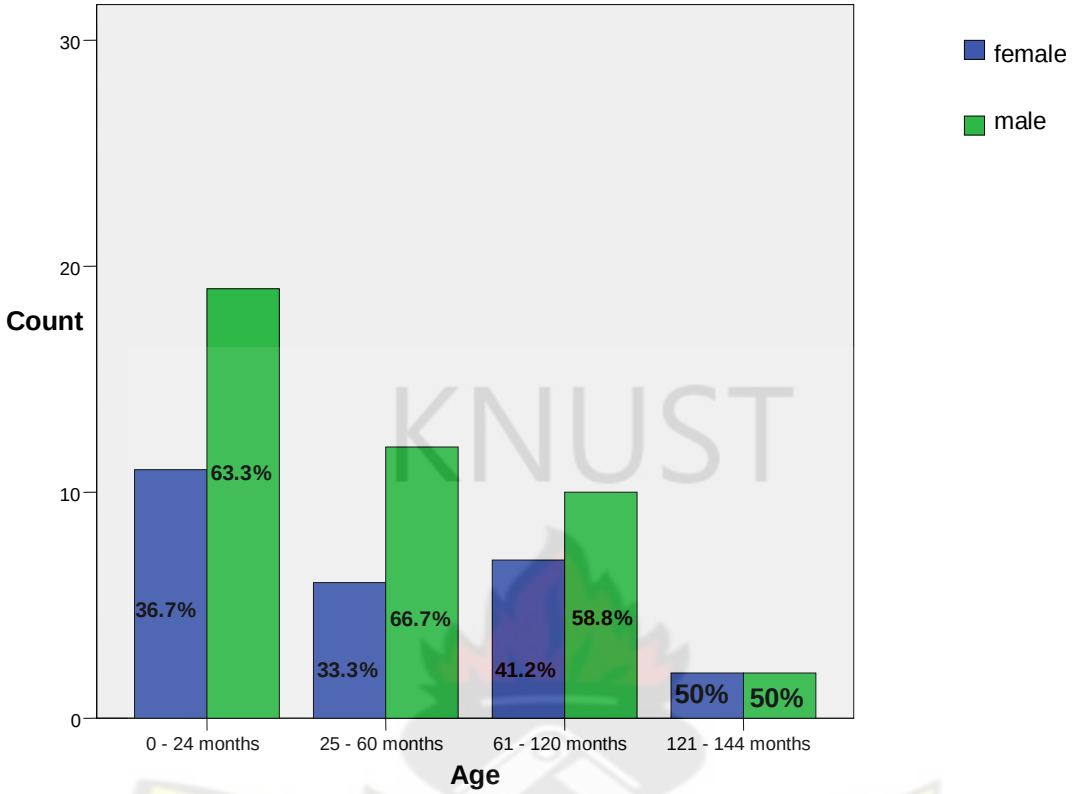

Figure 4.3: Age distribution of patients by sex

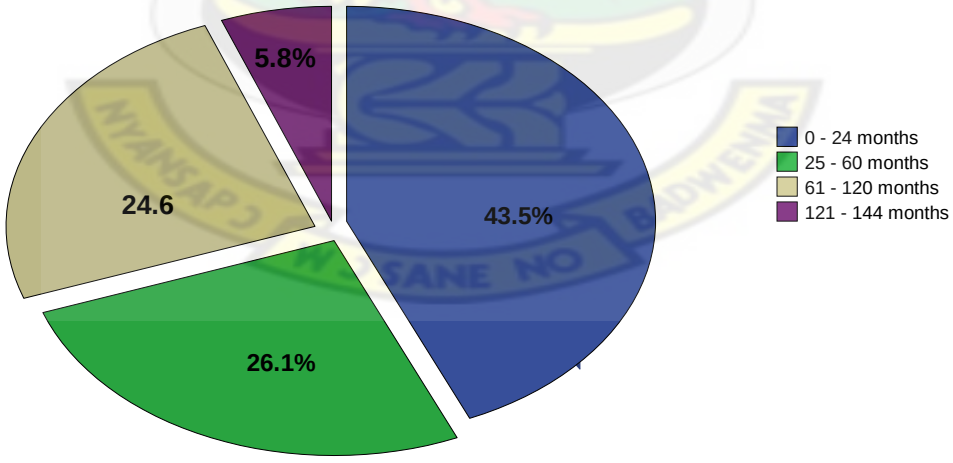

Figure 4.4: Age distribution of severe malaria cases

4.1.3 Source of patient

Majority (89%) of severe malaria admissions were of children who had been brought in directly from home, with or without any prior palliative treatment. The others comprised referrals from surrounding health centres and the case of neonatal malaria (Figure 4.5).

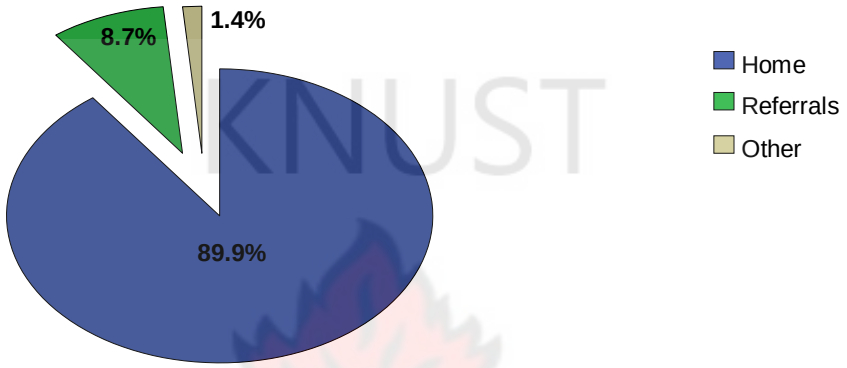

Figure 4.5: Source of patient – home or referral from pharmacy/community health centre

Thirty patients (43.5%) presented with at least one concomitant illness. Gastroenteritis (possibly malaria-associated), upper respiratory tract infections, enteric fever, meningitis and septicaemia ranked highest amongst these co-morbidities, in that order.

4.2 PREVIOUS MALARIA EPISODES

4.2.1 Details of previous episodes

Majority (97%) of children admitted with severe malaria had experienced at least one previous episode of malaria within the preceding 12 months (Figure 4.6).

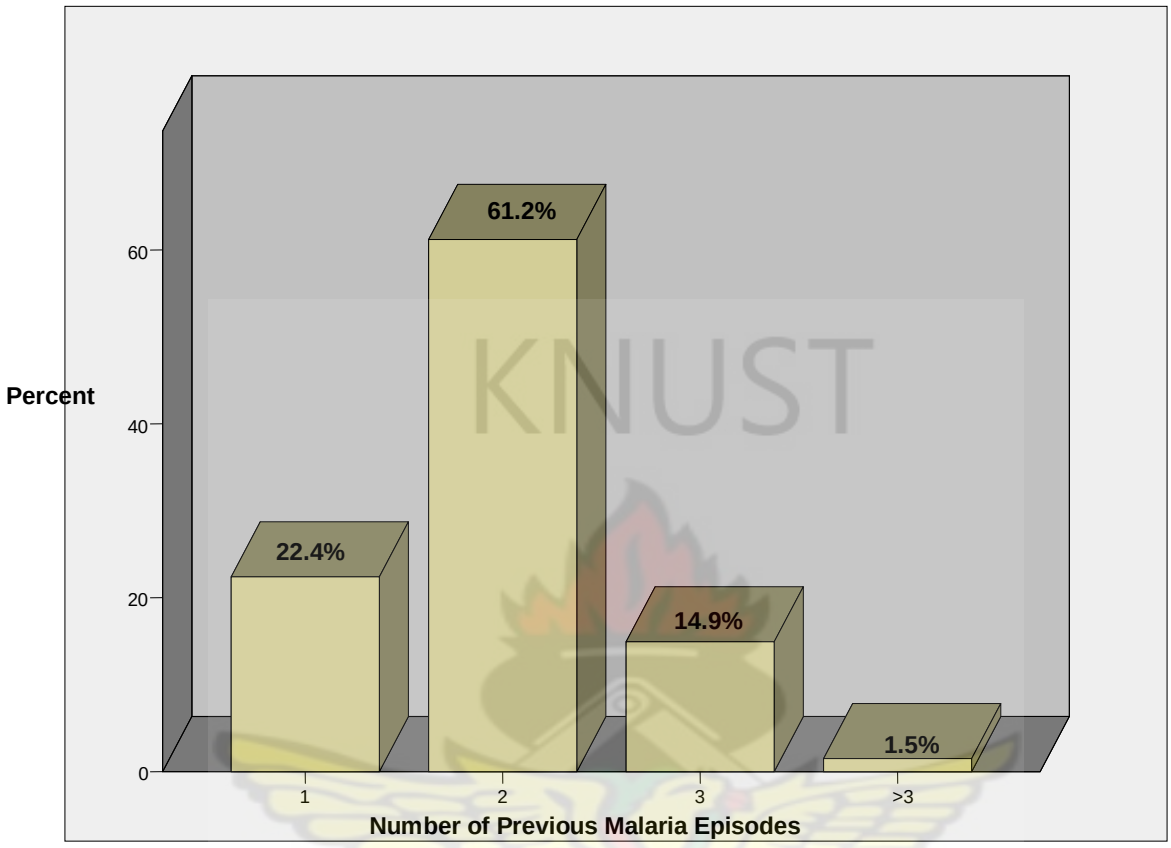

Figure 4.6: Previous malaria episodes within the preceding 12 months

4.3 OBSERVATIONS

4.3.1 Clinical and laboratory observations

Children aged less than 5 years generally presented with mean axillary temperature of 38°C. Mean haemoglobin levels and body weights were consistently higher in the older age groups, at time of admission (Table 4.2).

Table 4.2: Temperature, haemoglobin and weight by age. Data are presented as mean ± standard deviation.

Parameters	0-24 months	25-60 months	61-120 months	121-144 months
Temp. (°C)	38.5 ± 1.2	38.3 ± 1.1	36.5 ± 7.5	38.1 ± 2.0
Hb (g/dL)	8.0 ± 2.4	8.7 ± 2.8	12.0 ± 7.4	11.0 ± 1.5
Weight (kg)	9.6 ± 2.3	15.3 ± 4.2	24.6 ± 4.2	27.3 ± 2.9

On admission, means of both haemoglobin levels and axillary temperature were, on the whole, largely consistent across both gender groups. Female children however presented with a higher mean body weight (Table 4.3).

Table 4.3: Mean haemoglobin level, weight and temperature by sex. Data are presented as mean ± standard deviation.

Parameters	Males	Females
Hb(g/dL)	8.9 ± 2.4	8.9 ± 2.6
Weight(kg)	15.2 ± 7.3	16.9 ± 7.7
Temp(°C)	38.3 ± 1.3	38.6 ± 1.1

One-third of all patients were admitted with low parasitaemia, whilst the remainder showed differing levels of high parasitaemia (Tables 4.4 and 4.5).

Falciparum parasite load of greater than 10 parasites per single thick film field (4+) was observed only in children under 5 years (Table 4.4; Figure 4.7).

Table 4.4: Parasitaemia by age

Parasitaemia	0-24 months n(%)	25-60 months n(%)	61-120 months n(%)	121-144 months n(%)	Total n(%)
1+	10(33.3)	6(27.8)	6(35.3)	2(50.0)	23(33.3)
2+	6(20.0)	9(50.0)	5(29.4)	1(25.0)	21(30.4)
3+	10(33.3)	2(11.1)	6(35.3)	1(25.0)	19(27.5)
4+	4(13.3)	2(11.1)	0	0	6(8.7)
Total	30(100)	18(100)	17(100)	4(100)	69(100)

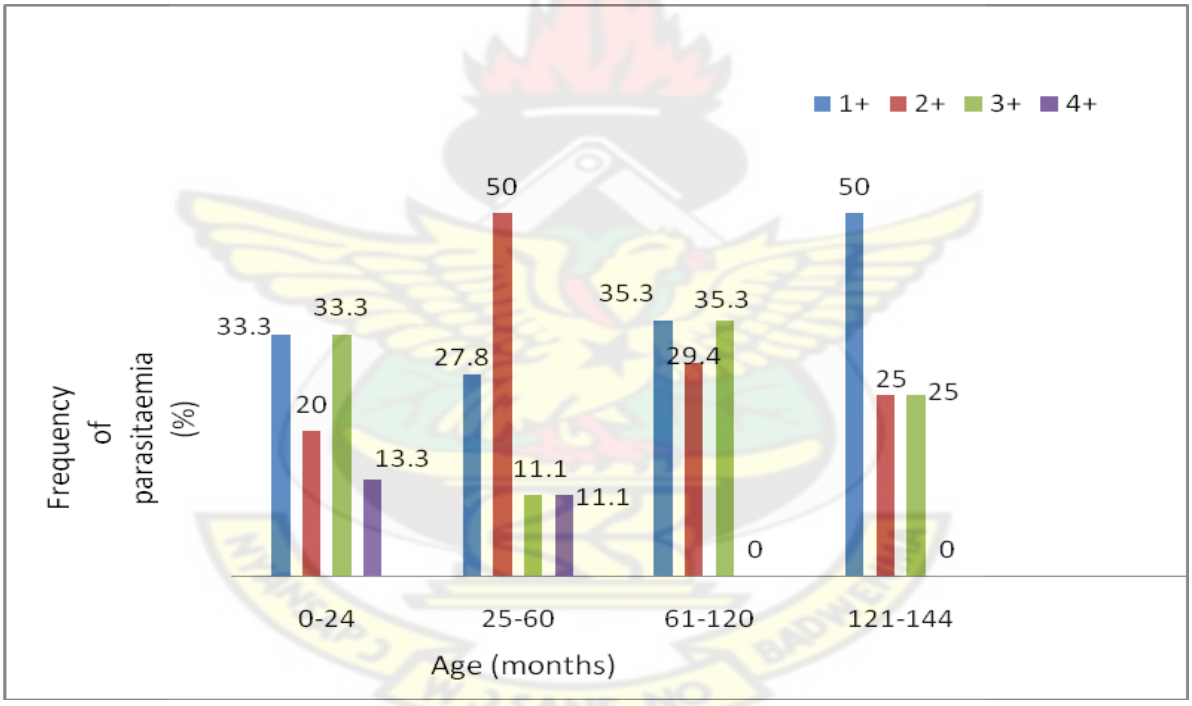

Figure 4.7: Parasite load by age

The respective frequencies of the different falciparum parasitaemia levels were largely similar across both male and female groups. Within each of these groups however, there was a decrease in proportions of parasitaemia from 1+ to 4+ (Table 4.5; Figure 4.8).

Table 4.5: Parasitaemia by sex

Parasitaemia	Males n(%)	Females n(%)	Total n(%)
1+	14(32.6)	9(34.6)	23(33.3)
2+	14(32.6)	7(26.9)	21(30.4)
3+	12(27.9)	7(26.9)	19(27.5)
4+	3(7.0)	3(11.5)	6(8.7)
Total	43(100)	26(100)	69(100)

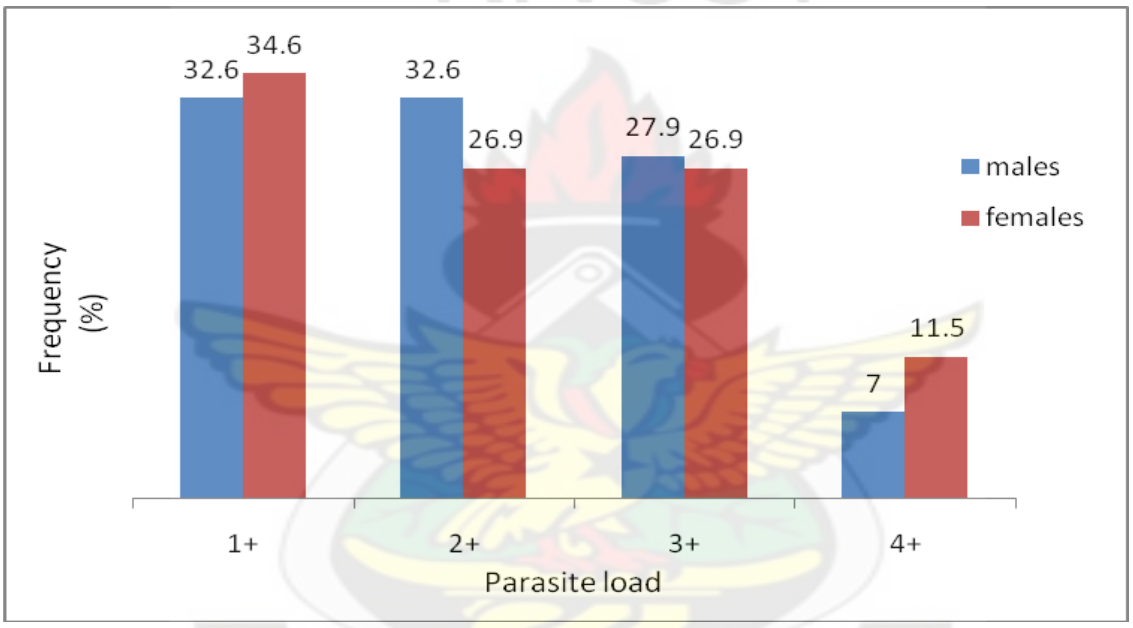

Figure 4.8: Parasite load by sex

Table 4.6 presents prevalence of clinical and laboratory observations for the different age groups studied. These observations are shown graphically from Figures 4.9-4.11 below.

Table 4.6: Clinical and laboratory observations by age

Observation	All ages n (%)	0-24 months n (%)	25-60 months n (%)	61-120 months n (%)	121-144 months n (%)
Mild/moderate anaemia	46(66.7)	20(66.7)	13(72.2)	11(64.7)	2(50.0)
Severe anaemia	10(14.5)	7(23.3)	3(16.7)	0	0
Fever	52(75.4)	24(80.0)	13(72.2)	13(76.4)	2(50.0)
Neurological symptoms and prostration					
Prostration only	43(62.3)	15(50.0)	9(50.0)	16(94.1)	3(75.0)
Prostration+ Convulsions	23(33.3)	15(50.0)	7(38.9)	1(5.9)	0
Prostration+ Impaired consciousness	2(2.9)	0	1(5.6)	0	1(25.0)
Prostration +Convulsions +Impaired consciousness	1(1.5)	0	1(5.6)	0	0

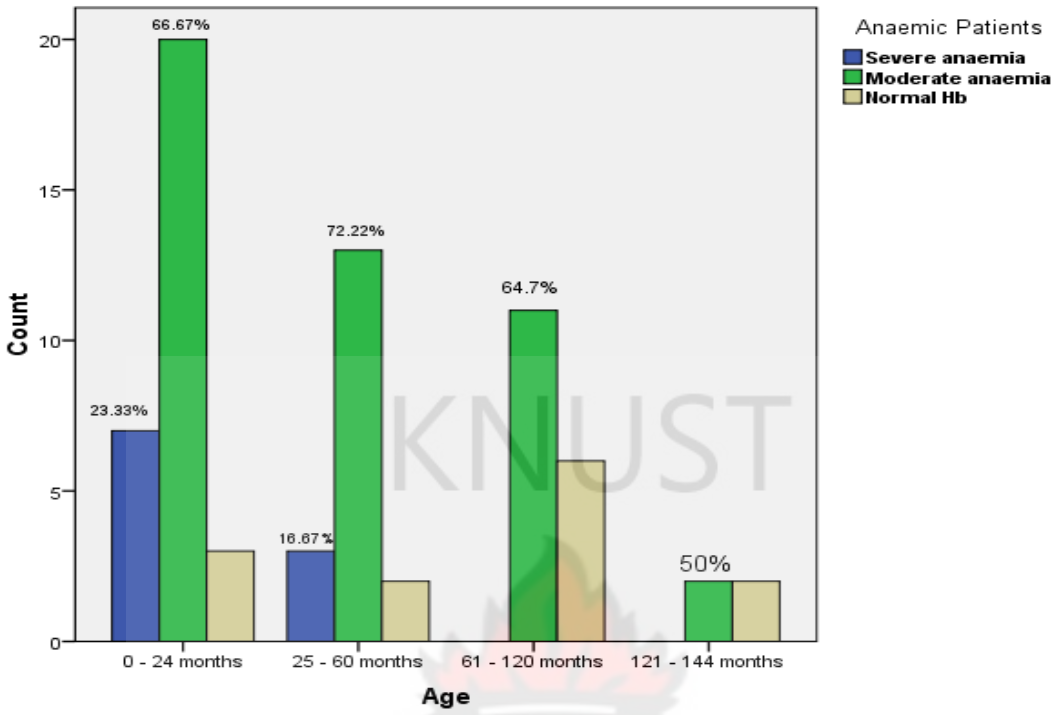

Figure 4.9: Prevalence of anaemia in different age groups

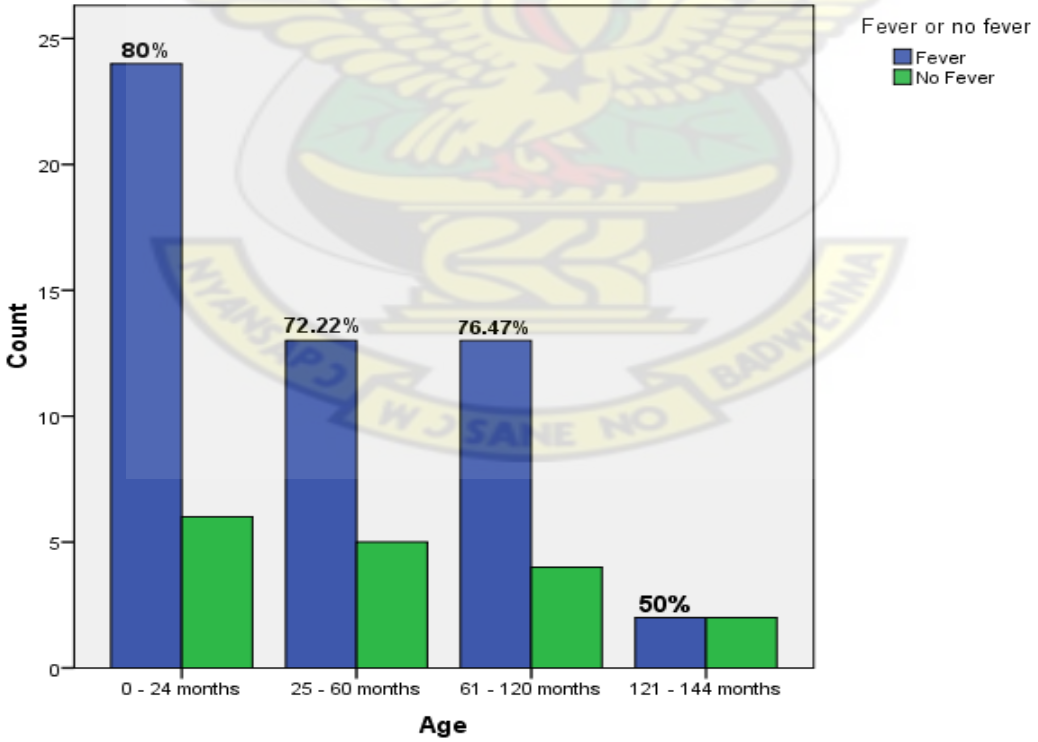

Figure 4.10: Prevalence of fever in different age groups

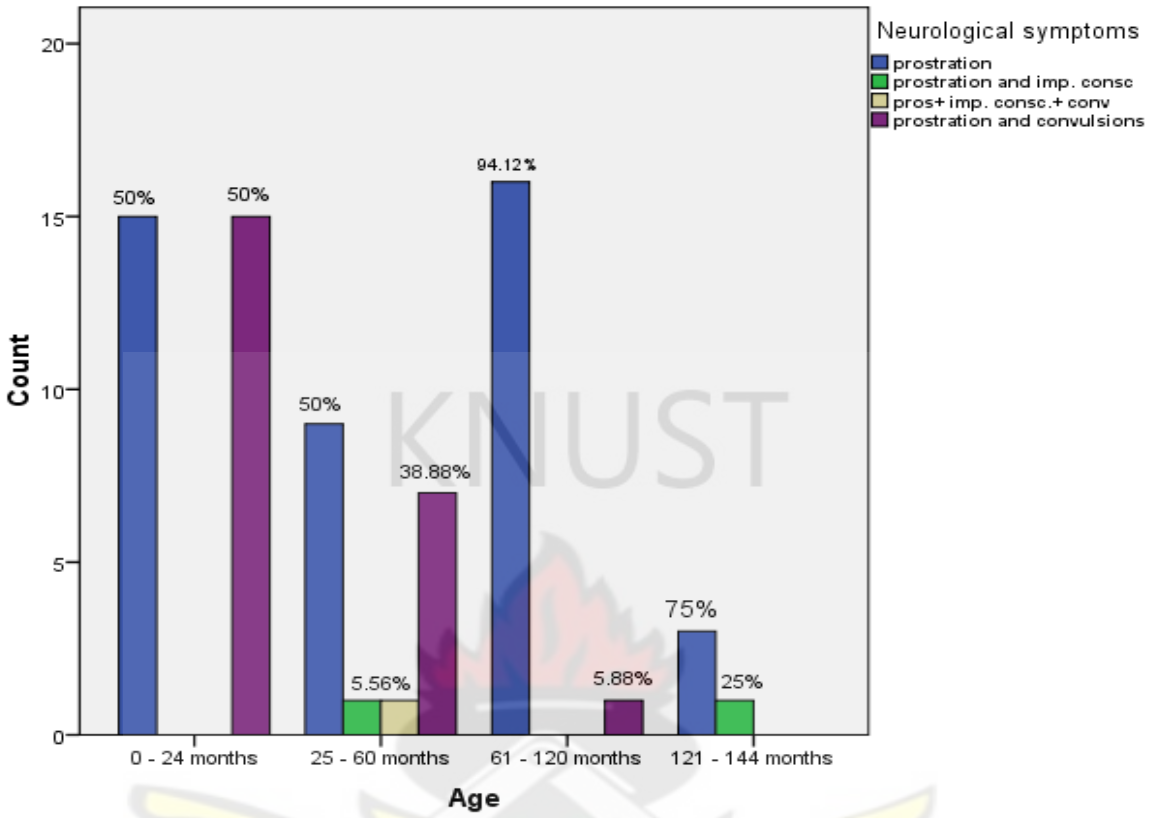

Figure 4.11: Prevalence of neurological symptoms in different age groups

To compare differences in prevalence of symptoms in the different age groups, age groups were compressed into 0-60 months (0-24, 25-60) and 61-144 months (61-120, 121-144).

In all children of both age groups under observation, anaemia of mild or moderate form was a common manifestation. Severe anaemia, on the other hand, was absent in older children. Overall, neurological symptoms were seldom observed in older children (Table 4.7; Fig 4.12).

Table 4.7: Prevalence of clinical observations by compressed ages

Observation	**0-60 months (N=48)** **n (%)[95% CI]**	**61-144 months (N=21)** **n (%)[95% CI]**
Mild/moderate anaemia	33 (68.8) [58.0 - 83.7]	13 (61.9) [36.0 - 78.3]
Severe anaemia	10 (20.8) [9.3 - 32.3]	0
Fever	37 (77.1) [65.2 – 89.0]	15 (71.4) [46.5 - 86.8]
Neurological symptoms and prostration		
Prostration only	24 (50.0) [35.9 - 64.2]	19 (90.5) [77.9 - 103.0]
Prostration+ Convulsions	22 (45.8) [31.7 – 59.9]	1 (4.8) [-4.4 – 13.9]
Prostration + Impaired consciousness	1 (2.1) [-2.0 – 6.1]	1 (4.8) [-4.4 – 13.9]
Prostration +Convulsion +Impaired consciousness	1(2.1) [-2.0 – 6.1]	0

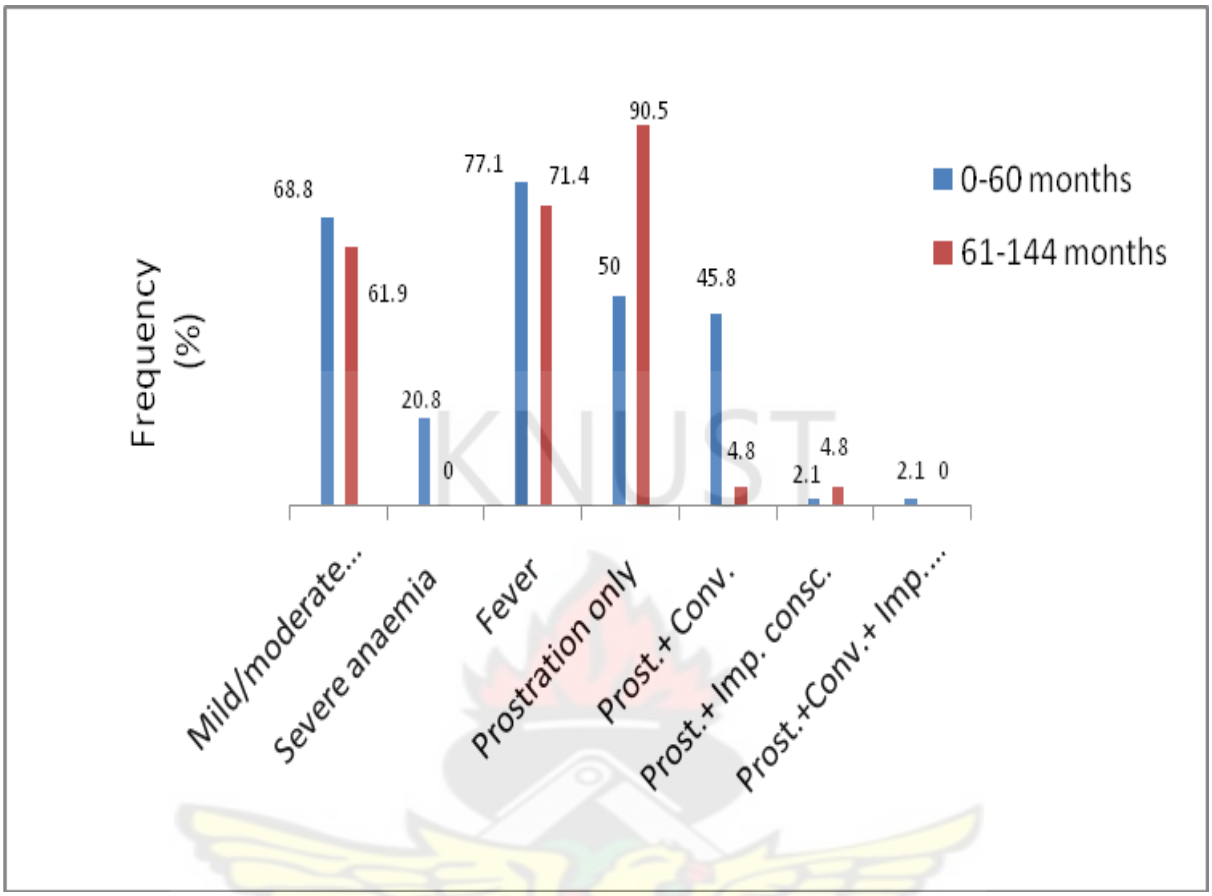

Figure 4.12: Prevalence of clinical and laboratory observations in compressed age groups

Proportions of anaemia (of both moderate and severe nature) and the neurological symptoms were significantly higher in the under 5-year group (anaemia-χ^2=0.31; p= 0.01; neurological symptoms-χ^2 = 0.36; p=0.001), as shown in Table 4.8.

Table 4.8: Differences in prevalence of symptoms in compressed age groups

Symptoms	Prevalence in age groups		χ^2 (p-value)
	0-60 months	61-144 months	
Anaemia (moderate + severe)	43/48 (89.6%)	13/21 (61.9%)	0.31 **(0.01)**
Fever	37/48 (77.1%)	15/21 (71.4%)	0.06 **(0.62)**
Neurological symptoms	24/48 (50%)	2/21 (9.5%)	0.36 **(0.001)**

Whereas mild to moderate anaemia was common in all patients, children under 60 months were more likely to develop severe anaemia and a combination of neurological symptoms - prostration, convulsions, impaired consciousness; ($\chi^2_{(corrected)}$ = 5.621; p=0.02 and $\chi^2_{(corrected)}$ = 8.541; p=0.001**,** respectively; Table 4.9). Presentation of fever was shown to be independent of age.

Table 4.9: Association between age and presentation of symptoms. Data are presented as percentages and chi-square with Yates' continuity correction, and p-values.

Symptoms	Prevalence in age groups		$\chi^2_{(corrected)}$ (p-value)
	0-60 months	61-144 months	
Anaemia (moderate + severe)	43/48 (89.6%)	13/21 (61.9%)	5.62 **(0.02)**
Fever	37/48 (77.1%)	15/21 (71.4%)	0.039 **(0.84)**
Neurological symptoms	24/48 (50%)	2/21 (9.5%)	8.54 **(0.001)**

More female children than males reported with fever and neurological symptoms (Table 4.10; Figure 4.13), albeit not significantly (Table 4.11). The presentation of neither anaemia nor the neurological symptoms was influenced by sex of the patient ($\chi^2_{(corrected)}$ = 2.73; p=0.10 and $\chi^2_{(corrected)}$ = 0.13; p=0.72, respectively). Similarly, no association between sex and the risk of developing fever was demonstrated (Table 4.12).

Table 4.10: Prevalence of clinical observations by sex

Observation	**Males (N=43)** **n (%)[95% CI]**	**Females (N=26)** **n (%)[95% CI]**
Mild/moderate anaemia	33 (76.7) [64.1 - 89.4]	13 (50.0) [30.8 – 69.2]
Severe anaemia	5 (11.6) [2.1 – 21.2]	5 (19.2) [4.1 – 34.4]
Fever	31 (72.1) [58.7 – 85.5]	21 (80.8) [60.7 – 93.1]
Neurological symptoms and prostration		
Prostration only	28 (65.1) [50.9 – 79.4]	15 (57.7) [38.7 - 76.7]
Prostration + Convulsions	13 (30.2) [16.5 – 44.0]	10 (38.5) [19.8 – 57.2]
Prostration +Impaired consciousness	1 (2.3) [-2.2 – 6.8]	1 (3.9) [-3.6 – 11.3]
Prostration+ Convulsions +Impaired consciousness	1 (2.3) [-2.2 – 6.8]	0

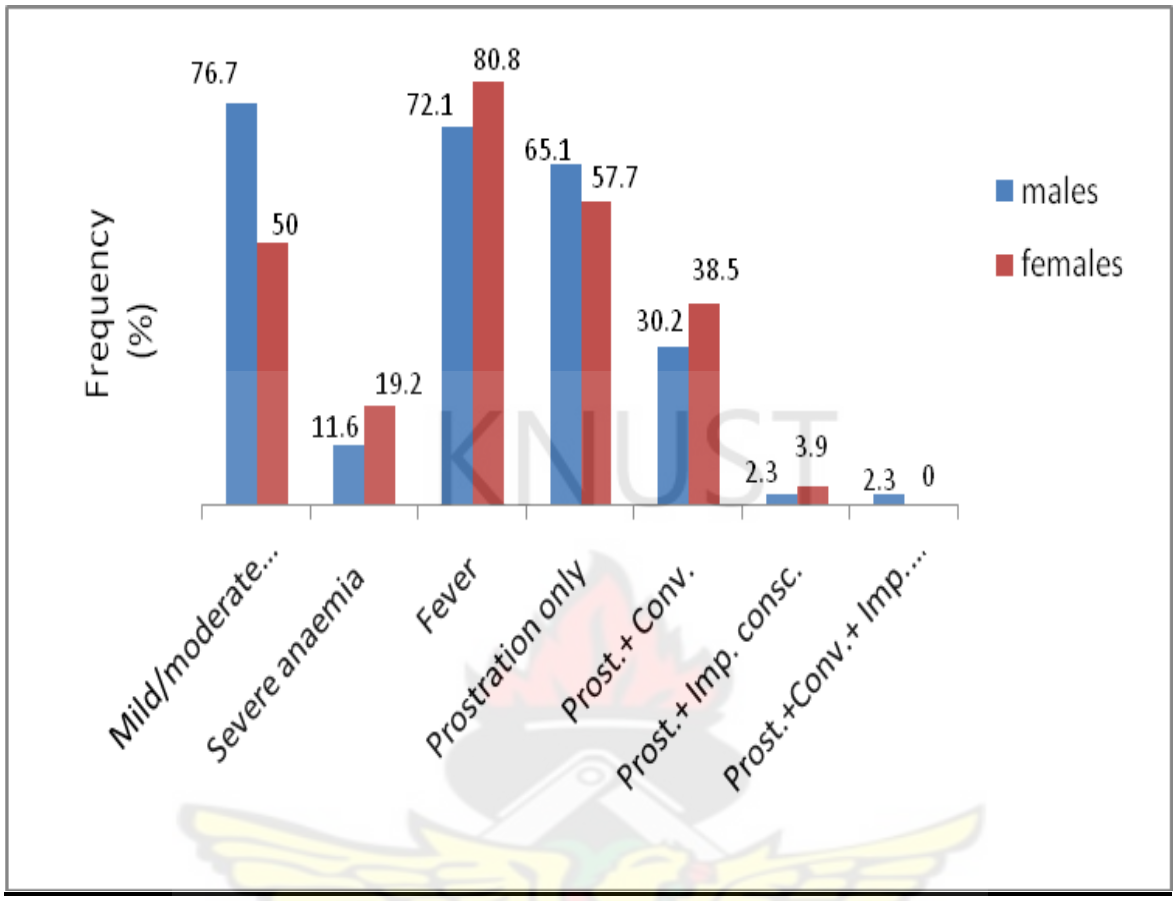

Figure 4.13: Prevalence of clinical and laboratory observations by sex

Table 4.11: Differences in prevalence of symptoms, by sex

Symptoms	Prevalence by sex		χ^2 (p-value)
	Males	Females	
Anaemia (moderate + severe)	38/43 (88.4%)	18/26 (69.2%)	0.23 **(0.05)**
Fever	31/43 (72.1%)	21/26 (80.8%)	0.10 **(0.42)**
Neurological symptoms	15/43 (34.9%)	11/26 (42.3%)	0.07 **(0.54)**

Table 4.12: Association between sex and presentation of symptoms. Data are presented as percentages and chi-square with Yates' continuity correction, and p-values.

Symptoms	Prevalence by sex		χ^2 (corrected) (p-value)
	Males	Females	
Anaemia (moderate + severe)	38/43 (88.4%)	18/26 (69.2%)	2.73 **(0.10)**
Fever	31/43 (72.1%)	21/26 (80.8%)	0.27 **(0.60)**
Neurological symptoms	15/43 (34.9%)	11/26 (42.3%)	0.13 **(0.72)**

Prevalence of fever was predictably significantly higher in patients with higher levels of parasitaemia (χ^2= 0.31; p=0.023; Table 4.13, 4.14). High parasitaemia levels were also shown to elevate the risk of developing fever as a symptom of severe malaria (Table 4.15). The risk of developing fever in children with high parasitaemia was increased by a factor of 4.29, as shown in Table 4.16.

Differences in prevalence of anaemia and neurological symptoms were observed between patients with low and high levels of parasitaemia (Table 4.13). However, these

differences were not significant (anaemia - χ^2= 0.21; *p*=0.08; neurological symptoms - χ^2= 0.21; *p*=0.08; Table 4.14).

Table 4.13: Prevalence of clinical symptoms in different levels of parasitaemia

Parasitaemia	Prevalence		
	Anaemia	Fever	Neurological symptoms
Low (1+)	16/23 (69.6%)	13/23 (56.5%)	5/23(21.7%)
High (2+, 3+, 4+)	40/46 (87%)	39/46 (84.8%)	21/46(45.7%)
Total	56/69 (81.2%)	52/69 (75.4%)	26/69 (37.7%)

Table 4.14: Differences in prevalence of symptoms, in groups with different levels of parasitaemia

Symptoms	Prevalence by parasitaemia		χ^2 (p-value)
	Low (1+)	High (2+, 3+, 4+)	
Anaemia (moderate + severe)	16/23 (69.6%)	40/46 (87%)	0.21 **(0.08)**
Fever	13/23 (56.5%)	39/46 (84.8%)	0.31 (**0.01)**
Neurological symptoms	5/23(21.7%)	21/46(45.7%)	0.21 (**0.08)**

Table 4.15: Association between parasitaemia level and presentation of symptoms. Data are presented as percentages and chi-square with Yates' continuity correction, and p-values.

Symptoms	Prevalence by parasitaemia		χ^2 (p-value)
	Low (1+)	High (2+, 3+, 4+)	
Anaemia (moderate + severe)	16/23 (69.6%)	40/46 (87%)	2.0 **(0.16)**
Fever	13/23 (56.5%)	39/46 (84.8%)	5.16 **(0.02)**
Neurological symptoms	5/23(21.7%)	21/46(45.7%)	2.27 **(0.13)**

Table 4.16: Odds ratio for risk of anaemia, fever and neurological symptoms in high parasitaemia

Symptom	Odds ratio (OR)	95% CI	*P*- value
Anaemia	2.92	0.85 - 10.03	0.08
Fever	4.29	1.35 - 13.56	0.01
Neurological symptoms	2.77	0.88 – 8.74	0.08

4.4 TREATMENT DETAILS

4.4.1: Antimalarial chemotherapy

Table 4.17 describes the pattern of antimalarial chemotherapy observed over the study period, with details of frequency of use, under-, over- and correct dosages. A total of 62 (89.9%) cases were given the right choice of medication (Artemisinin derivative: 26, Artemisinin+Amodiaquine: 19, Quinine:17) and of this number, 48 (77.4% - Artemisinin derivative: 22, Artemisinin+Amodiaquine:12, Quinine:14) received doses in accordance with the national guidelines . Chloroquine (obsolete) was used in five cases and Amodiaquine alone was used in one case. One case was treated with Artemisinin + Lumefantrine combination.

Table 4.17: Antimalarial chemotherapy

Drug	No. of children N=69, (%)	Under-dose n (%)	Over-dose n (%)	Correct dose n (%)
Chloroquine [n=5]	5 (7.3)	4 (80)	1 (20)	0
Artemisinin derivative only [n=26]	26 (37.7)	4 (15.4)	0	22 (84.6)
Amodiaquine only [n=1]	1 (1.5)	0	0	1 (100)
Artemisinin + Amodiaquine [n=19]	19 (27.5)	6 (31.6)	1 (5.3)	12 (63.2)
Artemisinin + Lumefantrine [n=1]	1 (1.5)	0	0	1 (100)
Quinine [n=17]	17 (24.6)	3 (17.7)	0	14 (82.4)
Total	69 (100)	17 (24.6)	2 (2.9)	50 (72.5)

4.5 ADVERSE DRUG REACTIONS

Overall, 13 ADRs were suspected in 11(15.9%) patients – 6 males and 5 females. Generally, female children aged less than 5 years did not show any ADRs (Table 4.18).

Table 4.18: Demographics of patients with ADRs

Age (months)	Males	Females	Total
0-24	1(9.1%)	0	1(9.1%)
25-60	3(27.3%)	0	3(27.3%)
61-120	2(18.2%)	3(27.3%)	5(45.5%)
121-144	0	2(18.2%)	2(18.2%)
Total	6(54.5%)	5(45.5%)	11(100%)

The median age of children with suspected adverse reactions was 108 months (AR= 18-144 months).

Incidence of ADRs was significantly higher in the older age group (61-144 months) than in the younger group (χ^2 =6.81; p=0.02), as shown in Table 4.19.

Table 4.19: Prevalence of ADR reports in the different age groups studied

Age group (months)	Number of ADR's reported	% of ADR reports (no. of reports ÷ total no. of reports)	Number of patients with ADR's	Total sample size per age group	Prevalence % (no. of pts. with ADR's ÷ total sample per age group)
0-24	1	7.7 (1/13)	1	30	3.3 (1/30)
25-60	5	38.5 (5/13)	3	18	16.7 (3/18)
61-120	5	38.5 (5/13)	5	17	29.4 (5/17)
121-144	2	15.4 (2/13)	2	4	50 (2/4)
Total	13	100(13/13)	11	69	15.9 (11/69)

Prevalence of ADRs was higher in females (5/26) than males (6/43); albeit not significant (χ^2= 0.06; p=0.81). Occurrence of adverse reactions was thus found to be independent of sex ($\chi^2_{(corrected)}$ = 5.08; p=0.56) (Table 4.20).

Table 4.20: Prevalence of ADR reports in the different gender groups studied

Sex	Number of ADR's reported	% of ADR reports (no. of reports ÷ total no. of reports)	Number of patients with ADR's	Total sample size per gender group	% incidence(no. of pts. with ADR's ÷ total sample per gender group)
Male	7	53.8 (7/13)	6	43	14.0 (6/43)
Female	6	46.2 (6/13)	5	26	19.2 (5/26)
Total	13	100 (13/13)	11	69	15.9 (11/69)

Suspected or observed reactions were mostly Type A reactions (Table 4.21), with the following drugs being commonly implicated:

- Antimicrobials – ceftriaxone, ciprofloxacin, amoxicillin, sulphamethoxazole/trimethoprim and griseofulvin.
- Antimalarials – chloroquine and amodiaquine
- NSAIDs – diclofenac
- Antihistamines – promethazine

Specific details of reactions are presented in Table 4.22.

Table 4.21: Reaction types

Type of reaction	Number of ADR reports	% of ADR reports (no. of reports ÷ total no.of reports)
Type A(augmented)	11	84.6 (11/13)
Type B(bizarre)	2	15.4 (2/13)
Total	13	100 (13/13)

Table 4.22: Organ systems affected

Organ system	Number of ADR reports	% of ADR reports (no. of reports ÷ total no. of reports)	Reaction	Number of ADR reports	% of ADR reports (no. of reports ÷ total no. of reports)
Gastrointestinal	8	61.5 (8/13)	Nausea	1	7.7 (1/13)
			Vomiting	2	15.4 (2/13)
			Abdominal pain	3	23.1 (3/13)
			Diarrhoea	2	15.4 (2/13)
Dermatological	1	7.7 (1/13)	Itching	1	7.7 (1/13)
CNS	4	30.8 (4/13)	Drowsiness	2	15.4 (2/13)
			Lethargy	2	15.4 (2/13)
Total	13	100 (13/13)		13	100 (13/13)

In all, 9 (69.2%) of the reported adverse reactions were determined as being unlikely to have a drug-related aetiology. Four reactions were found to be possibly attributable to antimalarial chemotherapy (Table 4.23). See Appendix I (Section 5.7) for assessment criteria.

Table 4.23: Causality assessment for observed ADRs

Causality association	Number of ADR reports	% of ADR reports (no. of reports ÷ total no. of reports)
Definite	0	0
Probable	0	0
Possible	4	30.8 (4/13)
Unlikely	9	69.2 (9/13)
Total	13	100 (13/13)

Using Hartwig's scale of assessment of ADR severity, all reported adverse reactions were deemed mild (Table 4.24).

Table 4.24: Severity assessment of ADRs, as determined with Hartwig's severity scale

Severity	Number of ADR reports	% of ADR reports (no. of reports ÷ total no. of reports)
Mild	13	100 (13/13)

Moderate	0	0
Severe	0	0
Total	13	100 (13/13)

The majority of reported or observed ADRs required neither a change in drug regimen nor additional treatment (Table 4.25). Two cases of abdominal pain were managed with antacids and spasmolytic agents.

Table 4.25: Management of reported ADRs

Action	Number of ADR reports	% of ADR reports (no. of reports ÷ total no. of reports)
Drug withdrawn	0	0
Dose altered	0	0
Additional treatment required/given	2	15.4 (2/13)
No change in drug regimen/no additional treatment	11	84.6 (11/13)
Total	13	100 (13/13)

As shown in Table 4.26, the concurrent use of 5 or more medicines was associated with the majority (84.6%) of all reported adverse reactions.

Table 4.26: Number of concurrent medicines and ADR reports

Number of medicines	Number of suspected ADRs	% of ADR reports (no. of reports ÷ total no. of reports)
3	2	15.4 (2/13)
5	5	38.5 (5/13)
6	3	23.1 (3/13)
7	3	23.1 (3/13)
Total	13	100 (13/13)

All but one patient with suspected adverse reactions to antimalarial treatment had recovered fully at the time of discharge (Table 4.27).

Table 4.27: Outcome of reported ADRs

Final outcome	Number of ADR reports	% of ADR reports (no. of reports ÷ total no. of reports)
Fatal	0	0
Damaging	0	0
Recovered	12	92.3(12/13)
Ongoing	1	7.7 (1/13)
Unknown	0	0
Total	13	100 (13/13)

CHAPTER FIVE

5.0 DISCUSSION

This study set out to describe the presentation of severe malaria in a hospital situated in an area of intense *Plasmodium falciparum* transmission. Eighty-four percent of paediatric admissions resulted from severe *falciparum* malaria over the study period; an indication of the intensity of transmission and clinical toll of the disease within the study area. One major difficulty with morbidity data is that figures are inferred from hospital records as there exists no systematic documentation of case reports at the community level. Therefore, although results gathered may indeed be a fair index of the prevalence of severe malaria within the study region, the figure does not reflect the prevalence of all malaria cases in the area as most cases of malaria infections are handled at either the household or community pharmacy level without ever getting to the hospital.

The proportion of male children admitted with malaria was significantly higher than females. This observation is consistent with reports from Tanzania (Schellenberg *et al*, 1999), northern Ghana (Oduro *et al*, 2007) and Gabon (Dzeing-Ella *et al*, 2005). Although males may indeed be more liable to develop severe malaria, sociological reasons often suggest that this trend is indicative of household-level gender bias in treatment-seeking behaviour for male children. A more plausible reason may be that older male children, by default, tend to spend longer periods outdoors, thereby increasing their exposure to the vector.

A greater part of the morbidity burden was borne by the under 5 age group; with children under 2, accounting for nearly half of all cases enrolled. This finding is in consonance with a report by Snow *et al* (1994). They report that in highly endemic zones, severe malaria mainly affects younger children. This predominance in younger children could be attributed to a lack of adequate clinical immunity against the disease.

Ninety-seven percent of enrollees had experienced at least one previous malaria episode within the 12 months preceding the study. Treatment for the majority of these had been effected outside of the hospital setting. Consequently, questions regarding the appropriateness of any previous therapy come up prominently. Current illness could therefore have resulted from either failure of previous treatments or from post-treatment re-infection.

Anaemia was a common clinical feature, presenting in over 80% of cases. Severe anaemia (Hb< 5g/dL or PCV< 15%) was however less frequently observed. Association of anaemia with malaria is expected from the effect of the life cycle of the plasmodium parasite in humans. The low prevalence of severe anaemia in our subjects may be explained by factors like patients Hb level before infection, duration of infection and self medication with haematinics before admission. At the time of admission, a good proportion of patients presented with gastroenteritis manifested by diarrhoea and vomiting. Dehydration-induced haemoconcentration could therefore have influenced an underestimation of severe anaemia prevalence by spuriously increasing haemoglobin concentrations. Similar to previous reports (Snow *et al*, 1994; Imbert *et al*, 1997), severe anaemia was associated with age, showing a significant inverse correlation. In contrast with this, sex did not influence the pattern of expression of severe anaemia.

Contrary to earlier reports of neurological involvement being more common in low transmission zones and in older children (Modiano *et al*, 1998), the symptoms, particularly convulsions, were more common in younger children in this study. Neurological symptoms were independent of sex of the patient.

Fever, a characteristic feature of *falciparum* infection, was seen in about 75% of all eligible cases. As with anaemia and neurological symptoms, fever was also independent of sex. Malaria infections are complicated syndromes involving many inflammatory responses mediated by host-derived factors such as cytokines. Parasite antigenic products stimulate the overproduction of tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and interleukin-1 (IL-1), which adversely affect disease progression (Jakobsen *et*

al, 1995). These cytokines, among other effects, cause changes in the host such as fever, suppression of bone marrow and erythrocyte production, coupled with direct destruction of host erythrocytes (Chen *et al*, 2000). It is reasonable to suggest, therefore, that high levels of parasitaemia would correlate directly with incidence of fever and anaemia. Fever was indeed significantly higher in the high parasitaemia group. However, the frequency of anaemia in both high and low parasitaemia groups showed no significant difference. Why was anaemia still considerably common at low parasite density? This finding could in part reflect repeated infections which may have eventually led to a gradual decrease in haemoglobin concentrations, prior to the current illness. Prior home treatment with anti-malarial agents may have reduced parasite density without necessarily modifying the course of the disease. Additionally, parasite sequestration may have led to a reduction in peripheral parasitaemia, whilst patients' condition deteriorated. The above observations advance the argument for a reconsideration of parasite density as a guideline for diagnosis and treatment of severe malaria. Considering the high mortality associated with the first hours of admission (*Bassat et al*, 2008), it would seem advisable that all malaria-related paediatric admissions receive prompt parenteral treatment, regardless of parasitaemia level. A sizeable proportion of severe malaria reports were afebrile on admission. Earlier reports have attributed this kind of observation to self-medication with antipyretics or anti-malarial medicines before reporting at the hospital (Ella *et al*, 2005).

The Ghana National Malaria Control Progamme promotes the use of either quinine or artemisinin derivatives for the treatment of severe *falciparum* malaria. Almost 9% of all cases studied received treatments (either chloroquine or amodiaquine only) other than the recommended regimen. Of this figure, 83.3% received chloroquine. Considering the overwhelming resistance of *Plasmodium falciparum* to chloroquine in Ghana, it remains unclear why this drug was still used in malaria chemotherapy. It is encouraging to note, however, that the majority of cases (91.3%) received appropriate drug therapy.

It was detected that even though patient weights were recorded in all cases, the majority of doses were based on the age-dose relation rather than being calculated according to

body weight. This consequently led to some flaws in dosing. High patient-doctor ratios may be a significant attributable factor. As shown in Table 4.17, nearly 25% (17/69) of all cases received treatments with doses lower than the recommended dosages for those drugs. This could lead to recrudescence. Only 3% of patients, however, received doses above the recommended. This could have contributed to the development of adverse effects, resulting from augmentation of the pharmacological actions of drugs involved. Thirty-seven percent of all case treatments involved the use of artemisinin derivatives alone. Of this proportion, 15% were under-dosed, with the remainder receiving correctly calculated doses. Compliance with dosage recommendations for Artesunate+Amodiaquine was appropriate in only 63.2% of the cases. The use of quinine accounted for 24.6% of all treatments. Eighty-two percent of quinine treatments were effected with the correct dose (20 mg quinine salt/kg body weight loading dose, followed by 10 mg quinine salt/kg body weight 8 hourly, given intravenously), while 17.7% of patients received under-dosages.

Adjunctive treatment included intravenous rehydration, paracetamol, diclofenac, analgin, promethazine and diazepam, as appropriate. Paracetamol was given either orally or rectally. Analgin and promethazine were given parenterally. Diazepam was administered as enema, with diclofenac being given through either the oral or parental routes. All patients presenting with anaemia received either blood transfusions or haematinics, as necessary. Tepid sponging was also often employed.

Adverse drug reactions can have detrimental effects on patients' well-being, as well as the general health- care system. Efficient monitoring of patients for ADRs therefore remains crucial to improving quality of life for patients and reducing morbidity and health-care costs. In this study, ADRs were suspected in 15% of severe malaria cases. This result should however be interpreted with caution since the majority of these suspected ADRs were more likely to be disease-related rather than drug-related. Concordantly, assessment of causality showed that 69% of these reactions had an unlikely drug cause. Nevertheless, it is impossible to be absolutely certain of a causal link between an ADR and a drug. The average bed stay in this study was found to be 3 days. Therefore, granted that all suspected ADRs were indeed drug-related, it is possible

that the actual prevalence could have been higher, had reactions of delayed onset (longer than bed stay) been taken into account. In addition, bearing in mind that most common reactions are less likely to be reported compared with uncommon or rare ones, these prevalence figures could be an underestimation of the actual.

The incidence of adverse reactions was significantly lower in children aged below 5 years. In these children, accuracy of locating and describing a painful stimulus is relatively lower and this may have limited the number of reports in this group. Overall prevalence was higher in females, albeit not significant.

Of the proportion of adverse reactions with a possible drug cause, culprit drugs were chiefly antimicrobials, antimalarials, NSAIDs and sedating antihistamines. Eighty-four percent (84%; 11/13) of suspected ADRs were rated as type A ; results consistent with the definition of type A as occurring more commonly (Pirmohamed *et al*, 1998). Determining the severity of an ADR is largely subjective. However, going by Hartwig's proposed algorithm (Hartwig *et al*, 1992), all suspected ADRs were adjudged to be mild. They were mostly self-limiting and of minor significance. These reactions did not prolong hospitalization.

Gastrointestinal reactions were most commonly observed. Other main categories were CNS and dermatological effects. Adverse reactions associated with the gastrointestinal tract and central nervous system were reported amongst the top three groups of ADRs in previous studies (Sharma *et al*, 2007; Peyriere *et al*, 2003).

The likelihood of developing an ADR increases with the number of co-prescribed drugs (Atkin *et al*, 1995). Although in this study the correlation was not directly proportional, a remarkable increase in ADR reports with increasing number of concurrently administered drugs, was observed. In 23% of patients in the ADR group, 7 drugs were given concurrently. Multiple concurrent drug use was hence identified as a risk factor in all patients with suspected ADRs.

Drug withdrawal or dose reduction is usually the first step in managing an ADR (Jose

and Rao, 2006). In this study, however, the majority (84%) of suspected adverse reactions resolved without any change in drug regimen or additional treatment. Specific treatment was required in only 15% of reports. Antacids and spasmolytic agents were given for abdominal pain in these cases requiring additional treatment. Only one (7.7%) report was ongoing at the time discharged. This patient was discharged before chloroquine-induced itching fully resolved, although general condition was quite satisfactory.

CONCLUSIONS

The following conclusions were arrived at:

- Severe malaria accounts for the majority of paediatric admissions
- Children under 5 are more vulnerable to the pathological effects of malaria
- Prostration, anaemia, fever and convulsions make up the clinical spectrum of severe paediatric malaria, in the study area.
- Clinical spectrum of severe malaria was independent of sex of patients
- High level of parasitaemia was associated with the presentation of fever
- Incidence of adverse drug reactions was independent of sex
- Incidence of adverse drug reactions increased significantly with age
- Multiple concurrent drug use predisposed patients to adverse drug reactions

RECOMMENDATIONS

- Prescribers need to be encouraged to comply with evidence-based national treatment guidelines for malaria

- Education of mothers and care-givers on the dangers of severe malaria and need for early appropriate care, should be intensified.

- Hospital studies could underestimate the burden of malaria. Extensive community-based epidemiological studies, therefore, need to be undertaken.

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A PPENDIX I

DEPARTMENT OF CLINICAL AND SOCIAL PHARMACY

COLLEGE OF HEALTH SCIENCES, KNUST, KUMASI

SECTION ONE: PATIENT DETAILS

1.1 Patient ID..... 1.2 Age ..... 1.3 Sex..... 1.4 Weight (kg).....

1.5 Height (m)..... 1.6 Date of admission.....

1.7 Source of patient - ☐ From home ☐ Referral from community pharmacy or health centre

1.8 Pre-existing medical condition(s).....

……..

SECTION TWO: DETAILS OF PREVIOUS EPISODES

2.1 Have you previously had malaria within the last twelve (12) months? (Y/N).....

2.2 If yes, how many malaria episodes have you experienced within this period? .....

SECTION THREE: OBSERVATIONS

3.1 Parasite load - ☐ + ☐ ++ ☐ +++ ☐ ++++

3.2 Temperature..... 3.3 Hb..... 3.4 RBS.....

3.5 Urine colour..... 3.6 Urine volume/day.....

3.7 Presenting signs – ☐ Coma ☐ Impaired consciousness

☐ Prostration ☐ Convulsions

SECTION FOUR: TREATMENT DETAILS

4.1 Malaria therapy information and dosage details (state generic name, with trade name in parenthesis)

Serial number	1	2	3	4	5
Drug name					
Labelled strength					
Manufacturer/Batch number					
Dose given					
Frequency and duration					
Route					
Therapy start date					
Therapy stop date					

4.2 Concomitant drugs (if start and stop dates unknown, state whether or not therapy is continuing)

Drug	Reason for use	Dosage regimen	Route	Start date	Stop date	Therapy continuing

SECTION FIVE: ADVERSE DRUG REACTIONS

5.1 Suspected adverse drug reactions - ☐ Diarrhoea ☐ Vomiting ☐ Dizziness

☐ Skin rashes ☐ Headache ☐ Abdominal pain

Other (specify).....

……

5.2 Date of reaction.....

5.3 Outcome of reaction – ☐ Hospitalization prolonged ☐ Required intervention

☐ Other (specify).....

5.4 How long was hospitalization prolonged as a result of adverse drug reaction? .....

5.5 Intervention required – ☐ Antihistamine ☐ Antidiarrhoeal ☐ Antiemetic

☐ Steroid ☐ Other (specify).....

5.6 Outcome of treatment – ☐ Fatal ☐ Damaging ☐ Fully recovered

☐ Ongoing ☐ Unknown

5.7 Causality association (answer Yes-Y, No-N or Not Applicable-NA)

Suspected drugs (s)	Did reaction abate after drug was stopped or dosage reduced?	Did reaction worsen with continued or increased dosage?	Did reaction reappear after drug was re-introduced?	Are there **alternative causes** (other than the drug) that could on their own have caused the reaction?