UNIVERSITY OF THE WITWATERSRAND

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RESEARCH REPORT

PROJECT TITLE

RISK FACTORS FOR MALARIA DEATHS AMONG CHILDREN UNDER 5 ADMITTED AT A RURAL DISTRICT HOSPITAL IN TANZANIA

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A Research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfillment of the requirements for the award of a degree of Master of Science (Med) in Population-based Field Epidemiology

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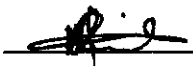
DECLARATION

I, Rose Nkirote Kiriinya declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in Population-based field Epidemiology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature: 

Full Name: **Rose Nkirote Kiriinya**

8th day of **May, 2007**

DEDICATION

DEDICATED TO

MY BELOVED HUSBAND GEOFFREY KINYUA

FOR HIS UNLIMITED PRAYERS AND SUPPORT

AND

MY BELOVED SON LEON MUMERO

FOR BEING AN INSPIRATION IN MY STUDIES

AND

MY LOVELY MUM BEATRICE KIRIINYA

FOR HER UNRESERVED LOVE AND CARE

ABSTRACT

Malaria remains a public health problem, and children are the most vulnerable to the disease. There is however, an alarming slow progress in reducing child deaths despite the availability of proven and low-cost interventions. Prompt and effective treatment of malaria is a critical element of malaria control but this can be hampered by inaccurate identification of illnesses in the rural poor health facilities.

The study explored the risk factors for malaria deaths and its association with anemia among hospitalized children in a pediatric ward.

The study involved secondary data analysis of clinical surveillance data collected at a pediatric ward of a district hospital (Saint Francis Designated District Hospital) in southern Tanzania from 2002 to 2005.

From 2002 to 2005, a total of 10,392 children under 5 years of age were admitted to the hospital. Of these, 7740 (75.5%) were diagnosed with malaria with or without other diagnoses. There were 634 deaths among those admitted; 328 were malaria related, of whom 153 (46.7%) were children <1 year of age. Malaria related mortality accounted for more than half of all pediatric deaths for the period between 2002 and 2005 and was significantly associated with age of the child, fitting, fever, diarrhea, anemia, the child's nutritional status, and the child having been seen at any health unit for the illness. Multivariate analysis showed that anemia [OR =1.6, CI: 1.2, 2.1], fitting [OR= 3.0, CI: 2.2, 4.0], diarrhea [OR=1.73 CI: 1.27, 2.37], sucking less than usual for children < 1 year [OR=1.58 CI: 1.18, 2.12] and malnutrition [OR= 2.4, CI: 1.5, 3.8] were independently related to the risk of dying from malaria. Results indicated that malaria is a leading cause of pediatric mortality in this hospital, and that anemia is an important risk factor for malaria deaths. Despite the implementation of previous malaria control interventions,

proportion of malaria related deaths among the admitted children did not indicate a significant decrease across years. This is an indication that severe malaria is still a challenge to the health care providers.

There is therefore need for more access to diagnostic services with accurate identification of risk factors to ensure prompt and effective treatment of malaria. We call for improved case detection and management (Roll out of IMCI guidelines) at peripheral health facilities.

Keywords: Malaria, mortality, anemia admission and children under five years

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DEFINITION OF TERMS

1. **Malaria** is a disease caused by the presence of the plasmodium in human or other vertebrate red blood cells and is transmitted to humans by the bite from an infected female anopheles mosquito, which previously sucked the blood from a person with malaria. (Stedman's medical dictionary, 25th international edition)
   Severe malaria is defined as parasitaemia of higher than 5%, a hemoglobin of <6 g/dl, spontaneous hypoglycemia or major organ dysfunction - particularly cerebral malaria.

2. **Plasmodium falciparum** is a species of protozoa that is the causal agent of falciparum malaria. It is most prevalent in the tropics and subtropics. (http://www.biology-online.org/ dictionary/plasmodium-falciparum.

3. **Anemia** in malaria is caused by the destruction of red blood cells (haemolysis) in the body or the depression of red blood cell production in the bone marrow. According to International standards, anemia is defined as haemoglobin level<11g/dl or haematocrit <33%. Anemia is mainly caused by malaria, malnutrition, parasitic infestation like hookworm and HIV and other chronic infections. The prevalence of anemia is best determined by measuring haemoglobin (Hb) concentration. However, packed cell volume or haemotocrit (Hct) has been widely used as an alternative in malaria studies due to its cost. A threefold conversion is commonly used to equate the two measures. For example according to i-STAT system, hemoglobin (g/dl) =hematrocrit (% PCV) x 0.34. Though, centrifuged Hct has been shown to underestimate Hb due to plasma trapping (1). The standard Hct cut-offs used to define anemia (Hct = >25% to 33%), moderate anemia (Hct = >15% to 25%) and severe anemia (Hct = <15%) are likely to under estimate the burden of anemia in individuals and populations, compared with the equivalent Hb cut-offs (Hb= >8g/dl to <11g/dl, Hb= >5g/dl to 8g/dl and Hb= <5g/dl respectively). For this study PCVs were read using a Hawkesley (Lancing, United Kingdom) heamatocrit reader at IHRDC after centrifugation of capillary blood in micro-capillary tubes. Previous studies in the area have described in details the methods employed (2, 3).

NOMENCLATURE

CI	Confidence Interval
CO	Clinical Officers
CSS	Clinical Surveillance System
DHS	Demographic and Health Survey
DSS	Demographic Surveillance System
EIR	Entomological Innoculation Rate
HBMF	Home Based Management of Fever
INDEPTH	International Network for Demographic Evaluation of Population and Their Health
IMCI	Integrated Management of Childhood Illness
IRB	Institutional Review Board
IRS	Indoor Residual Spraying
IHRDC	Ifakara Health Research and Development Centre
ITNs	Insecticide Treated Nets
IV	Intravenous
NCHS	National Centre for Health Statistics
PVC	Packed Cell Volume
RBM	Roll Back Malaria
SFDDH	Saint Francis Designated District Hospital
SP	Sulfadoxine /Pyrimethamine
STATA	Statistical Software for data Analysis
WHO	World Health Organization

CHAPTER ONE: GENERAL INTRODUCTION

1.0 Literature review

1.1 The burden of disease

Malaria is Africa's leading cause of under-five mortality (20%) and constitutes 10% of the continent's overall disease burden. It accounts for 40% of public health expenditure, 30-50% of inpatient admissions, and up to 50% of outpatient visits in areas with high malaria transmission (3). In endemic African countries, malaria accounts for 25–35% of all outpatient visits, 20–45% of hospital admissions and 15–35% of hospital deaths (4). Malaria is also a major cause of infant mortality and anemia in children. Among various malaria associated characteristics, anemia is an important presentation of malaria in high transmission intensities and particularly in children who have no access to potentially life-saving blood transfusions (5). It contributes synergistically with HIV/AIDS to morbidity and mortality of neonates and infants in areas where both infections are highly prevalent, such as in Africa south of the Sahara (6). Co infected pregnant women are at very high risk of anaemia and malarial infection of the placenta, which contributes to poor birth outcomes. For approximately 70 percent of the deaths before age five, the cause is a disease or a combination of diseases that would be preventable in a high-income country: malnutrition, acute respiratory infections, diarrhea, measles, and malaria. (7).

In order to attain the Millennium Development Goal (MDG) which calls for the reduction of child mortality by two thirds, between 1990 and 2015, there is need to scale up the existing interventions to reach children. However, 2004 UNICEF *Progress for Children* report (UNICEF, 2004a) reveals alarmingly slow progress in reducing child deaths despite the availability of proven, low-cost interventions. There is some evidence that prevention of malaria using

insecticide-treated nets and early treatment can reduce child mortality (5, 8, 9, 10, 11, 12), but this has been inhibited by multiple problems.

First, there is concern from previous epidemiological studies that bednet implementation in regions of high transmission intensity may aggravate the incidence of severe disease by delaying the acquisition of immunity and shifting it to an older age-group (13). Second, there are complexities associated with formulating case definition for clinical malaria especially among children because the early symptoms of malaria in infants are quite variable and hard to recognize. Due to lack of basic laboratory equipment in most health centers in Africa, diagnosis of disease is based on clinical criteria without parasitological confirmation. The accuracy of clinical diagnosis is also limited by the low specificity of symptoms and signs of malaria (14). This may lead to over-diagnosis or under-diagnosis of malaria, with the result that antimalarials are given to people who do not need them and not given to children who do.

In health care facilities without laboratory services, a detailed history and a thorough physical examination is essential in order to diagnose diseases other than malaria (15) and to differentiate between uncomplicated and severe disease.

On the other hand, health facilities cannot detect all malaria cases because many Africans, especially those living in the rural areas have limited access to medical care. This has led to development and evaluation of alternative methods that are community-conscious. In Eastern and Southern Africa UNICEF is supporting the Integrated Management of Childhood Illnesses (IMCI) at community level, which empowers families and communities to treat malaria at home. Parents and caregivers are empowered with knowledge on home management of malaria and other common childhood illnesses and are trained to recognize danger signs that require urgent referral

of very ill children to hospital. It is therefore of great need to identify and document the commonest and most important complications of *Plasmodium falciparum* infection in African children and the risk factors for death.

In Tanzania, malaria is a leading cause of morbidity and mortality in both outpatient attendances and inpatient admissions, accounting for 40% of overall outpatient attendances (16). This however may be subject to under-diagnosis of malaria in the community attributed to poor training and faulty case definition. As such, *P. falciparum* malaria continues to pose a high burden in both societal and economic terms in Tanzania despite the government's commitment to the control, prevention and treatment of malaria. This burden has serious implications on the economic growth of the country due to increased expenditure on causes that are preventable and that also affect the general national budget.

1.2 The parasite-Causes of malaria and mechanisms

Malaria is caused by a parasite. The parasite spends most of its life in the red blood cells of humans. Female mosquitoes transmit the parasites by first ingesting them when feeding on an infected person's blood and then injecting them when biting another person (17).

Four species of malaria parasites cause disease in humans: *Plasmodium vivax, P. malariae, P. falciparum* and *P. ovale*. *P. falciparum* is the most common and causes the most deaths. The onset of the disease is chills and, probably, a headache, nausea and vomiting. A fever develops and as it falls, a person is drenched in sweat. The symptoms can occur 10 to 16 days after infection and may appear in regular intervals of every two or three days. Depending on the

species of parasite, an infected person may feel well between bouts and recover, or may never feel fine and can die from the disease.

1.3 Epidemiology: Age

Malaria affects all age groups but children and pregnant women are most at risk. Most children experience their first malaria infections during the first year or two of life, when they have not yet acquired adequate clinical immunity - which makes these early years particularly dangerous. Ninety percent of all malaria deaths in Africa occur in young children (18). Older children develop their own immunity from repeated bites of the mosquito. Newborns have considerable resistance to infection with Plasmodium, which is normally attributed to the high foetal hemoglobin level and transplacental immunity. But still some cases of congenital malaria do occur.

1.4 Diagnosis and treatment of malaria

Malaria is an acute disease. Patients usually present with fever, chills and profuse sweating. The clinical features of malaria vary from mild to severe, according to the species of the parasite present, the patient's state of immunity, the intensity of the infection and the presence of accompanying conditions such as malnutrition, anemia and other diseases. Fever is the most common feature of malaria. It may persist for several days, accompanied by headache, aching joints and general discomfort. The classic presentation of malaria with high fever, chills, shivering and sweating however may not occur.

In P. falciparum infections headache, nausea and vomiting are usually more severe than in other malarial infections and there is a greater tendency towards the development of delirium,

hemolytic jaundice and anemia (15). The mortality is much greater than in other forms of malaria. Those who survive but who have continuing infection as a result of inadequate or no treatment may suffer several weeks or months of poor health. Anemia, weakness and febrile episodes are characteristic of these cases.

1.4.1 Manifestations and treatment strategies in children

In infants the early symptoms of malaria may be quite variable and hard to recognize. They may be limited to poor appetite, restlessness and loss of normal interest in the surroundings. Some patients, especially children, may present with a cough and/or diarrhea. (15)

Chemoprophylaxis protects against infection by preventing parasite proliferation within the human body. In infants, intermittent treatment (IPT) for malaria has been found to reduce clinical malaria and severe anemia. A study conducted in southern Tanzania demonstrated a 60% reduction in episodes of clinical malaria and anemia in infants given weekly chemoprophylaxis (19). A sustainable delivery of IPT in infants could be achieved through Expanded Program on Immunization (EPI). A randomized controlled study in Tanzania showed that a single dose of SP given to asymptomatic infants attending for routine vaccination at two, three, and nine months of age reduced episodes of clinical malaria by 59% and episodes of anemia by 50% during the first year of life (20). Similar findings were reported from a study conducted in northern Tanzania using amodiaquine (21). The WHO also recommends that IPT, be given to pregnant women in areas of stable malaria. (8)

1.5 Strategies to reduce malaria

There are treatments and tools that can help. Sleeping under insecticide treated nets and prompt access to effective treatment can reduce child mortality. Also, indoor residual spraying remains

highly effective for malaria vector control (22). Intermittent preventive treatment of malaria during pregnancy can significantly reduce the proportion of low birth weight infants and maternal deaths.

1.5.1 Prompt and effective treatment

Malaria must be recognized promptly in order to treat the patient in time and to prevent further spread of the infection. In April 2000 during the Abuja Summit, African heads of state resolved to have at least 60% of those suffering from malaria have prompt access to and be able to use correct, affordable and appropriate treatment within eight hours of the onset of symptoms (8). The WHO recommends, as one of the strategy for Integrated Management of Childhood Illness (IMCI), that all children under five with fever, to be presumptively treated with antimalarials (9). To achieve this, it necessitated the introduction of Home-based management of fever (HBMF) as a community level intervention particularly for the isolated areas. The analysis of 2003 HBMF data in Uganda revealed significant accomplishments in the management of childhood fever, with a substantial room for improvement. (10)

Treatment of malaria aims at:

- Eradication of parasites
- Dealing with different clinical manifestations of malaria
- Rendering the patient non-infective to mosquitoes

1.5.2 Insectcide treated mosquito nets (ITNs)

Insectcide-treated bed nets (ITNs) are amongst the most effective tools at the disposal for reducing malaria transmission and mortality.

Studies carried out in Kenya, Ghana, Gambia and Tanzania (5, 11, 23, 24) showed that malaria intervention using ITNs, could significantly reduce deaths from all causes, not just malaria, in young children in diverse areas of Sub-Saharan Africa where malaria is prevalent. A trial from a high transmission setting in western Kenya found that the protective efficacy of ITNs was highest in infants 1–11 months old compared with older children (25). The ITNs reduced the incidence of both clinical malaria and anemia by 60%, and the reduction was greatest in infants 1–3 months of age (26). Sleeping under ITNs was not only beneficial to the immediate users, but also for those living in the immediate vicinity of a netted village (27). The findings also confirmed the efficacy of insecticide-treated nets for improving child survival. However, the Roll Back Malaria (RBM) set target of 60% coverage of ITNs by 2005, was hard to attain (28).

In Tanzania for example, use of insecticide-treated mosquito nets is a primary health intervention to reduce malaria transmission in the country. However, only 47% of urban households and 14% of rural households reported owning at least one ITN according to the DHS results (16). There is hope of rapid increase in coverage following the implementation of the national voucher scheme that provides ITNs to pregnant women. In Kilombero district, coverage of mosquito nets is quite high due to a recently completed social marketing programme of ITNs and presence of an active private sector for mosquito nets (29).

1.5.3 Environmental vector control by insecticide spraying

Indoors residual spraying (IRS) remains the most widely used method of vector control and one of the most effective for obtaining a rapid large-scale impact at an affordable cost. Mortality and

morbidity can be checked through reduced transmission by controlling vectors. Most of the insecticides having residual effect are sprayed indoors. The mosquitoes after having bite on an infective person will rest in the house and will pick up sufficient insecticide particles sprayed on the walls and other indoor surfaces of the house, thus reducing its longevity such that it does not survive to become infective. Some African countries are using DDT for the control of epidemics, for example South Africa and Ethiopia although its use is now very much restricted (30). WHO recommends residual spraying as part of a coherent malaria control programme if it responds to epidemiological indications, can be correctly applied and if its results can be sustained (22).

In practice, the effectiveness of house spraying for malaria control depends on adherence to the specified criteria of the insecticide and application procedure, public acceptance of spraying, the availability of well maintained equipment, adequately trained spraying personnel, efficient supervision and strong financial support. The size of the area depends on local circumstances and is influenced by the distribution of malaria and malaria vectors; distance from important breeding sites, the flight range of the vectors and demographic features.

1.6 Malaria treatment policy

In the absence of effective vaccines, drugs are the best way to prevent disease and treat patients with malaria. However, the emergence and spread of drug-resistant malaria parasites, especially among *Plasmodium falciparum* calls for an urgent need for new drugs. More still is the need for effective case management because this species can become life threatening within just 48 hours.

In Tanzania, molecular studies that monitor malaria drug resistance showed that by the late 90's resistance of malaria parasites to chloroquine had grown to a magnitude of over 50% (31). In

order to curtail the morbidity and mortality associated with chloroquine failure, the ministry of health recommended Sulfadoxine pyrimethamine to replace chloroquine as the first line drug since the year 2002. Amodiaquine was identified as the second line or first line where SP was contraindicated and Quinine was reserved for severe malaria or when there was proven resistance to the other two drugs (15). The use of these policy guidelines was aimed at minimizing incorrect prescription of anti-malarial drugs and their indiscriminate use. This would in turn slow the emergence of resistant strains of Plasmodium falciparum. There was expected that adherence to the new guidelines would eventually lead to much reduced morbidity and mortality due to malaria at all levels of health care delivery including the community. Sulfadoxine- pyrimethamine was considered as a bridging strategy while preparing to adopt an appropriate combination therapy. As part of the roll out of artemisinin combination treatment, the national malaria control programmes of several countries, including Tanzania, have considered deploying rapid diagnostic tests in the formal healthcare system. In Tanzania, Artemisinin- based Combination Therapy (ACT) is expected to be implemented towards the end of the year, 2006.

1.7 Contribution of risk factors to malaria and malaria fatality

The commonest and most important complications of *Plasmodium falciparum* infection in African children are cerebral malaria, severe anemia, respiratory distress and hypoglycemia (32). These conditions are associated with most malaria-related fatalities and morbidity. Other complications of falciparum malaria are less common in children than in adults. A previous study on impact of malaria control concluded that malaria control reduces childhood anemia, and therefore may be a useful indicator of the burden and of the progress in malaria control (33). Of the more than 500,000 African children who develop cerebral malaria (a severe form of the

disease that affects the brain) each year, 10-20% die and approximately 7% are left with permanent neurological damage. Children with malaria normally develop fever, vomiting, headache and flu-like symptoms and if untreated, the disease may progress rapidly (often within 24 hours) to convulsions, coma, and death. Malaria is a major cause of anemia in many parts of the world, and chronic anemia may adversely affect a child's growth and intellectual development. Repeated episodes of malaria may lead to severe, life-threatening anemia. Blood transfusions may save lives in these circumstances, but also expose the child to the risk of HIV and other blood-borne infections (36).

Previous studies carried out in West Africa (37) as well as those in East Africa (2, 38), have shown a relationship between transmission and the clinical patterns of severe malaria. In these studies, it was shown that in high transmissions, severe malaria affects mainly younger children and severe anemia represents the most frequent condition. Although malaria plays a key etiologic role in anemia in endemic countries, it is clear that poor nutritional status, micronutrient deficiencies, intestinal helminthes, HIV infection, and hemoglobinopathies make important additional contributions (39). In addition, repeated malaria infections make young children more susceptible to other common childhood illnesses, such as diarrhea and respiratory infections, and thus contribute indirectly to mortality (40).

In Tanzania, the community prevalence of anemia (PCV < 33%) in children less than five years old is 87% and the annual incidence of severe anemia (PCV < 25%) is 0.6 episodes per infant (41). Intestinal parasites and hemoglobinopathies are unlikely to be causes of anemia of public health relevance in children less than five years old in this setting (33, 42). In the proposed study area, an assessment of chemoprophylaxis in infants in mid 1990s showed that over 60% of

anemia could be due to malaria (20). A malaria morbidity study during implementation of ITNs programme in the same area, Kilombero district, indicated that use of ITNs resulted into a significant reduction of both malaria parasitemia and anemia between 1997 and 1999 (43). It has also been shown that recurrent infections with *Plasmodium falciparum* may result in severe anemia especially in young children in tropical Africa with frequent infections that are inadequately treated (41). However, children sleeping under mosquito nets, especially insecticide treated nets (ITNs), have a reduced risk of anemia, which indicates that malaria may be important in causing anemia (43).

The study seeks to explore the risk factors for malaria deaths with particular focus on its association with anemia and determine malarial presentations among hospitalized children in a pediatric ward. This is of paramount importance in guiding treatment and determining effective strategies of improvement of malaria control and treatment, and development of sustainable measures for the prevention of anemia.

1.8 Aims and Objectives

1.8.1 Outcome measures

The outcome measure in this study is deaths associated with malaria

1.8.2 General objective

To assess risk factors for malaria deaths in children less than 5 years of age

1.8.3 Specific objectives

1. To determine anemia prevalence among the malaria admission cases and other manifestations of malaria
2. To measure associations between malaria deaths and anemia, demographic and nutritional variables of the child
3. To determine patterns and changes over time in years of proportions of malaria admissions and case fatality over time.

CHAPTER TWO: MATERIALS AND METHODS

2.1 Study area

The study area, Kilombero district has intense all-year malaria transmission with an estimated entomological inoculation rate (EIR) of more than 300 infectious bites per person per year (3), which represents an endemic malaria situation. The pediatric ward at SFDDH comprises 70 beds out of the hospital's 375 beds. The hospital functions as a first care for the surrounding community and as a referral for the rest of the Kilombero district and at some extent to the neighboring district of Ulanga. At the time of the surveillance sulfadoxine/ pyrimethamine (SP) was the first line treatment, and quinine was the 2nd line treatment reserved for severe malaria cases or when there was proven resistance to SP and amodiaquine.

2.2 Sample size

The study population involved all under five children admitted at the pediatric ward of SFDDH between 2002 and 2005. There has been a clinical surveillance in place since mid 1990s but this study was restricted to the data collected between 2002 and 2005 which was most current and complete. Children older than five years were excluded from this study.

2.3 Design

The study is hospital-based, involving analysis of secondary data collected routinely from a clinical surveillance maintained by Ifakara Health Research and Development Centre (IHRDC) at a pediatric ward of the Kilombero district hospital (SFDDH).

2.4 Measurements

Hospitalization depended on severity of the disease, classified as child with convulsions, excessive vomiting, child unable to suck or feed, dehydration, level of consciousness or drowsy. At admission, children were diagnosed as malaria cases if laboratory tests indicated presence of blood slide positive for asexual *Plasmodium falciparum* parasites. Severe malaria definition, and other signs/ symptoms are recorded elsewhere (2)

The data included PCV readings taken for all the children, and this study used this as a proxy to measure anemia. Anemia was defined as a PCV<25%. This is locally defined, and the reason for this cuff-off for anemia is because it is known to be associated with increased mortality in the region (5). Other studies carried out in the area have used the same cut-offs (19, 20). The current study differs with the previous in that it covers a different time period and uses different analytical method. The previous study also took place during the time when chloroquine was the first line drug for malaria, while during the present study, SP was the first line drug.

Malnutrition was defined as weight-for age (WAZ) score<-2 based on US National Center for Health Statistics (44) reference data and as previously used by Tanzania Demograpic and Health Survey (2004). One limitation with this measure however is that underweight is used as a composite indicator to reflect both acute and and chronic under nutrition and therefore may not correctly distinguish them. This differs with WHO criteria for severe malnutrition which is defined a score of less than 60% WA as very low weight. Weight-for-age was chosen because it is the most widely used indicator of child nutritional status in developing countries.

2.5 Data processing and analysis

The data used in this study is part of an ongoing clinical surveillance done by IHRDC. It was obtained using standardized forms that were completed by clinicians who attended the child at the hospital (Appendix 1). Part of the information that was collected and which was of particular importance to this study included age, sex, weight, height, symptoms, diagnosis, treatment given, laboratory measured PCV and malaria parasitemia. Data was double entered and checked in FoxPro 2.6 (Microsoft Corporation). Data cleaning was done by running frequecies and perfoming logical and range checks. For analysis, data was transferred to a statistical package, STATA version 8.0 (Stata Corp, TX, USA) using statransfer software. Microsoft Office Excel 2003 was used for graphics.

Both descriptive and analytical statistics were done. Proportions were compared by chi-square tests, and test for independence by Kendall's tau non-parametric test. Multivariate analysis was performed using a logistic regression model adjusting for possible confounding variables identified in the univariate analysis. The outcome variable was dichotomized as **1** and **0** for children under five years who died of malaria related illness and those who had malaria and survived respectively. A similar dummy variable was constructed for children under five years who died of malaria related illness versas under five children who died of other causes (infective or non-infective). Confidence intervals for the adjusted and unadjusted odds ratio were interpreted as no evidence of effect of the factor under consideration if they included 1. Otherwise, there was an effect of the particular factor.

2.6 Ethical consideration

During the surveillance, specially trained clinical officers (COs) from the hospital sought and obtained verbal informed consent to complete standardized forms on all children on admission (32). The study protocol was reviewed and approved by IHRDC Institutional Review Board (IRB), and by the Ethics committee of the University of Witwatersrand in Johannessburg, South Africa (ethics clearance certificate: Appendix 2). A written permission to analyze the data was obtained from IHRDC, who are the owners of the data (Appendix 3).

Copies of the final report will be made available to the hospital (SFDDH) and IHRDC.

CHAPTER THREE: RESULTS

This chapter presents results from analysis of a dataset for children under five years of age admitted at a rural district hospital in Tanzania, Saint Francis Designated District Hospital (SFDDH) for four years (2002-2005). The chapter starts with a brief description of the study sample followed by examination of the prevalence rates of some clinical symptoms and signs, and their association with malaria mortality. Changes and patterns of admission and case fatality rates over the years between 2002 and 2005 are also included.

3.1 Admissions

A total of 10, 392 children under the age of five years admitted in the pediatric ward at St Francis Designated District hospital between January 2002 and December 2005 were included in the study. Table 1 shows the percentage distribution of pediatric admissions according to selected baseline characteristics.

Table 1: Baseline characteristics of pediatric admissions at SFDDH

Characteristics	Number#	(%)
Sex		
Male	5,785	(55.6)
Female	4,607	(44.3)
Age		
Median=17.5 months [Inter Quartile range; 9.3; 30.9]		
Age$^{\tau}$ categorized		
< 1 year	3,668	(35.3)
1 years	2,928	(28.2)
2 years	1,871	(18.0)
3 years	1,166	(11.2)
4 years	753	(7.3)
Nutritional status		
Median=-1.49 SD [Inter Quartile range; -4.67; 2.17]		
Normal (WAZ score >-2 SD)	4,629	(53.5)
Undernourished (WAZ score between -2 SD & -3 SD)	577	(6.7)
Severely undernourished (WAZ score<-3 SD)	3436	(39.8)
Anemia		
Not severe anemia (PCV ≥25%)	8,009	(79.4)
Severe anemia (PCV<25%)	2,083	(20.6)

$^{\tau}$ Age refers to completed number of years
Number do not add up due to missing values

Table 1 shows that there were more admission cases among children less than one year old (35.3%) and the numbers decreased significantly with age (χ^2 =475.6, p=0.000).

Admissions of the children under five years of age were highest in year 2003 (37.7%, 3922)[‡] followed by 2005 (25.1%, 2607), 2002 (22.4%, 2323), and 2004 (14.8%, 1540)[*] respectively. Three thousand, four hundred and eighty nine (75.7%) of female child admissions were diagnosed with malaria, and differed significantly with male child malaria admissions, 4,242 (73.3%) (χ^2=7.78, p=0.005. Both undernourished and severely undernourished accounted for 46.3% (4,013) of the children, and the median WAZ score was -1.49 SD [Inter Quartile range; -4.67; 2.17]. In total, seven thousand, seven hundred and forty (75.5 %) of the patients were diagnosed with malaria with or without other diagnosis, and the leading associated diagnoses were anemia (2,229, 21.7 %), pneumonia (2,154, 21.0 %) and the rest had other various diseases[⇒].This was an indication that malaria was the principal diagnosis in most cases, though this may be overestimated since 98.8% of the children had multiple diagnoses. There were a total of 14,978 diagnoses out of the 10,254 valid pediatric admission cases, and 138 cases had missing values.

3.2 Symptoms/ Signs and treatment

The prevalence of symptoms/ clinical signs (1st diagnosis) among the malaria admission as compared to infective and non-infective admissions is shown in Table 2.

[‡] A demographic surveillance system in the same district recorded higher under five children mortality in 2003 as well.

[*] 2004 should be interpreted with caution because records were not completed for all cases

[⇒] Most (98.8%) of the children had more than one diagnosis; therefore the proportions do not add up to 100 per cent.

Table 2: Prevalence of 1st symptoms/clinical signs for children admitted to hospital (SFDDH)

Symptoms/Signs	Proportion in malaria associated cases; n (%)* (n=6276)	Proportion in other infections; n (%)* (n=782)	Proportion in other diagnoses; n (%)* (n=3194)	P- value
Fever	6013 (95.8)	543 (69.4)	2658 (83.2)	<0.001
Cough	1975 (31.5)	209 (26.7)	1799 (56.3)	<0.001
Fitted	1131 (18.0)	12 (1.5)	352 (11.0)	<0.001
Diarrhea	1102 (17.6)	647 (83.1)	353 (11.1)	<0.001
Vomiting	2646 (42.2)	559 (71.5)	837 (26.2)	<0.001
Pneumonia	595 (9.5)	32 (4.1)	1526 (47.8)	<0.001
Splenomegaly	886 (14.1)	49 (6.3)	479 (15.0)	<0.001
Sucking				
More than usual	268 (4.3)	35 (4.5)	94 (2.9)	<0.001
Less than usual	3761 (60.0)	506 (64.7)	1907 (59.7)	
Packed Cell Volume (PCV)				
Anemia	1153 (18.9)	55 (7.3)	856 (27.5)	<0.001
Nutrition status:				
Undernourished	336 (6.4)	50 (7.7)	179 (6.8)	<0.001
Severely undernourished	1775 (33.9)	438 (67.2)	1182 (44.8)	

* Denominators are variable due to missing values

As shown in Table 2, symptoms and signs were significantly associated with the type of diagnosis among the under five children admitted at the pediatric ward. There was a significant higher prevalence of fever with or without other symptoms/ signs among malaria related admissions, 6,013 (95.8%) as compared to patients with other infections 543 (69.4%) and other non-infectious admissions 2,658 (83.2%). The prevalence of anemia (PCV<25%) was significantly higher for the malaria related admissions; 1,153 (18.9%) as compared to patients who were admitted with other infections; 55 (7.3 %). The results also showed that history of vomiting was higher among the malaria related patients; 2,646 (42.2%) than patients with other diseases but lower than those with other forms of infection, 559 (32.8 %). The proportion of fitting was higher among malaria related patients; 1,331 (18.0%) than patients with other infections; 12 (1.5%). However, there were more patients from other infections who reported a history of diarrhea, 647 (83.1%) than the malaria related patients; 1,102 (17.6%). More patients were severely undernourished among the patients with other infections; 438 (67.2%), as compared to the malaria related patients; 1,775 (33.9%). Of the malaria cases, 1,986 (25.7%) children were also diagnosed with anemia and 979 (12.7%) with pneumonia. Most of the children diagnosed with malaria were treated with quinine with or without a combination of other drugs, 7,260 (93.9 %). Only 331 (4.3%) of these were treated with SP, which was the first line treatment for malaria in the country at the time of the study. Very few (0.3%, 23) were treated using amodiaquine which is identified as a second line drug. Two hundred and one (2.8 %) of malaria cases received a combination of quinine and SP.

Two thousand one hundred and seventy four (34.9%) of all malaria related admissions had been seen at other health facilities before being admitted at SFDDH. This compares to 351 (45.1%) of other infections and 1,328 (41.8) of patients with non-infectious diseases. Being seen at other

health facility before admission at SFDDH was significantly associated with cause of admission (χ^2=61.2; p<0.001). Those who had visited another health unit had higher chances for disease severity thus necessitating admission. This was explained by high prevalence of fever (94.1%, 3581), anemia (27.4%, 749), spenomegaly (14.7%, 416), fits (20.5%, 580) and vomiting (44.8%, 1266) for the malaria related cases that had been seen at other health facilities. Lack of prompt access to health care services and referral to hospital may be reflected by the long duration a patient would stay with symptoms and thus the high prevalence. For instance, malaria related admissions, who had been seen at other health units, had higher mean number of days with fever (5.3 days) than those who had not been seen at other health units (mean days with fever =2.8 days). Patients were not asked for previous treatment history either by self or from the health facilities visited before coming to SFDDH and no reason was given for attending the clinic. We assume that having been seen at other health facility did not necessarily mean they were referred but an indication of service sought elsewhere since this was not confirmed. It is also not clear whether treatment was given where care was sought first; no information was provided.

By use of IMCI guidelines which is a simplified system of diagnosis and treatment, we did analysis for the sensitivities and specificities of the 'general danger signs' and risk factors. Compared with the physicians' diagnosis, the sensitivities and specificities of the IMCI guidelines were 60% and 97% for the detection of any malaria; 78% and 8% for the infective illnesses. The specificities for the danger signs in detecting most of the illnesses were low (Table 3)

Table 3: Sensitivities and Specificities of the of diagnosed cases for Malaria, infectious, non-infectious, diarrhea, Anemia, pneumonia and malnutrition

Symptoms/Signs	Sensitivity %(n/N)	Specificity %(n/N)
Malaria	59.9	97.1
Other infectious	78.1	7.5
Non-infectious	1.7	98.7
Diarrhea	72.4	16.0
Anemia	86.2	26.7
Pneumonia	66.3	12.5
Malnutrition	89.6	6.3

3.3 Childhood mortality

The under-five mortality rate is a well-accepted indicator of a country's overall health status. From 2002 to 2005, a total of 634 under 5 pediatric deaths occurred in the hospital, 328 (51.7%) of which were attributed to malaria.[♣] The analysis excludes children whose outcomes were missing (112 cases). Table 4 presents a 4-year survey of malaria admissions and deaths at SFDDH, Tanzania.

[♣] However, this might be an over estimation because 98.8% of the cases had multiple diagnosis and death certificates were not available to confirm the specific causes of death.

Table 4: All cause and malaria specific mortality of the under five children admitted at SFDDH, Tanzania, 2002 to 2005

Factors	Total admissions	Total Deaths	No of malaria admissions	No of deaths from malaria	All cause MR (p-value)	Case Fatality Rate (p-value)
Age						
< 1 year	3646 (35.5)	316 (49.8)	1841 (29.4)	153 (46.7)	8.7 %	8.3%
1-4 years	6634 (64.5)	318 (50.2)	4432 (70.6)	175(53.3)	4.8 %	3.9%
					(p<0.001)	(p<0.001)
Sex						
Male	5727 (55.7)	346 (54.6)	3453 (55.0)	177 (54.0)	6.0%	5.1%
Female	4553 (44.3)	288 (45.4)	2823 (45.0)	151 (46.0)	6.3%	5.3%
					(p=0.532)	(p=0.565)
All	10280 (100)[a]	634 (100)	6276 (100)	328 (100)		

a- 112 cases had missing outcome values hence not included in the analysis. Gender distribution in this group was the same as the working group but distribution was different across age groups. In this case we used a non-parametric test (Kendall's tau rank orders test).

Table 4 indicates that all cause mortality and malaria case fatality among admitted children are significantly associated with age but not with sex of the child. The proportion of all cause mortality was almost twice as much for the children less than 1year of age compared to children between one and four years admitted at the hospital (p<0.001). Similarly malaria fatality rate for children under one was almost twice that of children between one and four years (p<0.001). However, there was no significant difference between all cause mortality between male and female children; (p=0.532), nor in malaria case fatality rate (p=0.565).

More than half of all deaths for the period between 2002 and 2005 occurred to children who were diagnosed with malaria (328/634, 51.7 %). This is an indication that malaria is a major cause of mortality among the under_5 children in the hospital's pediatric ward.

3.4 Risk factors for malaria deaths

Table 5 presents unadjusted and adjusted odds ratios with 95% confidence interval (CI) obtained from univariate and multivariate logistic regression models for the analysis of risk factors for malaria deaths. The comparison here involves malaria related deaths against those who survived and had been diagnosed with malaria.

At 5% level of significance, the results of the univariate logistic model showed that age of the child was a risk factor for malaria related death. Children under one year of age were twice at risk of dying of malaria than children aged between 1 and 4 years old (OR=0.50, 95% CI: 0.40, 0.63). Sex of the child, history of fever, coughing and vomiting were not statistically significant and therefore no evidence that they were risk factors for malaria mortality. The explanatory variables whose unadjusted odds ratios were significant were included in the multivariate model.

Table 5: Adjusted and unadjusted Odds Ratios with 95% confidence intervals of the risks for malaria deaths as compared to those who survived from malaria disease

Variable	Univariate (unadjusted)		Multivariate (adjusted)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex				
Male	1			
Female	1.04 (0.83 – 1.30)	0.720	-	-
Age group				
< 1 year	1			
1 – 4 years	0.50 (0.40 – 0.63)	<0.001	0.73 (0.41- 1.31)	0.293
Fever				
No	1			
Yes	0.68 (0.43 – 1.08)	0.102	-	-
Vomiting				
No	1			
Yes	1.04 (0.83-1.30)	0.731	-	-
Coughing				
No	1			
Yes	1.24 (0.99- 1.56)	0.065	-	-
Diarrhea				
No	1			
Yes	1.95 (1.53- 2.50)	<0.001	1.75 (1.27-2.37)	0.001
Seen elsewhere				
No	1		1	
Yes	2.20 (1.76 – 2.75)	<0.001	1.78 (1.37 – 2.30)	<0.001
Fitted				
No	1			
Yes	2.33 (1.84 – 2.97)	<0.001	2.95 (2.18 – 3.99)	<0.001
Sucking				
Normal	1		1	
More than usual	0.93 (0.46- 1.88)	<0.001	1.48 (0.71- 3.08)	0.290
Less than usual	1.71 (1.32- 2.21)	<0.001	1.58 (1.18- 2.12)	0.002
Packed Cell Volume (PCV)*				
None	1			
Anemia	1.56 (1.22 – 1.99)[6]	<0.001	1.56 (1.17 – 2.09)	0.002
WAZ score				
Normal	1			
Undernourished	2.65 (1.71- 4.12)[ù]	<0.001	2.37 (1.48 – 3.77)	<0.001
Severely undernourished	2.52 (1.93 – 3.29)[ù]	<0.001	2.47 (1.84 – 3.32)	<0.001

*Cut off points for anemia: PCV ≥25 = no severe anemia; PCV<24 = anemia

[6] was statistically significant only for age 1-4 years; OR=2.34 (1.71- 3.19)

[ù] was statistically significant only for age 1-4 years; undernourished :OR=2.66 (1.71-4.13), Severely malnourished: OR=1.98 (1.11-3.52)

The multivariate analysis results showed that anemia (defined by PCV<25%), child had fitted, had been seen in another health unit, sucking less than usual, diarrhea and malnutrition (defined by weight-for age z scores) were independent risk factors for malaria deaths. The model was highly significant (χ^2=143.64, p<0.001). In particular, the children who were diagnosed to be anemic were 1.4 times more likely to die than those who didn't have anemia (adjusted OR=1.39, 95% CI: 1.04, 1.86) after adjusting for age, diarrhea, fitting, seen elsewhere, sucking and nutrition status of the child. However, on stratifying by age in the univariate and multivariate analysis, only the children aged between one and four years were statistically associated with malaria mortality (unadjusted OR=2.34, 95% CI: 1.71, 3.19 and adjusted OR=2.12, 95% CI: 1.46,3.09). Other factors that predicted mortality of both infants and other children were fitting, seen elsewhere, diarrhea and sucking less than usual. Children who had fitted were 2.9 times more likely to die than those who hadn't (adjusted OR=2.95 95%CI: 2.18, 3.99). The results also showed that those who had been seen at other health units were 1.8 times more likely to die of malaria related illness than those who hadn't (adjusted OR=1.78, CI: 1.37, 2.30). Those who had diarrhea were 1.7 times more likely to die of malaria than those who didn't have diarrhea (adjusted OR=1.73 95% CI: 1.27, 2.37). Children who were less than one year old and sucked less than usual, were 1.6 times at higher risk of dying of malaria than those who sucked normally (adjusted OR=1.58 95% CI: 1.18, 2.12). Malnutrition predicted malaria mortality of the children aged 1-4 years only. Admitted children who were also malnourished and aged between one and four years old, were over two times more likely to die than normal children (adjusted OR=2.37 95% CI: 1.48, 3.77 for undernourished; OR=2.47 95% CI: 1.84, 3.32 for the severely undernourished). Univariate and multivariate analysis was done, stratifying by age and the results showed that nutrition status never predicted malaria mortality for children less than one year old. The effect of anemia on malaria mortality for the under nourished was not the same as

for the severely undernourished (χ^2=38.5, p<0.001). Significant associations for anemia and nutritional status were found for the children aged between one and four years only. Anemia predicted mortality of the undernourished children but did not predict death of the severely undernourished children. The analysis did not attempt to establish causality.

Table 6 presents unadjusted and adjusted odds ratios with 95% confidence interval (CI) obtained from univariate logistic regression models for the analysis of risk factors and WHO IMCI 'general danger signs' for 0-2 moths for malaria deaths compared to those who died from infective and non-infective diseases.

At 5% level of significance, the results of the univariate logistic model showed that 0-2 months old infants who died of malaria were 3.9 times more likely to have convulsed for the last hour as compared to the children who died from other infectious illnesses (95% CI: 1.97, 7.71). Sucking less than usual was not statistically significant and therefore no evidence that this was important risk factors of malaria mortality relative to the other infections' deaths, but generally, sucking les than usual contributes to 1.3 times the risk of dying of malaria related illness. Vomiting everything is protective and a child is 35% less likely to die of malaria related illness than other infections' deaths. Infants (0-2months) who do not convulse are 0.14 times more likely to survive from malaria related cause than other infections. However, the infants who had convulsed and died of malaria related illnesses were more than three fold times likely to die than the malaria related patients who did not convulse. Convulsion therefore is a risk factor to malaria mortality in infants 0-2 months old.

Table 6: Adjusted and unadjusted Odds Ratios with 95% confidence intervals of the risks of IMCI 'danger signs' for malaria deaths as compared to deaths from infective and non-infective illnesses for 0-2 months old infants

Variable	Infective diseases (unadjusted)		Non-infective diseases (adjusted)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Vomiting				
No	1			
Yes	0.35(0.19-0.64)	0.001	0.27 (0.03- 2.26)	0.227
Convulsion				
No	0.14 (0.17- 1.11)	0.063	0.50 (0.58- 4.36)	0.534
Yes	1			
Sucking				
Normal	1			
More than usual	0.15 (0.02- 1.36)	0.091	2.84 (0.28 – 29.2)	0.380
Less than usual	1.27 (0.67- 2.42)	0.464	0.06 (0.01- 0.56)	0.013
Malaria related deaths as compared to those who had malaria and survived by IMCI 'danger signs'				
Vomiting			**	
No	1			
Yes	0.87(0.62-1.21)	0.402		
Convulsion				
No	1			
Yes	4.0 (1.97- 7.71)	<0.001		
Sucking				
Normal	1			
More than usual	2.40 (0.81- 7.11)	0.114		
Less than usual	1.26 (0.88- 1.81)	0.202		

**There were no observed statistical differences between other infectious deaths and non-infectious deaths.

Vomiting was protective for children 0-2 months with malaria related diseases as compared to infectious illness (35% less likely to die), while sucking less than usual was a risk factor for the same group but not statistically significant (table 6). Children aged 0-2 months who sucked less than usual were 1.26 times more likely to die of malaria related illness than infectious illness.

Convulsion can increase by four times the chance of dying for children 0-2 months with malaria related illness (OR=4.0, CI=1.97-7.71)

The multivariate analysis results showed that anemia, fits, history of fever, and vomiting were independent risk factors for malaria related deaths than the other cause mortality. The model was highly significant (χ^2=51.45, p<0.001). The effect of anemia in the univariate analysis was stratified by age and the results showed that anemia was associated with childhood mortality for the children aged between one and four years only (unadjusted OR=3.03, 95% CI: 1.80, 5.09), and were significantly associated with the risk of dying with malaria than those who died of other causes (adjusted OR=1.80, 95% CI: 1.13, 2.85). Children who died of malaria were 3.8 times more likely to have fitted than those who died from other causes (adjusted OR=2.61 95%CI: 1.57, 4.33). The results also showed that those who died of malaria related illness were 2.4 times more likely to have had a history of fever than those who died of other causes (adjusted OR=2.38, 95% CI: 1.28, 4.45). Those who died of malaria related illnesses were 1.6 times more likely to have had a history of vomiting than those who died of other (adjusted OR=1.58 95% CI: 1.07, 2.33). Causality was also not accessed.

Among the children who survived, the prevalence of fits, fever, anemia and vomiting were associated significantly with malaria morbidity (OR=2.35 95% CI; 1.84, 2.99, OR=9.42 95% CI; 7.87, 11.28, OR=1.60 95% CI; 1.35, 1.89, OR=1.84 95% CI; 1.60, 2.11, respectively). Those who had a history of coughing, history of diarrhea, and malnutrition, and survived, were less likely to be associated with malaria related illness but significantly associated with other illnesses (OR=0.34 95% CI; 0.30, 0.39, OR=0.68 95% CI; 0.55- 0.80, OR=0.72 95% CI; 0.57-0.92, respectively). Older children (1-4 years old) were 1.8 times more likely to survive from malaria than other illnesses (OR=1.79 95% CI; 1.58- 2.04).

Table 7: Adjusted Odds Ratios with 95% confidence intervals of the risks for malaria deaths as compared to those who survived from malaria related illness and deaths from other causes stratified by age of the child (infants and other children)

Factors	malaria related illness		other illnesses related deaths	
	< 1 years	1-4 years	< 1 year	1-4 years
Fitted				
No	1	1	1	1
Yes	2.87 (1.67-4.94)	3.29 (2.24-4.83)	1.23 (0.58-2.59)	5.98 (2.57-13.91)
Fever				
No	1	1	1	1
Yes	1.06(0.47-2.38)	0.31 (0.15-0.63)	1.74 (0.63-4.81)	2.16 (0.90-5.23)
Sex				
Male	1	1	1	1
Female	0.91(0.62-1.33)	1.07 (0.75-1.54)	0.94 (0.56-1.60)	0.94 (0.51-1.72)
Seen				
No	1	1	1	1
Yes	1.77 (1.20-2.60)	1.69 (1.18-2.42)	0.80 (0.46-1.38)	1.17 (0.63-2.18)
Packed Cell Volume (PCV)				
None	1	1	1	1
Anemia	0.78 (0.47-1.29)	2.12 (1.46-3.09)	1.22 (0.61-2.45)	1.92 (0.92-3.99)
Vomiting				
No	1	1	1	1
Yes	0.57 (0.37-0.87)	1.21 (1.45-3.09)	1.08 (0.59-1.99)	3.16 (1.58-6.34)
Cough				
No	1	1	1	1
Yes	1.52(1.03-2.22)	0.94 (0.62-1.42)	0.83 (0.48-1.42)	0.48 (0.25-0.92)
Diarrhea				
No				
Yes	1.86 (1.20-2.89)	1.79 (1.06-3.01)	1.26 (0.67-2.37)	0.31 (0.14-0.66)
Sucking				
Normal	1	1	1	1
More than usual	2.66 (0.85-8.27)	1.13 (0.42-3.05)	1.18 (0.19-7.28)	0.54 (0.10-2.77)
Less than usual	1.56 (1.02-2.41)	1.98 (1.25-3.24)	0.62 (0.33-1.18)	0.79 (0.37-1.66)
WAZ score				
Normal		1		1
Undernourished		2.26 (1.40-3.65)		2.08 (0.86-5.0)
Severely undernourished		1.83 (0.98-3.67)		0.96 (0.38-2.43)

3.5 Changes and patterns

This section summarizes causes for pediatric admissions and deaths at Saint Francis Designated Hospital pediatric ward between 2002 to 2005.The data presented here are based on numbers of diagnosis events, not numbers of unique individuals hospitalised. As shown in figure 1, the proportion of pediatric admissions from all causes remained relatively constant across the years, with malaria standing out as a single leading cause for admission. The proportion malaria related admissions rate depicted no specific pattern but remained relatively above 50% across the years (56.9% in 2002, 61.4% in 2003, 59.7% in 2004 and 62.6% in 2005). It is however, important to note that some malaria cases had more than one diagnoses, and data did not include a primary diagnosis. It is therefore a limitation of the study since multiple diagnoses could have overestimated malaria specific causes

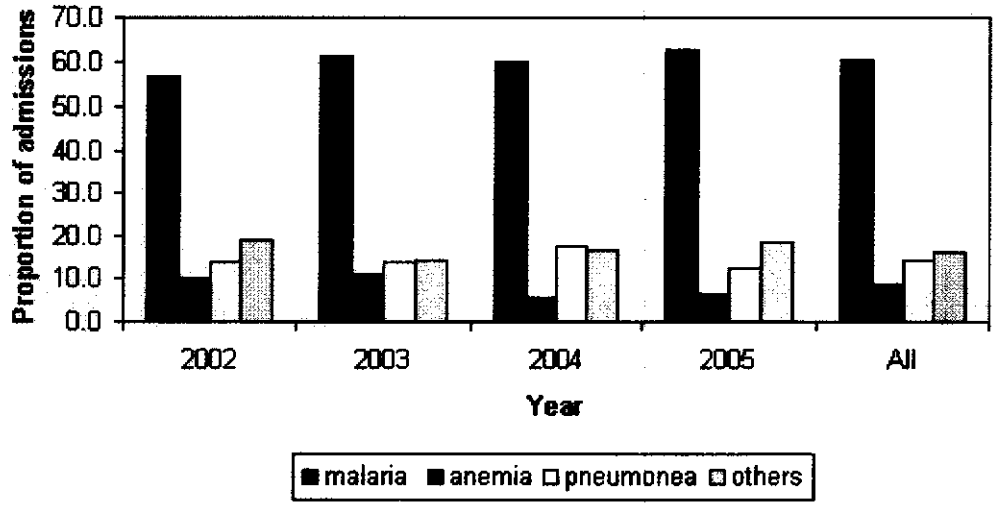

Figure 1: Proportion of pediatric admissions calculated as a fraction of the total diagnoses, by causes across the years[§]

[§] Because of multiple response of diagnoses the total of the percents exceed 100%. The diagnoses are not mutually exclusive

Malaria admissions seemed to rise upwards from 2002 towards 2003. This is confirmed by results from a demographic surveillance system in the same district that recorded high under five mortality in 2003. Pediatric admissions were highest in the first quarter, declined in the second and started rising again before dropping towards 2004 (figure 2). There was a problem of shortage of medical personnel to collect the information in 2004, thus data for this year may not be reliable. Admissions in 2005 depicted a rising trend which started dropping towards the fourth quarter.

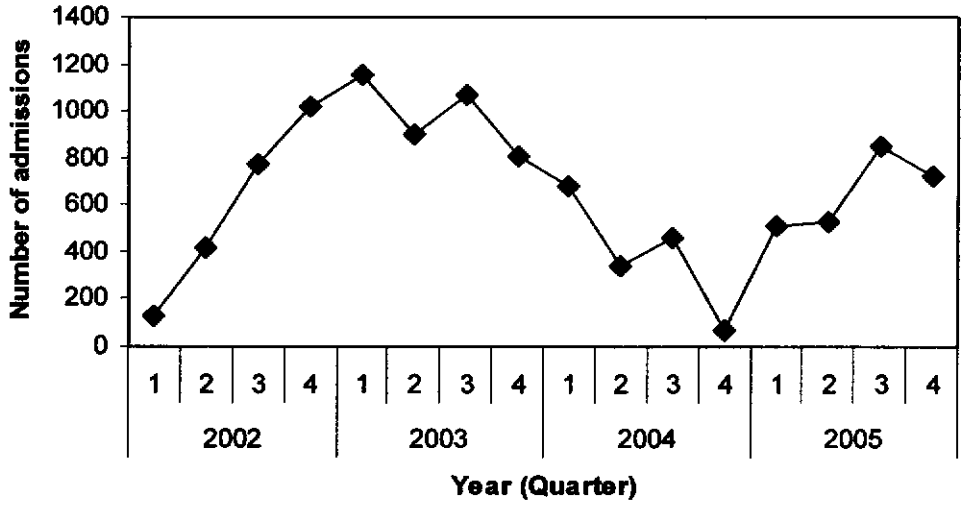

Figure 2: Malaria admissions by year and by quarters

Malaria contributes greatly to the total pediatric deaths (51.7% of all deaths between 2002 and 2005). The proportion malaria associated mortality rate increased with years as shown in figure 3; 23.4% in 2002, 27.3% in 2003, 33.3% in 2004 and 45.6% in 2005.

Other causes of death included anemia with a mean mortality rate of 11.5%, pneumonia (mean mortality rate of 23.9%), and other causes (mean mortality rate of 31.6%), per year.

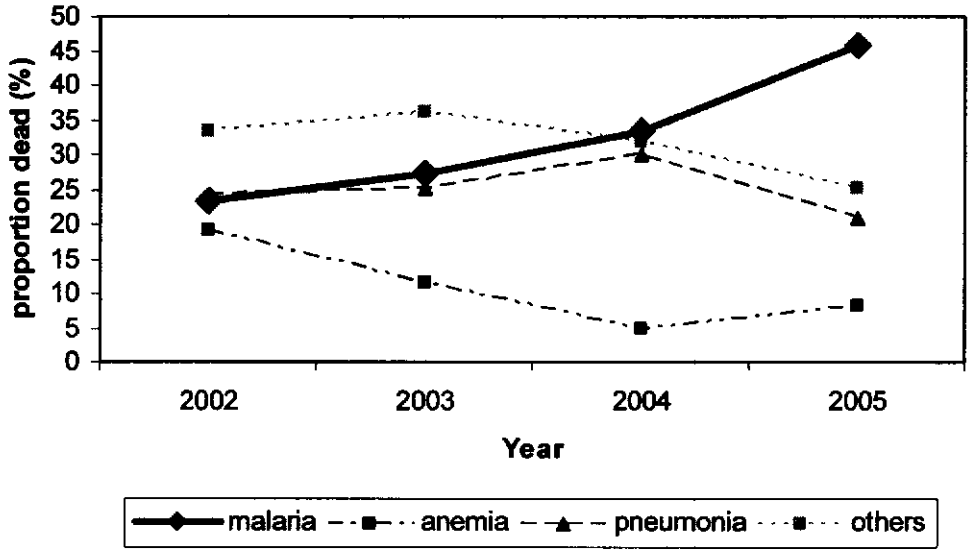

Figure 3: Cause specific mortality rates**

The results from the study showed a decline in malaria associated case fatality rate between 2002 and 2004, with an increase in malaria associated case fatality rate for year 2005. The proportion of malaria deaths increased (fig-3) but case fatality rate decreased (fig-4) between 2002 and 2004 because, though the deaths increased over the period, the malaria admissions remained constant.

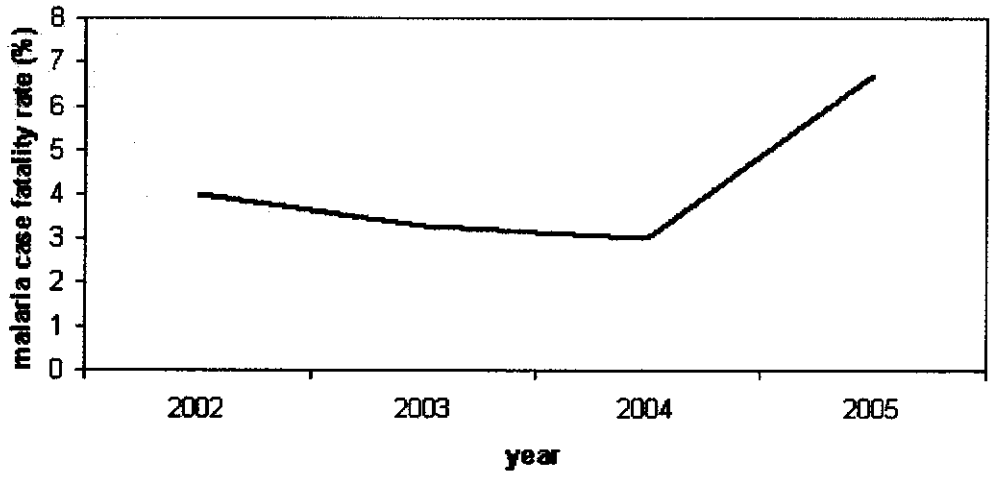

Figure 4: Malaria associated case fatality rates

** The diagnoses are not mutually exclusive but each disease might have been mentioned in combination with another, hence the graphs are not compared in this case.

3.6 Results summary

The study has shown clearly that malaria is an important contributor of pediatric admission in SFDDH. Most of the patients who present to the hospital had several symptoms, with fever as the most important diagnostic symptom of malaria together with other symptoms. A substantial number of cases presented with fits, suggesting that some children were admitted with severe/ complicated malaria, an increased risk for death. Anemia prevalence was quite high among malaria admissions and may have been an important contributor towards malaria mortality as seen in the more than double fold increased risk among the older children. Quinine was the single most used drug to treat malaria cases in this hospital. Gender, history of vomiting, and history of coughing were not risk factors for malaria mortality, but anemia, fits, diarrhea, sucking less than usual, malnutrition, and whether the child was seen at another health unit contributed independently to malaria deaths. Fever, vomiting, fitting and severe anemia were important risk factors for malaria deaths than deaths from other causes. However, anemia varied significantly with age, children 1 to 4 years olds being more anemic. Anemia was associated with malaria mortality of the undernourished children. Despite the limitation of incomplete data for 2004, there was an evidence of increasing pattern of malaria mortality over the years, though the proportion of malaria admissions remained relatively constant above 50% across the years. It is not quite clear why mortality rate among the admitted children increased in 2005 even after many interventions had taken place in the area, or may be due to overestimation of malaria specific causes on admission. However, it should be remembered that the data used in this study is hospital-based.

CHAPTER FOUR: DISCUSSION

The success of malaria control programmes relies heavily on the understanding of the risk factors for malaria deaths. Using the clinical surveillance data collected in a pediatric ward in a rural district hospital between 2002 and 2005, the study explored the different manifestations of malaria among the admitted children and assessed risk factors for malaria deaths in children under 5 years of age.

This chapter therefore, discusses in the light of other studies, the important contributors of malaria mortality among pediatric children under 5 years of age, which also contribute to global burden of the disease. The study has shown important factors that are associated with malaria mortality such as fits, history of diarrhea, anemia, sucking less than normal, child's nutritional status and whether the child had been seen in another health unit. When malaria deaths were compared with other causes' deaths, most children who die of malaria are more likely to have had fever, vomiting, fits and anemia than those who died of other causes.

Malaria is the leading and major cause of pediatric morbidity (75.5%) and mortality (51.7%) in hospital admitted children. Though this may be true, the figures are higher than what has been reported for endemic areas where admission rate is between 20%-45%, and therefore the precision of these estimates still needs improvement in order to promptly and accurately identify the true burden the disease. The estimates are an approximation with many limitations as seen in our study where 98.8% of the children had multiple diagnoses due to overlap in sign and symptoms and therefore making a single diagnosis was inappropriate. These findings are also higher than those found in a hospital-based study in Kinshasa where malaria constituted 70% of all children under 5 admissions, and 13.2% of malaria mortality (45). Therefore, more similar

studies should be conducted in areas with varying malaria epidemiology and HIV prevalence so as to validate our results.

The number of pediatric deaths (634, 6.2%) observed in this study is similar to those reported in other malaria related mortality in Africa. One most surprising finding in this study was the increase in malaria mortality in 2005, though the admissions (morbidity) remained almost constant across the years. There was no particular reason to explain these results, but perhaps this was an over estimation due to lack of reliable diagnosis as seen in the multiple diagnosis without a leading cause. However, a similar trend was observed in Kinshasa and Malawi upon the emergence of Chloroquine resistant malaria (45, 46) and therefore drug resistance though not explored may be a possible cause. Intervention trials through ITNs trials have shown major effects on all-cause under five mortality and reduction of malaria infections in areas with both low and intense malaria transmission (47, 48), and scaling up could contribute to mortality reductions

4.1 Demographic factors, signs and symptoms

There is a considerable overlap in signs and symptoms of several of the major childhood diseases and therefore a single diagnosis for the sick children was inappropriate. The WHO/UNICEF Integrated Management of Childhood illness (IMCI) guidelines are very necessary if one is to make accurate identification of illnesses. Compared with the physician's diagnosis, there sensitivity of the 'danger signs' for 0-2 months in detecting most of the major childhood illnesses were high (Malaria, Pneumonia, Diarrhea, Malnutrition and anemia). Except for malaria (97%), there was however low specificities for several conditions which may imply a need for refinement of guidelines and training of the health workers in identifying the signs. The most common symptom was high prevalence of fever (65.2 %) among the malaria associated

admissions and 5.9 % among infective causes and 28.9% for non-infective, which was also associated with the risk of dying. Multivariate results show that fever is an important risk factor of malaria associated morbidity and mortality than other risk factors. Children who died of malaria related causes were more than twice likely to have had a history of fever than those who died of other causes. This supports what has been found in other studies where most patients presenting to clinics with malaria have either fever or a history of fever (5). Studies have also suggested that the presence of high fever of short duration and with no other obvious cause that occurs during the rainy season is most likely associated with malaria (49). The presence of fever where malaria is endemic has also been used to define acute malaria even without laboratory confirmations (36). Fever may therefore be used as a diagnostic symptom of malaria, but its usefulness varies (50, 51).

There was an association between malaria related mortality and history of diarrhea in this study, which is in consistent with a previous study done in the same area that found increased risk of dying among younger children was associated with diarrhea (5). In both univariate and multivariate analysis, children who had malaria and presented with a history of diarrhea were 1.6 times more at risk of dying than those who didn't have diarrhea. While some studies support these findings, others have found no association between diarrhea and parasite rate, parasite density or clinical malaria (52, 53, 54). When compared with deaths from other causes, diarrhea was not an important factor of malaria deaths than other causes. This may suggest that history of diarrhea is an important association not only with a malaria death but also with other causes.

The observation that age is a risk factor of malaria mortality is very important in targeting interventions to those who are in greatest need. Infants were identified in the study as being at

high risk of malaria attributed mortality. The case fatality rate among hospitalized malaria cases was highest for infants (6.4 %). However, these findings were not unusual since acquired immunity to malaria is least developed among this age group, making them "the age at greatest risk". Analysis of the surveillance data from the same source but for earlier years indicated that, 54% of pediatric malaria deaths were in children under one year of age (5). Proportion of all cause mortality was almost twice as much for less than 1 year olds as compared to 1 to 4 years. Age was also a statistically significant risk factor for other causes of death; children less than one year old had an increased risk of dying from any other cause. This is an indication that infants are at a greater risk and therefore requires prompt and effective management if infected.

Results also show that fitting is highly associated with childhood malaria mortality in the study population. This has been seen in the study area in a previous study and elsewhere; where convulsions were seen to associate specifically with falciparum malaria in uncomplicated patients of malaria (5, 55). Fitting which is also a sign of severe malaria, increased the risk of dying of malaria by more than two times that of other causes of death. Those who had malaria and died were 2.9 times more likely to have had fitted than the children who had malaria and survived. Fitting can therefore be considered a significant factor to define the severity of malaria. In pediatric patients, convulsions of cerebral malaria need to be differentiated from febrile convulsions.

4.2 Seen elsewhere

The data seem to imply that most children who develop symptoms that are suggestive of malaria are first treated at the peripheral health units before they are referred or taken to SFDDH.

In this study, 37% of the malaria cases had been seen at other health facilities before being referred or taken to SFDDH. Usually, people tend to seek care elsewhere when they don't get better after first treatment or consultation. The observation of high prevalence of symptoms: fever, fitting, diarrhea, anemia and sucking less than usual among malaria admissions than other causes may suggest that malaria cases reach the hospital at a severe stage, thus increasing the risk for dying. This could further suggest possibility of delays in obtaining effective anti-malarial therapy, further leading to serious complications. People's beliefs have been known to influence the choice for healthcare; at times choosing to specifically rely on local medicines (56). Earlier studies in Kilombero district found a problem of access due to poor transport facilities and cost, which caused delays in referral cases (57). However, having been seen elsewhere was not a predictor of malaria deaths than other causes of death. These findings emphasize the need for improving case detection and management at peripheral health facilities to reduce the number of moderate cases from advancing to severe stage that would be difficult to manage or lead to fatal outcomes.

The treatment practices in the hospital did not differ with those of the malaria treatment guide of Tanzania, but the results showed that the most common drug used to treat malaria related cases in SFDDH is Quinine (93.9%). SP was the first line treatment at the time of the study according to treatment policy by the Tanzania's Ministry of health Malaria Treatment guidelines, and quinine was meant to treat severe cases. Based on the guidelines, our data suggests that admitted cases at SFDDH were mostly severe. This confirms the implication on delayed diagnosis with effective treatment as evident with high prevalence of risk symptoms for the children who had been seen at other health units, and subsequent risk of death. Mechanisms for monitoring the

diagnosis capabilities and case management of medical staff in the remotely located health facilities may be very helpful.

4.3 Anemia

Anemia is an important cause of morbidity and probably mortality in patients with acute *Plasmodium falciparum* infection and it is also one of the complications of malaria in endemic areas (5, 32). The prevalence of severe anemia (25.7%) increased with age and was associated with 1.4 times increased risk of malaria mortality only in the older children (1-4 years). This study also found that anemia had a significantly higher association with a malaria death than deaths from other causes. However, a previous study in the area found the association was only significant in younger children, but the prevalence depicted a similar pattern with the findings of this study (17). The importance of severe anemia as a risk factor for malaria deaths is clear since the association is supported by many other studies done in the same study area (3, 32, 48). For instance, the study by Abdulla observed a reduction of anemia prevalence and malaria parastemia among children who used bed nets, thus implying an association between malaria and anemia. Studies that used datasets from various countries to establish malaria/disease burden indicated that the number of deaths attributable to malaria associated anemia is estimated at 190 000 to 974 000 a year (39, 58). We could therefore say that anemia is prevalent among children under five years of age who present with malaria and therefore should not be ignored in the part of clinical management.

Our results may reflect the contribution of anemia to pediatric malaria deaths, and that anemia control measures might reduce the problem. However, caution is needed in designing interventions (a call for further investigations) given the findings of a recent study in Pemba,

Tanzania, where control of anemia in children with iron supplementation was found to contribute to adverse health outcomes (59). The study found that introduction of iron plus folic supplementation was associated with an increase in outcome of severe illness episodes and mortality risk in high malaria-transmission setting. In addition, as an important cause of anemia, malaria frequently leads to blood transfusions, which is a potential risk factor for HIV infection. Another useful preventive measure would be presumptive intermittent treatment of malaria with amodiaquine which can reduce malaria fever as well as anemia in infants (21).

4.4 Nutrition

The observed high prevalence of underweight malaria cases (35.1%) is of particular concern because malnutrition among children increases their risk of morbidity and mortality. Malnutrition predicted death in older children than the infants; however it was not associated with more malaria deaths than other causes. The results showed that only children aged 1-4 years were significantly associated with malnutrition and subsequent risk of death. There was an increased risk of dying associated with low weight-for-age for malaria mortality (OR=2.37, CI 1.48-3.77, OR=2.47 95% CI: 1.84-3.32) for malnourished and severely malnourished respectively). Similar observation has been documented by other studies (5, 60, 61). The risk of death is elevated because under nutrition is the underlying cause for most deaths associated with severe infections. Under nutrition is still very prevalent in many regions of the world; the average z scores for sub-Saharan Africa showing quite high malnutrition (between –1.35 to less than –3 SDs). This contrasts so much with those of America and Europe (average z score is 0), as expected in a healthy population (61). Protein energy malnutrition is a common nutritional disorder in Africa and is also associated with anemia (62). Children who were malnourished (as indicated by a low weight for age) had a higher incidence of severe malaria compared to children

with normal weight. A number of nutritional deficits can contribute to anemia, and further investigations would be needed to identify the causes for anemia in the children in this study. Possibilities to be considered include lack of folic acid or iron (62). Without appropriate measures to address the rising prevalence, the situation may become bleak, because malnutrition makes children more likely to succumb to the disease. Malaria is less likely to be diagnosed, because malnutrition causes the symptoms of the disease to be less recognizable (63). This is because malnutrition is also the commonest cause of anemia and therefore may compound any malaria relationship.

Neurological, respiratory and cardiovascular variables were not included in our model. However, we have shown some important clinical signs/symptoms that are risk factors for death in children at a rural Tanzania district hospital. These findings could further be validated to other areas so as to assess the children "at risk", to assist in developing a tool for targeting for effective clinical management.

4.5 Limitations of the study

The limitations of our study include:

1. Hospital based studies may not reflect the disease patterns in the community.

2. Multiple possible confounders that might explain an ill -defined part of the associations were ignored.
    - Few socio-economic and demographic variables were collected ; important factors like bed nets usage and coverage, age and education status of the mother might have been useful

3. The study assumes malaria as a single diagnosis.

- Many children (98.8%), considered in this study were admitted with several coexisting problems and making single diagnosis, is often difficult or inappropriate. Multiple diagnoses could have overestimated malaria specific causes.
- The clinical features of common illnesses are often indistinguishable.

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

1. Our study has shown a number of symptoms and clinical signs that are important in predicting outcome of malaria disease. These could be used in the assessment of the risk for death in pediatric admissions and identifying children at risk for targeted case management.
2. Since the risk factors are not specific to the study area, they could be applicable in settings with similar malaria entomology and epidemiology.
3. Malaria is a leading cause of pediatric mortality in this hospital and infants are at a greater risk
4. Anemia is an important risk factor for malaria deaths. It accounts for 31.2% of malaria related deaths
5. There is a possibility of delays in obtaining effective anti-malarial therapy, further leading to serious implications

5.2 Recommendations

- There is need for more access to diagnostic services with accurate identification of risk factors to ensure prompt and effective treatment of malaria.
- We call for improved case detection and management (Roll out of IMCI guidelines) at peripheral health facilities
- There is need for the improvement of the tools used for routine data collection in the surveillance to include more socio economic variables
- The newly adopted tool for malaria diagnosis, rapid diagnostic test (RDT) may be a useful breakthrough that need to be up scaled

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APPENDICES

APPENDIX 1. QUESTIONNAIRE

INPATIENT SURVEILLANCE FORM

IDENTIFICATION

1	Date admitted (dd/mm/yy)	|__|__| / |__|__| / |__|__|
2	Hospital number	|__|__|__|__|__|__|__|__|
3	Study number	|__|__|__| / |__|__|__|__|__|__|/ |__|__|__|
4	Check digits (xxx=missing)	|__|__|__|
5	Child's first name	|__|__|__|__|__|__|__|__|__|__|
6	Date of birth (dd/mm/yy)	|__|__| / |__|__| / |__|__|
7	Sex (1=male, 2=female)	|__|
8	Mother's first name	|__|__|__|__|__|__|__|__|__|__|
9	Father's first name	|__|__|__|__|__|__|__|__|__|__|
10	Family name of father	|__|__|__|__|__|__|__|__|__|__|
11	Village	|__|__|__|__|__|__|__|__|__|__|
12	Balozi	|__|__|__|__|__|__|__|__|__|__|

HISTORY

13	Fever (1=yes, 2=no / no days)	|__| / |__|__|
14	Cough (1=yes, 2=no / no days)	|__| / |__|__|
15	Dyspnoea (1=yes, 2=no / no days)	|__| / |__|__|
16	Child sucking / drinking 1=more than usual, 2=less than usual, 3=as usual)	|__|
17	Diarrhoea (1=yes, 2=no / no days) *If no, go to question 20*	|__| / |__|__|
18	Nº of stools in the last 24 hours	|__|__|

19 Stool type (1=Watery, 2= bloody, 3=mucoid) |__|

20 Dysentery (1=yes, 2=no / no days) |__| / |__|__|

21 Vomiting (1=yes, 2=no / no days) |__| / |__|__|

22 Has the child fitted during this illness? (1=yes, 2=no) |__|
If no, go to Q25

23 N° of seizures within the last 24 hours |__|__|

24 Other significant history _____

25 Has the child been seen at any health unit for that illness? (1=yes,2=no) |__|

26 If yes, where? _____

27 Treatment given:

a _____ |__|__| d _____ |__|__|

b _____ |__|__| e _____ |__|__|

c _____ |__|__| f _____ |__|__|

EXAMINATION

General

28 Height (cm) |__|__|__|

29 Weight (kg) |__|__| : |__|

30 Axillary temperature(°C) |__|__| : |__|

31 Pallor (1=yes, 2=no) |__|

32 Jaundice (1=yes, 2=no) |__|

33 Skin rash (1=scabies, 2=other (mild), 3=other (severe), 4=none) |__|

34 Visible pus in ears ? (1= yes, 2 = no) |__|

35 Oral candidiasis (1=yes, 2= no) |__|

Respiratory & Cardiovascular

36 Pulse (timed over full minute) |__|__|__|

37 Respiratory rate (time over full minute) |__|__|__|

38 Nasal flaring (1=yes, 2=no) |__|

39 Indrawing (1=yes, 2=no) |__|

40 Crackles/creps/bronchial breathing (1= yes, 2=no)

41 Wheeze/ronchi (1=yes, 2=no) |__|

42 Gallop rhythm (1=yes, 2=no) |__|

43 Hepatomegaly (1=yes, 2=no /length cm) |__| / |__|__|

44 Splenomegaly (1=yes, 2=no /length cm) |__| / |__|__|

Nutritional & Hydration Status

45 Flaky paint skin (1=yes, 2=no) |__|

46 Orange hair (1=yes, 2=no) |__|

47 Visible wasting (1=yes, 2=no) |__|

48 Oedema (1=general, 2=face, 3=periphery, 4=other, 5 =none) |__|

49 Mucous membranes (1=moist, 2=dry, 3=very dry) |__|

50 Skin pinch goes back (1=quickly, 2=slowly, 3= very slowly) |__|

51 Dehydration (none=1, some =2, severe=3) |__|

Neurological

52 Level of consciousness (1=well/alert, 2=restless/irritable, 3=lethargic/unconscious) |__|

53 Fontanelle (1=normal, 2=sunken, 3=bulging, 4=na) |__|

54 Position (1=decerebrate, 2=decorticate, 3=opisthotomia, 4=normal) |__|

55 Neck stiffness (1=yes, 2=no) |__|

56 Can the child sit down? (1=yes, 2=no) |__|

57 Eye movements (0=not directed, 1=directed) |__|

58 Verbal response (0=none, 1=inappropriate cry, 2=appropriate cry) |__|

59 Motor response (0=none, 1=withdraw from pain, 2=localises pain) |__|

60 Has the child had a convulsion in the last hour or anticonvulsant treatment in the last 6 hours? (1=yes, 2=no) |__|

LABORATORY AND COMPLEMENTARY INVESTIGATIONS

61 Microcapillary tube and blood slides sent to IC lab? (1=yes, 2=no) |__|

62 Sample brady number? (affix sticker here)

63 Blood glucose (mg/dl) |__|__|__|

64 Hospital PCV on admission (%) |__|__|

65 Initials of admitting officer |__|__|

AT DISCHARGE

66 Hospital parasitaemia on admission (1=positive, 0=negative) |__|

67 Chest x-ray taken (yes=1 ,no=2) |__|

68 If yes (normal=1 ,abnormal=2) |__|

69 LP done (1=yes, 2=no) |__|

70 If yes (normal=1,abnormal=2) |__|

71 Has the child received a blood transfusion during admission? (1=yes, 2=no) |__|

72 Date of transfusion |__|__| / |__|__| / |__|__|

73 What was the last hospital PCV recorded before transfusion? |__|__|

74 Final diagnosis 1: |__|__|__|

75 Final diagnosis 2: |__|__|__|

76 Date of discharge (dd/mm/yy) |__|__| / |__|__| / |__|__|

77 Outcome: (Alive=1, dead=2, absconded=3, 4=transferred) |__|

78 Treatment received during admission:

a_____ |__|__| d_____ |__|__|

b_____ |__|__| e_____ |__|__|

c_____ |__|__| f_____ |__|__|

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Kiriinya

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M050909**
PROJECT	The Burden of Malaria and Anaemia among Under 5 Children Admitted at a Rural District Hospital in Tanzania
INVESTIGATORS	Ms RN Kiriinya
DEPARTMENT	School of Public Health
DATE CONSIDERED	05.09.30
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 05.11.09 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr E Marinda

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2. PERMISSION LETTER

Dr Khin San Tint
Academic coordinator
School of Public Health
University of Witwatersrand
School of Public Health
Medical School, 7 York Rd, Parktown, 2193

June 16, 2005

Ref: PERMISSION TO USE DATA

The above heading refers. Ifakara Health Research and Development Centre (IHRDC) is a collaborator in the INDEPTH-network L& D masters programme. Student Rose Nkirote has been identified to do her field attachment and her project at our institution. Her research needs to use data collected by IHRDC at a district hospital.

With this letter the IHRDC director grants her permission to use the data for her project only for years 2001 to 2004 and to specifically address her research question only.

Yours sincerely

Dr Hassan Mshinda
Director, IHRDC

APPENDIX 4: STUDY SITE MAP