Effects of sustained use of insecticide-treated bednets on malaria specific morbidity in childhood in Asembo, Rarieda Division, Bondo District western Kenya.

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A thesis submitted in partial fulfilment of the requirements for the degree of Master of Public Health and Epidemiology of Kenyatta University.
DECLARATION

This thesis is my original work and has not been submitted for a degree to any other University

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We certify that this work has been carried out by Frank Ouma Odhiambo under our supervision and has been submitted after examination with our approval as University Supervisors.

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LIST OF ABBREVIATIONS

CBS  Central Bureau of Statistics
CDC  U.S. Centres for Disease Control and Prevention
EDTA  Ethylene diamine tetraacetic acid
EIR  Entomological inoculation rate
ITBN  Insecticide-treated bednets
KEMRI  Kenya Medical Research Institute
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DEFINITION OF TERMS

Clinical malaria: Parasite density above an age-specific threshold (Bloland et al., 1999) with axillary temperature ≥37.5°C.

Cross-sectional survey: The scrutiny of a population at a given time point in order to determine the frequency of occurrence of a disease and other factors suspected of causing it.

Diagnosis: The process of determining health status and the factors responsible for causing it.

Efficacy: The extent to which a specific intervention produces a beneficial result under ideal conditions.

Endemic disease: The constant presence of a disease or infectious agent within a given geographical locality.

Holoendemic disease: A disease for which a high prevalence level of infection begins early in life and affects most of the child population, leading to a state of equilibrium such that the adult population shows evidence of the disease much less commonly than do the children.

Malarial anaemia: Defined as a haemoglobin level (Hb) <11g/dl with concomitant parasitaemia.

Moderate to severe malarial anaemia: Defined as Hb <7g/dl with concomitant parasitaemia.

Morbidity indicator: A variable susceptible to direct measurement that reflects the state of health of persons in a community.

Prevalence: The proportion of the population with a particular disease.
Randomized controlled trial: An epidemiological experiment in which subjects in a population are randomly allocated into groups usually called 'study' and 'control' groups, to receive or not to receive an experimental intervention.
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DEDICATION

This thesis is dedicated to the memory of my late father, may he rest in peace.
ABSTRACT

Malaria is a major global public health problem today in more than 90 countries inhabited by 2,400 million people - 40% of the world population. Insecticide treated bed nets (ITBNs) have proven effective in reducing exposure to malaria parasites. However, there is concern that sustained reduction in exposure from birth in endemic areas may result in a shift in the age and clinical spectrum of malaria from severe anaemia in younger children towards cerebral malaria in older ones. Such a shift may lead to a paradoxical rise in disease risk throughout childhood. The lack of evidence on the impact of the sustained use of ITBNs on malaria specific morbidity has generated considerable debate and speculation, which has caused concern among WHO, UNDP, UNICEF, the World Bank and others who are engaged in promoting their use in endemic areas with intense malaria transmission.

The objective of the study was to determine whether the sustained use of ITBNs for vector control in an area of intense perennial transmission results in a shift in the age and clinical spectrum of malaria with reference to parasite densities and haemoglobin levels. The study area included 60 villages in Asembo, Rarieda Division, Bondo District, Western Kenya. A follow-up cross-sectional survey was conducted in May 2000. The study subjects included 1,055 children under 6 years of age. They were traced from a total of 1,347 children who participated in a baseline survey conducted in June 1999. Signs and symptoms of recent illness like fever, headache, body pains, coughs and diarrhoea
were recorded. Slides with thick smears made from the subjects' blood samples were read using a microscope to assess the prevalence of parasitaemia. Haemoglobin levels were determined using a hemocue machine. Between 1999 and 2000, the geometric mean parasite density decreased from 4,759 parasites/µl to 4,267 parasites/µl. The mean value of haemoglobin levels rose from 10.1 g/dl to 10.4 g/dl. The proportion of children with clinical malaria declined from 23.5% to 20.3%, while moderate to severe malarial anaemia defined as Hb <7 g/dl with any malaria parasitaemia, also declined from 6.0% to 2.7%. The results of the study demonstrated that the sustained use of ITBNs in childhood in Asembo, Rarieda Division, Bondo District, Western Kenya (a holoendemic area of intense perennial transmission) led to a reduction in the prevalence of clinical malaria and malarial anaemia, whereas, the levels of haemoglobin were raised. The study provided evidence of the beneficial health impact associated with sustaining the use of ITBNs from infancy to a period of at least 3 years in endemic areas, where children under 2 years of age bear the greatest burden of malaria.
CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 GENERAL INTRODUCTION

Malaria is an enormous global public health problem today and by far the most important vector-borne disease (Gilles and Warrell, 1993). Recent WHO estimates indicate that worldwide there are 300-500 million cases of clinical malaria annually, with 1.4-2.6 million deaths occurring, mainly among young children in African, older children and pregnant mothers (WHO, 2002).

Up to 55% of the world's population is exposed to malaria: around 80% of those exposed live in sub-Saharan Africa (Lankinen et al., 1994). In Africa, it has been estimated that 10% of deaths from all causes for children under five years of age are due to the direct effects of malaria (Khare, 1999). Of all infectious diseases in Kenya, malaria is the most significant contributor to morbidity and mortality. It accounts for 30% of all outpatient illnesses nation-wide (Republic of Kenya, 1997). Among approximately 20 million people who are exposed to stable malaria transmission in Kenya, UNICEF estimates that 3.5 million are children aged below 5 years and 26,000 of them die each year (72 children die each day) from direct consequences of malaria infection (Ouma, 1998). Another 145,000 children will develop severe complications of the disease (Ouma, 1998). Children between the ages of 6 to 24 months who have low or non-existent protective immunity to the disease are at a high risk of developing severe disease and dying if infected by
malaria. Apart from the fact that a significant proportion of household income may go to malaria treatment, malaria morbidity lowers productivity in schools and places of work due to frequent absenteeism. Thus the disease is an impediment to development in the country (Republic of Kenya, 1997; Munguti, 1998; Mutero et al., 1998).

1.2 LITERATURE REVIEW

1.2.1 Epidemiology of malaria

Malaria is characterized by cyclical bouts of fever with joint pains, rigors and sweating. It is caused by parasites of the genus *Plasmodium*. The parasite is transmitted via the bite of a female mosquito of the genus *Anopheles*. For transmission to occur, it is necessary that a susceptible human host be exposed to the infective bite of a female anopheline mosquito that is infected by one of the four species of *Plasmodium*: *P. ovale*, *P. malariae*, *P. vivax* and *P. falciparum*. *Plasmodium falciparum* is the most dangerous species in terms of mortality. It is responsible for the most dangerous complications such as cerebral malaria and is the most virulent and potentially lethal species to humans (Molyneaux, 1997). In China, East Asia and the Pacific, *P. vivax* is more common. In Africa, *P. falciparum* is the predominant species. The same species accounts for at least 90% of malaria infections in Kenya (Ouma, 1998). In a cohort study carried out in Western Kenya between 1992 and 1994, 80% of the blood smears obtained showed a pure *P. falciparum* infection (Bioland et al., 1999). The source of
malaria infections is either a patient or an asymptomatic carrier. The principal mosquito vectors in Western Kenya include *Anopheles gambiae s.s.*, *Anopheles arabiensis* and *Anopheles funestus* (Beach et al., 1993).

1.2.1.1 Naturally acquired immunity to malaria

The newborn infants of mothers living in areas of endemic malaria usually acquire immunity from their mothers and are protected for a few months (3–6) after birth, after which they have to develop their own immunity from exposure to malaria infection. Naturally acquired immunity plays a key role in determining whether a child develops clinical malaria or remains asymptomatic. With every successive attack of malaria survived, the individual develops immunity (Brinkmann and Brinkmann, 1991). Therefore, exposure to infection is essential for the development of natural immunity. In time, this naturally acquired protective immunity is manifested as the ability to limit parasite densities despite the persistent exposure experienced in endemic areas with high perennial transmission rates. This may be observed as the different critical levels of parasite densities that determine the development of clinical malaria in specific age groups (Bloland et al., 1999). The multiplicity of infective strains has also been found to boost the development of protective immunity (Fraser-Hurt et al., 1999). Other features may also influence the acquisition of natural immunity, these include: human population dynamics, socio-economic conditions, vector
species, vector feeding habits, climate and topography (Oloo et al., 1996; Munguti, 1998; Mutero et al., 1998).

1.2.2 Global malaria control strategies

Several countries, including the USA, the former Soviet Union, Italy, Korea and many Caribbean Islands, have succeeded in eliminating malaria through intensive and costly control programmes (Curtis, 1996). In many tropical areas and especially sub-Saharan Africa, such control programmes have not been feasible (Curtis, 1996). In response to the worsening situation with regard to malaria, a Ministerial Conference was convened in Amsterdam in 1992. A Global Malaria Strategy was agreed upon and endemic countries committed themselves to strengthening already existing malaria control efforts and initiating others in order to reduce the disease burden at every level. The strategy aimed to curb socio-economic loss due to malaria by preventing mortality and reducing morbidity and by progressively improving and strengthening the local and national capabilities for the control of malaria at all levels.

The two main objectives set were as follows:

i. of the countries affected 90% had to implement appropriate malaria control programmes by the year 1997;

ii. malaria morbidity be reduced by at least 20% compared to 1995 in at least 75% of the affected countries, by the year 2000
Unfortunately, the strategy has not been successful for many of the countries involved. Such countries have lacked adequate financial resources and appropriate technical capabilities necessary for the successful implementation of malaria control programmes (WHO, 1992a).

1.2.3 Roll Back Malaria

Roll Back Malaria strategy (RBM) is a product of joined efforts between WHO, UNDP, UNICEF and the World Bank, whose aim was to mobilize support for local and national malaria control initiatives worldwide. It was initiated in 1998 and seeks to work with governments, NGOs, and private sector companies to reduce the human and socio-economic costs of malaria. RBM is promoting strategies that are evidence-based, outcome focused and cost-effective (WHO, 2000). These include four main strategies as follows:

a) Prompt access to treatment;

b) Insecticide-treated mosquito nets;

c) Prevention and control of malaria in pregnant women;

d) Malaria epidemic and emergency response (WHO, 2000).

The programme has set some possible goals, to halve the burden of malaria worldwide by the year 2010 and halve that again by 2015 using techniques which already exist and need wider dissemination, or which can rapidly be developed (WHO, 200).
1.2.4 Malaria control strategies in Kenya

In 1992, Kenya became a signatory to the commitment for malaria control by endemic countries at the Ministerial Conference in Amsterdam and the National Plan of Action for Malaria Control was formed in the same year (Ouma, 1998). In 1994, a Malaria Control Unit (MCU) was established and a Five Year Plan officially launched by the Ministry of Health (Ouma, 1998).

The plan addressed five key issues:

i. improving and sustaining services within the community for reducing malaria morbidity and mortality;

ii. coordinating and focusing the control efforts of Ministries, Divisions, International Agencies and the private sector on malaria as a National Health Problem;

iii. guiding and empowering the community members to protect themselves from malaria related illnesses and death;

iv. using current and completed research findings to target appropriate interventions to regional malaria problems; and

v. ensuring the availability of appropriately trained personnel at all levels for effective implementation of the plan (Republic of Kenya, 1995).

1.2.5 Policy for malaria control in Kenya

In 1997, the Kenya National Policy guidelines for malaria control, which included prevention, diagnosis and treatment were developed. These guidelines covered a wide range of activities and intervention measures,
including adopting the most appropriate technologies, for example, the use of ITBNs as a means of personal protection against malaria (Republic of Kenya, 1997).

1.2.5.1 Intervention measures

Malaria control efforts in most of Kenya have remained weak, and this calls for the development of new methods and utilization of available control strategies. The control methods, which have been used over the past include the following:

(a) Chemoprophylaxis

The widespread use of antimalarial drugs for prophylaxis has generally been associated with poor compliance and under dosing (Zoguereh and Delmont, 2000). This has contributed to the emergence of resistance of *P. falciparum* to many drugs, notably chloroquine. There is evidence that large-scale chemoprophylaxis is not useful in endemic areas because it hampers the development of naturally acquired protective immunity (Menendez et al., 1997). So, it should be restricted to the following high-risk groups: pregnant women, non-immune immigrant workers, travellers and people who have been away from the endemic area for several years. Depending on the local parasite strains, the general guideline is to reserve mefloquine for short-term prophylaxis and maloprim combinations for long-term prophylaxis (Zoguereh and Delmont, 2000).
(b) Vector control

After ingestion by a mosquito, *Plasmodium* gametocytes undergo changes within the mosquito gut and after 10-14 days become infective sporozoites. If mosquitoes are killed during the parasite's extrinsic incubation period, they have no opportunity to transmit the disease. This has been the key concept used in most of the successful malaria vector control programmes (Curtis, 1996). The following are some of the methods used to reduce human-vector contact and thus reduce malaria transmission:

i. spraying inside houses with residual insecticide;

ii. personal protection in the form of mosquito repellants, mosquito coils, insecticide sprays and use of ITBNs (Curtis, 1996).

The most widely used insecticide for house spraying had been DDT. In areas of DDT-resistance or where it is banned, organophosphate or carbamate compounds such as malathion or bendiocarb are used (Curtis, 1994). Currently modern pyrethroid insecticides are recommended for spraying because they are effective at far lower doses than DDT, are relatively harmless to humans, leave no visible deposits on walls and also kill nuisance insects such as cockroaches (Curtis, 1996).

(c) Diagnosis

Clinical malaria has proved rather difficult to define in a precise manner. The variety of symptoms that accompany a typical case of clinical malaria include: fever, headache, body pains, cough and diarrhoea
(Snow and Marsh, 1998). A study in Western Kenya found that the association between risk of fever and the density of parasitaemia was age-specific (Bloland et al., 1999). Critical parasite densities associated with febrile episodes attributable to malaria increased sharply from 1,500 parasites/μl for infants 0-5 months old to 7,000 parasites/μl for children 12-23 months old. In older children the densities gradually decreased to 3,500 parasites/μl for children 36-47 months old, up to a low of 500 parasites/μl for children over 10 years old (Bloland et al., 1999). The very same symptoms may be due to other illnesses and severe malaria may not be readily distinguishable from other severe diseases, such as pneumonia, typhoid and meningitis that require very different therapy (Molyneaux, 1997). This lack of a precise definition for clinical malaria becomes a major hindrance in making a correct diagnosis in endemic areas with a high rate of transmission where over 80% of the children have some level of parasitaemia (Snow and Marsh, 1998). A recent study found that only 20% of patients clinically diagnosed with malaria had a positive blood slide (Khare, 1999).

It has been found that fever accompanied by other clinical signs, such as pallor or splenomegaly is predictive of malaria but there are other causes of splenomegaly, for example, schistosomiasis (Greenwood, 1997). In endemic areas with high transmission, anaemia due to malaria is the most important sign of the disease. *P. falciparum* infection was associated with reduced haemoglobin concentrations
($\leq 5 \text{g/dl}$), in 46% of children admitted to hospital with severe anaemia in an area of high seasonal transmission (Newton et al., 1997). A study conducted in Western Kenya found that 55% of severely anaemic children were below the age of 1 year and the greatest burden of anaemia was observed among children aged 6 to 18 months old (Bloland et al., 1999). In non-endemic areas with seasonal transmission, the most important manifestation of severe malaria is cerebral malaria. The following symptoms are associated with cerebral malaria: coma, hyperparasitaemia, fever and convulsions (Esamai et al., 1999).

Microscopy remains one of the most reliable tools for diagnosis of malaria (Beadle et al., 1995). Therefore, many of the definitions for clinical malaria actually combine predictive symptoms with the presence of parasitaemia. This makes it important to have a suitable definition for a given area in a particular transmission setting though in endemic areas even microscopy cannot detect sub-patent parasitaemia that has been frequently observed in such areas (Fraser-Hurst et al., 1999).

Results from a study carried out in The Gambia suggested an alternative approach, using a model that is applicable to data in any endemic area. Using a case definition consisting of fever together with any given cut-off level in parasite density the model is used to obtain estimates of sensitivity and specificity (Armstrong-Schellenberg et al., 1994). A case of febrile illness is then assigned a probability that the illness was due to malaria, rather than trying to qualify some cases as
clinical malaria and disqualifying other cases (Armstrong-Schellenberg et al., 1994).

(d) Chemotherapy

Since the 1980s, widespread chloroquine resistance has been noted across the East African region (Bloland et al., 1993). In Asembo, Rarieda Division of Bondo District, where the project site is situated, chloroquine resistance is about 80% (Rapuoda et al., 1997). Fortunately, sulphadoxine-pyrimethamine (Fansidar®) is still largely effective (Ouma, 1998). It was implemented as the first line drug for treatment in 1999. It has been proposed that non-falciparum malaria and chloroquine-sensitive falciparum malaria should be treated with chloroquine taken orally or by injection in case the patient is vomiting (Khare, 1999). In areas of chloroquine-resistance, quinine dihydrochloride and Fansidar® are recommended. Quinidine may be used for treatment as an alternative to quinine. Tetracycline or doxycycline may be used as alternatives to Fansidar® if antimetabolite resistance is common or if a patient is allergic to sulphonamides. Other alternatives to quinine include mefloquine, halofantrine and artemisinin and its derivatives. These drugs may also be used to treat chloroquine-resistant malaria (Khare, 1999).

1.2.6 Insecticide-treated bednets

Initially, impregnation of bed nets was designed to add a safe chemical barrier to the sometimes-imperfect physical barrier presented by the net
Pyrethroids paralyze the insect’s nervous system and kill it within minutes (Curtis, 1996). They also irritate and drive away mosquitoes before they can find some way to enter a damaged net. Furthermore, the synthetic netting is a favourable substrate for a residual insecticide and needs only a small amount for treatment (Curtis, 1996). In what is probably the world’s largest ITBN programme, up to 2.5 million bed nets in Sichuan Province of China, were treated annually by spraying deltamethrin and a remarkable decline in malaria morbidity was recorded (Chen et al., 1995). In most other projects, dipping them in a pyrethroid emulsion treated bednets.

1.2.7 Observed relationship between malaria transmission intensity and malaria mortality

A recent review of the available epidemiological data, mostly derived from hospital-based studies, indicated that severe malaria morbidity was low under conditions of low stable malaria transmission, it then increased to a moderate level and stabilized under intense stable malaria transmission, and it was at its highest under moderate unstable malaria transmission (Snow and Marsh, 1998). This implies that reducing transmission in highly endemic areas may result in an increase in malaria morbidity. Some publications from defined community based studies essentially supported the hospital-based findings (Trape and Rogier, 1996; Mbogo et al., 1996).

Other studies suggested that if indirect malaria mortality and other causes of death concentrated early in life were considered, then the
long term impact of a sustained reduction in exposure (such as that resulting from use of ITBNs) on all-cause mortality would probably always be beneficial (although less than the short-term), even if there was some increase in direct malaria mortality (Molyneaux, 1997b). Also, a relationship between transmission intensity and ITBN efficacy was noted, with the highest efficacy seen in areas of lowest malaria transmission (Snow and Marsh, 1998).

Randomized controlled trials in different malaria transmission settings have shown that ITBNs and curtains were effective in reducing mortality and morbidity (D’Alessandro et al., 1995; Binka et al., 1996; Nevill et al., 1996; Habluetzel et al., 1997). The evidence available from large-scale malaria control studies that aimed to reduce transmission pressure remains controversial. Whereas some researchers suggested protection against other causes of death (Molyneaux, 1995; Alonso et al., 1991), others had found no evidence for such effects (Nevill et al., 1996; Langford, 1996). The relationship between the intensity of malaria transmission and malaria morbidity in children may have important implications for the expected long-term benefits of malaria control measures like ITBNs which aim at reducing exposure to malaria vectors early in life.

1.2.8 Effects of ITBN use on malaria specific morbidity

Insecticide treated bed nets (permethrin, deltamethrin, lambdacyhalothrin and alphacypermethrin) have been used for malaria control in studies in The Gambia, Burkina Faso and Tanzania where a drop of 60% was
noted in the number of children with parasitaemia higher than a critical threshold (Carnevale et al., 1991). A study involving children <2 years old in Tanzania reported significant increases in mean haemoglobin levels and a significant decrease of 16.4% in the prevalence of parasitaemia after 6 months of ITBN use (Fraser-Hurt et al., 1999). Another similar study also conducted in Tanzania over a period of 2 years found that mean haemoglobin levels rose from 8.0 g/dl to 8.9 g/dl and that the prevalence of anaemia decreased from 49% to 26% (Abdulla et al., 2001). In The Gambia a significant reduction of 50% in parasitaemia and an increase of 0.9% in the mean packed cell volume was reported in children <9 years old (D'Alessandro et al., 1995). Other studies in Africa have also reported similar results and it has been established that the use of ITBNs for a period of 2 years in different transmission settings results in a substantial reduction in transmission and reduces malaria specific morbidity. A study carried out on the Kenyan coast reported a 33% reduction in childhood mortality in children aged under 4 years, and a 41% reduction in paediatric ward admissions for severe malaria cases (Nevill et al., 1996). Current programmes with ITBNs are based on the expectation that it is generally better to live with a lower degree of exposure to malaria than a higher one (Lines, 1997). The long-term impact of malaria control measures which reduce parasite exposure remains the subject of considerable debate and speculation and has caused concern among those engaged in promoting the use of ITBNs in communities with
intense malaria transmission (Lines, 1997; Snow et al., 1997; Molyneaux, 1997a; D’Alessandro et al., 1995). However, the effects of sustained use of ITBNs for a period of at least 3 years in endemic areas of intense perennial transmission have not been exhaustively studied.

1.3 RATIONALE OF THE STUDY

1.3.1 Statement of the problem

Previous studies have suggested that in areas of intense malaria transmission, sustained ITBN use may merely cause a shift in the age and disease spectrum from severe malarial anaemia in younger children to cerebral malaria in older children (Snow et al., 1997; Snow and Marsh, 1998; Trape and Rogier, 1996). If that were the case then one would expect that the children who have used ITBNs for a period of up to 1 year would have relatively lower levels of haemoglobin, experience fewer episodes of clinical malaria and moderate to severe malarial anaemia. It is therefore paramount that, the age factor and the pattern of age distribution of malaria morbidity in the study area should be considered.

On the other hand, the children who have sustained the use of ITBNs for a period of at least 3 years would be expected to have relatively higher levels of haemoglobin, although episodes of clinical malaria and cerebral malaria might increase. Such a situation may lead to a paradoxical net increase in malaria specific morbidity as a result of sustaining an ITBN intervention for a long period and could be detrimental to the population.
1.3.1 Research questions

i. Does a sustained reduction in exposure to the malaria parasite in endemic areas result in an increase in malaria specific morbidity in older children who have sustained the use of ITBNs for a period of at least 3 years?

ii. Are there any health benefits realized from the continued use of ITBNs by children below the age of 6 years in the study area?

iii. Should children less than 6 years of age, in malaria endemic areas, be encouraged to use ITBNs from birth, and to sustain their use for a period of at least 3 years?

1.3.1 Justification

Whereas, one of the main strategies employed by the Roll Back Malaria initiative for vector control involves the widespread use of ITBNs, this crucial issue of bednets significantly reducing the burden of malaria has not been previously investigated in a community situated in a holoendemic area of intense perennial transmission. This study was therefore undertaken to determine the impact of sustained use of ITBNs on malaria parasite densities and haemoglobin levels. The findings of this study may have the potential for implementing policies on the widespread use of vector control measures that aim at reducing transmission in malaria endemic countries.
1.4 HYPOTHESIS

H₀: For children less than 6 years of age, there is no significant difference in the age and clinical spectrum of malaria between those who have sustained the use of ITBNs for a period of at least 3 years and those who have used ITBNs for a period of up to 1 year.
1.5 OBJECTIVES OF THE STUDY

1.5.1 General objective

To determine whether the sustained use of ITBNs by children less than 6 years of age results in a shift in the age and clinical spectrum of malaria with reference to parasite densities and haemoglobin levels.

1.5.2 Specific objectives

a) To investigate whether the prevalence and age distribution of clinical malaria differs between children who have sustained the use of ITBNs for a period of at least 3 years and those who have used ITBNs for a period of up to 1 year.

b) To determine the prevalence and age distribution of moderate to severe malarial anaemia in children who have sustained the use of ITBNs for a period of at least 3 years and those who have used ITBNs for a period of up to 1 year.

c) To identify changes in haemoglobin levels over a one-year period in children who have sustained the use of ITBNs for a period of at least 3 years as compared to those who have used ITBNs for a period of up to 1 year.
CHAPTER 2: MATERIALS AND METHODS

2.1 THE STUDY AREA

The study was carried out in Rarieda Division, locally known as Asembo in Bondo District, lying northeast of Lake Victoria in Nyanza Province of Western Kenya (Fig. 1). The site is situated about 65 km from Siaya town and Kisumu city. The geographical limits of the site were predefined using local administrative boundaries and the community lives in 75 discrete villages. Rarieda Division with an area of about 178 km$^2$ had a population of 56,883 people in 1999 (Republic of Kenya National Census, 1999) with children under 6 years of age making up 19.5% of the total population. The population is culturally homogeneous; over 95% are members of the Luo community who make their livelihood from subsistence farming and fishing. Malaria is holoendemic, and transmission is intense and perennial in this area (Beier et al., 1994). The entomological inoculation rate (EIR) is comparable with the highest rates documented worldwide (average 100-300/year) (Beier et al., 1994).
Figure 1: CDC/KEMRI FIELD STATION IN ASEMBO, RARIEDA DIVISION, BONDO DISTRICT, WESTERN KENYA

Site of Asembo Study area
Site of the main KEMRI/CDC laboratory at Kisian
Equator

Kisumu

Kenya

Kisumu
2.2 THE STUDY SUBJECTS

2.2.1 Sampling and sample size

The study was longitudinal in design with a baseline cross-sectional survey in June 1999 (results of this survey were available for use, courtesy of Anja Terlouw) and a follow-up survey in May 2000. In 1999, at least 40% of all the 10,000 households in 60 villages were selected by simple random sampling. From the 4,000 households selected, a total of 1,347 children <5 years old were recruited for the baseline survey. During the year 2000, 1,100 children were traced and invited to participate in a follow-up survey. Of those invited 1,055 actually turned up and were recruited for the follow-up in May 2000.

2.2.2 Ethical considerations

Children did not incur additional risks of contracting malaria because of their participation in the study. A written consent for participating in the project was obtained from the caretaker of the child (Appendix I). It was stressed that participation in the study was voluntary and parents were free to withdraw their children at any time without any effect on the family members. A clinical officer formed part of the team and gave each child a thorough physical examination. Children who were found to be ill during the survey were given free treatment with the severely ill being referred to hospitals for admission. The study was approved by the National Ethical Review Committee of Kenya Medical Research Institute (KEMRI) and the Institutional Review Board of Centers for Disease Control and Prevention (CDC), Atlanta.
2.2.3 Inclusion criteria

A child was included in the study if: the child participated in the baseline survey, was living within the study area and was <6 years old.

2.2.4 Exclusion criteria

A child was excluded from the study if found to be homozygous for the sickle cell trait, was ≥6 years old, excluded from the baseline survey, living outside the study area at the time of the survey or their blood sample could not be analyzed.

2.3 DATA COLLECTION

2.3.1 Clinical data

After obtaining a written, informed consent from the parent or caretaker, a unique code identifier was assigned to each participant at registration and pre-printed stickers were used to mark blood samples. The identifier consisted of the examining team number, the participant village number, a three-digit number and a check digit. The check digit was programmed to disallow the entry of a wrong code during data entry. The check digit was computed using a mathematical formula that used the values of the digits from the entered code (SAS Institute, Cary, NC).

A structured questionnaire was designed and used to obtain information on malaria specific morbidity (Appendix II). Every child was examined by a village health worker for signs and symptoms of malaria, like fever, headache, body pains, coughs and diarrhoea. Some basic demographic information and the child’s illness history were taken. The
parent or caretaker was asked prompted and unprompted questions on signs and symptoms of illness observed in their children in the last 2 weeks. The axillary temperature, height/length and weight were measured. Two independent readings were taken for each measurement and their mean value was used. A finger-prick blood sample was taken and finally, a clinical officer gave each child a thorough physical examination and treatment if indicated. The ages of the children were obtained from vaccination cards (if available) after verbal verification with the parent or caretaker. For those children with an unknown date of birth, the 15th day of the month was used as the date of birth.

2.3.2 Blood samples

Blood smears were collected using standard procedures. The health worker used a new pair of protective gloves for each child, the middle finger tip of the left hand was disinfected with methylated spirit, gently squeezed and pricked with a sterile lancet. The slides were marked with the code identifiers and the appropriate dates. The first drop of blood was placed in a hemocuvette and the haemoglobin level measured in a Hemocue® machine (HemoCue AB, Angelholm, Sweden). The second two drops were used to make two thick blood-smears on a single slide, and then approximately 1.5ml. of blood was taken in an tube containing ethylene diamine tetraacetic acid (EDTA) (used for storing blood samples) and mixed gently in order to avoid clotting or haemolysis of the red blood cells. Blood slides were air dried.
in slide folders and then placed in a slide box for transportation to the laboratories at Kisian. The EDTA tubes were stored in cool-boxes (Temp 5°C) and transported every afternoon to the CDC/KEMRI laboratories at Kisian.

2.3.3 Laboratory methods

A full blood count, including repeat haemoglobin measured in g/dl was determined immediately using a Coulter Counter machine (Coulter Corporation, Miami, FL). Blood slides were stained using Giemsa solution and examined under a microscope for the presence of malaria parasites, and expressed as the number of asexual parasites counted against 500 white blood cells (WBCs); parasite densities were calculated assuming 8,000 WBCs/μl.

2.4 DATA MANAGEMENT AND ANALYSIS

The data were coded and double entered into the computer using custom designed data entry screens (created using Visual FoxPro® software) with built-in range and error checks. Running logical checks and making error listings completed the data cleaning process.

Differences in means of continuous variables were assessed using the Paired Student’s t-test. The Paired Student’s t-tests were carried out to establish whether there were significant differences in the values of parasite densities and levels of haemoglobin within the study subjects for those children who participated in both the baseline and follow-up surveys.
Differences in rates of changes over time were assessed using repeated measures analysis. The models constructed incorporated longitudinal data analysis techniques (generalized estimating equations) (SAS Institute, Cary, NC). Treatment effects were the use of ITBNs for a period of ≥3 years and the use of ITBNs for a period of ≤1 year. Study subjects were the children using the ITBNs. The covariates were clinical malaria and malarial anaemia. Age was categorized into groups and the models were controlled for age. Appropriate covariance structures were built into the models to allow for the correlation that exists between repeated measures over time for the same individual and adjusted odds ratios (OR) obtained with 95% confidence intervals (CI). All statistical analysis was carried out using the SAS® 6.12 system (SAS Institute, Cary, NC).
CHAPTER 3: RESULTS

3.1 DEMOGRAPHIC INFORMATION FOR THE SURVEYS IN 1999 AND 2000

Out of the 1,347 children under 5 years of age who took part in the baseline survey in June 1999, 1,055 children were traced and came for the follow-up survey in May 2000. As at the time of the follow-up survey, 41 children (3.0%) of the baseline sample had died, while 222 (16.5%) were not found in the study area and 29 (2.2%) did not show up. Due to missing blood samples for 2 children, the final sample size for the survey decreased to 1,053. Children aged 1 year old constituted the smallest proportion (1.5%), whereas the 3 to 5 years age group contributed the largest proportion (40.3%) (Table 1). A total of 487 (46.2%) children had used ITBNs for a period of ≥3 years, whereas 566 (53.8%) children had used ITBNs for a period of ≤1 year.
Table 1: DEMOGRAPHIC INFORMATION FOR THE BASELINE AND FOLLOW-UP SURVEYS

<table>
<thead>
<tr>
<th>SURVEY</th>
<th>CHILDREN IN BASELINE IN 1999</th>
<th>CHILDREN IN FOLLOW-UP IN 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study subjects</td>
<td>1,347</td>
<td>1,053</td>
</tr>
<tr>
<td>Females</td>
<td>710 (52.7)</td>
<td>555 (52.7)</td>
</tr>
<tr>
<td>Males</td>
<td>637 (47.3)</td>
<td>498 (47.3)</td>
</tr>
<tr>
<td>Age groups (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 11</td>
<td>349 (25.9)</td>
<td>16 (1.5)</td>
</tr>
<tr>
<td>12 to 23</td>
<td>273 (20.3)</td>
<td>252 (23.9)</td>
</tr>
<tr>
<td>24 to 35</td>
<td>262 (19.5)</td>
<td>201 (19.1)</td>
</tr>
<tr>
<td>36 to 59</td>
<td>463 (34.4)</td>
<td>425 (40.3)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>-</td>
<td>159 (15.1)</td>
</tr>
</tbody>
</table>

Note: Values are frequencies and (percentages).
3.2 CHARACTERISTICS AND HEALTH STATUS OF CHILDREN IN 1999 AND 2000

A significant decrease was observed in the mean parasite density from 4,759 par/μl in 1999 to 4,267 par/μl in 2000 (paired t-test; $t = -3.89$; $P=0.0001$), whereas the mean haemoglobin level significantly increased from 10.1g/dl to 10.4g/dl (paired t-test: $t = 4.52$; $P<0.0001$), $N=1,053$ (Table 2). There was a significant decline in the proportion of children who presented with the following malaria morbidity indicators: a positive smear for malaria (63.1% to 55.6%); clinical malaria (as defined by Bloland et al., 1999) (23.5% to 20.3%); malarial anaemia (defined as Hb <11g/dl) (46.5% to 35.1%) and moderate to severe malarial anaemia (defined as Hb <7g/dl) (6.0% to 2.7%).
Table 2: CHARACTERISTICS OF CHILDREN AT THE BASELINE AND FOLLOW-UP SURVEYS

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CHILDREN IN BASELINE IN 1999</th>
<th>CHILDREN IN FOLLOW-UP IN 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some parasitaemia</td>
<td>826 (63.1)</td>
<td>585 (55.6)</td>
</tr>
<tr>
<td>Clinical malaria</td>
<td>306 (23.5)</td>
<td>214 (20.3)</td>
</tr>
<tr>
<td>Anaemia (Hb &lt;11 g/dl)</td>
<td>626 (46.5)</td>
<td>370 (35.1)</td>
</tr>
<tr>
<td>Mod.-severe Anaemia (Hb &lt;7 g/dl)</td>
<td>81 (6.0)</td>
<td>27 (2.7)</td>
</tr>
</tbody>
</table>

Note: Values are frequencies and (percentages).
3.2.1 Clinical malaria at baseline in 1999

The greatest burden of the disease (expressed as the percentage of all cases of clinical malaria in a specific age group of children) was observed in the 12 to 17 months old age group for both the children who had used bednets for a period of ≥ 2 years and those for a period of ≤ 1 year. This was especially evident (over 22% of all cases) for those children who had used bednets for a period of ≥ 2 years. The burden of disease increased slightly in successively older age groups, from around 5% in the 24 to 29 months old age group up to 7% in the 54 to 59 months old age group, after which it decreased sharply to 3% in the 60 to 65 months old age group. It was generally lower for those children who had used bednets for a period of ≥ 2 years (Fig 2).
Figure 2: BURDEN OF CLINICAL MALARIA IN CHILDREN AT BASELINE IN 1999

Proportion of all cases of clinical malaria in a specific age group [%]

Age groups of children [months]

- ITBNs for >2 years
- ITBNs for <1 year
3.2.2 Clinical malaria at follow-up in 2000

The burden of disease followed a similar trend to that observed in the baseline survey in 1999. It was relatively high at 6.5% for children in the 18 to 23 months old age group, who had used bednets for a period of $\leq 1$ year. Then, it gradually increased with successively older age groups, from around 5% in the 24 to 29 months old age group up to 7% in the 60 to 65 months old age group, after which it declined steeply to 2% in the 72 to 77 months old age group. It was generally lower for the children who had used bednets for a period of $\leq 1$ year (Fig 3).
Figure 3: BURDEN OF CLINICAL MALARIA IN CHILDREN AT FOLLOW-UP IN 2000

Proportion of all cases of clinical malaria in a specific age group [%]

Age groups of children [months]

- ITBNs >3 years
- ITBNs <1 year
3.2.3 Malarial anaemia at baseline in 1999

The burden of the disease was expressed as the percentage of all cases of moderate to severe malarial anaemia in a specific age group of children. The greatest burden, 15% was observed in the 12 to 17 months old age group. The age distribution of the burden of disease at the baseline survey was evidently skewed to the right, with the highest values of 10% and 15% observed among younger children in the 12 to 17 months old age group and the 24 to 29 months old age group respectively. Whereas, the lowest values of around 2% were observed among the older children between the 36 to 65 months old age groups, and they were generally lower for those children who had used bednets for a period of <1 year (Fig 4).
Figure 4: BURDEN OF MALARIAL ANAEMIA (Hb <7 g/dl) IN CHILDREN AT BASELINE IN 1999

Proportion of all cases of malarial anaemia in a specific age group [%]

Age groups of children [months]

- ITBNs >2 years
- ITBNs <1 year
3.2.4 Malarial anaemia at follow-up in 2000

The greatest burden of the disease at 25% was observed in the 18 to 23 months old age group for children who had used bednets for a period of ≤1 year, while the same burden of 25% was also observed in the 24 to 29 months old age group for children who had used bednets for a period of ≥3 years. The age distribution of the burden of disease was leptokurtic, with peak values of 25% as previously observed and then it rapidly declined to around 5% in the 30 to 35 months old age group (Fig.5).
Figure 5: BURDEN OF MALARIAL ANAEMIA (Hb <7 g/dl) IN CHILDREN AT FOLLOW-UP IN 2000

Proportion of all cases of malarial anaemia in a specific age group [%]

Age groups of children [months]

ITBNs >3 years  ITBNs <1 year
3.2.5 Mean values of haemoglobin levels at baseline in 1999

The mean values of haemoglobin levels at baseline decreased sharply from 11g/dl in the 6 to 11 months old age groups down to 9g/dl in the 12 to 17 months old age groups in both categories of children with differing periods of bednet use. The lowered levels were maintained across the 12 to 29 months old age groups, after which they gradually rose back to around 11g/dl and stabilized at that level. Though, the trend was similar in both categories of children, it was observed that the levels were about 1g/dl higher for the children who had used ITBNs for a period of \( \geq 2 \) years, than for those who had used ITBNs for a period of <1 year (Fig. 6).
Figure 6: MEAN VALUES OF HAEMOGLOBIN LEVELS IN CHILDREN AT BASELINE IN 1999

The mean values of haemoglobin levels in children at baseline in 1999 are presented in the figure. The levels are shown for different age groups of children (months) and are distinguished by age groups (ITBNs > 2 years and ITBNs < 1 year). The haemoglobin levels generally decrease as the age of the children increases, with levels being higher in younger children. There is a noticeable increase in haemoglobin levels among the 42 to 50 months old age group, with levels being significantly higher, by around 0.5 g/dl, for those who had used...
3.2.6 Mean values of haemoglobin levels at follow-up in 2000

In the follow-up survey, a sharp increase in haemoglobin levels from around 9g/dl up to 10g/dl was observed. This increase was relatively rapid, between the 18 to 23 and 24 to 29 months old age groups for the children who had used ITBNs for a period of \( \leq 1 \) year, while it was more gradual, between the 18 to 23 and 30 to 35 months old age groups for those who had used ITBNs for a period of \( \geq 3 \) years. The levels of haemoglobin for the older children rose gradually up to around 11g/dl. It was noted, that those levels among the 42 to 59 months old age groups were slightly higher, by around 0.5g/dl for those who had used ITBNs for a period of \( \leq 1 \) year (Fig. 7).
Figure 7: MEAN VALUES OF HAEMOGLOBIN LEVELS IN CHILDREN AT FOLLOW-UP IN 2000

Age groups of children [months]

<table>
<thead>
<tr>
<th></th>
<th>ITBNs &gt;3 years</th>
<th>ITBNs &lt;1 year</th>
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<tbody>
<tr>
<td>6 to 12</td>
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<td>13 to 18</td>
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<td>31 to 36</td>
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<td>37 to 42</td>
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<td>49 to 54</td>
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<td>55 to 60</td>
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<td>61 to 66</td>
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<td>67 to 72</td>
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<tr>
<td>73 to 77</td>
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</tbody>
</table>
3.3 MIXED LONGITUDINAL ANALYSIS OF THE IMPACT OF ITBNS ON MALARIA SPECIFIC MORBIDITY BETWEEN CHILDREN WHO HAD USED BEDNETS FOR PERIODS OF ≤1 YEAR AND ≥3 YEARS.

Repeated measures analysis performed while controlling for age, showed the following; clinical malaria (OR=0.99; 95% CI 0.97 to 1.00), moderate to severe malarial anaemia (OR=0.97; 95% CI 0.95 to 0.98), and haemoglobin levels <7g/dl (OR=0.96; 95% CI 0.95 to 0.97). None of the ORs observed were significant or important, so basically there was no difference between the two groups of children.
CHAPTER 4: DISCUSSION

The long-term effects of sustained use of ITBNs in endemic areas of intense perennial malaria transmission is still an open question. Long-term controlled bednet trials have not been carried out, for obvious ethical reasons, and also due to concerns that in the long run, the ITBNs may merely lead to an increase in mortality and morbidity in the older age groups of children (Snow et al., 1997; Snow and Marsh, 1998; Trape and Rogier, 1996). The reason for expecting such a rebound in mortality and morbidity is that sustained reduction to exposure may delay the development of naturally acquired immunity, which is gradual and depends on exposure to infective mosquitoes (Brinkmann and Brinkmann, 1991).

Furthermore, an ecological comparison of five study sites in The Gambia and Kenya with different transmission conditions, showed that the risk of malaria morbidity was highest in the areas with moderate unstable malaria transmission and lowest in the areas of stable malaria transmission (Snow et al., 1997). Therefore, this study was carried out to shed some light on the issue raised above.
4.1 PREVALENCE AND AGE DISTRIBUTION OF CLINICAL MALARIA AMONG STUDY SUBJECTS FOLLOWING THE SUSTAINED USE OF ITBNs FOR A PERIOD OF ≤1 YEAR OR ≥3 YEARS

It was noted that the use of ITBNs, even for a period of ≤1 year, was beneficial especially for children <2 years old. The study revealed modest but significant reductions in the prevalence of clinical malaria within the subjects from 1999 to 2000. It was observed that the prevalence of clinical malaria was several times higher in children aged >1 year if compared to those aged <1 year. These findings are consistent with those of earlier studies in Southwestern Tanzania covering Kilombero and Ulanga Districts, which are areas of intense perennial malaria transmission (Fraser-Hurt et al., 1999; Abdulla et al., 2001). Another study in Tanzania, in Bagamoyo District, where malaria is holoendemic, also found similar results (Premji et al., 1995).

Greater reductions have been observed in areas of low to moderate and seasonal malaria transmission. These include studies in The Gambia, Burkina Faso and Tanzania, where reductions of up to 60% were reported (Carnevale et al., 1991). A study under conditions of seasonal malaria transmission in The Gambia reported a 45% reduction in the prevalence of fever associated with malaria parasitaemia (D'Alessandro et al., 1995). From the above discussion it would seem that the impact of using ITBNs in areas of low to moderate and seasonal malaria transmission leads to remarkable reductions in the prevalence of clinical malaria, while their use in areas of intense perennial malaria
transmission results in relatively lower reductions in the prevalence of clinical malaria.

However, in spite of the reductions within the study subjects, the adjusted ORs after controlling for age did not show any significant difference in the prevalence and age distribution of clinical malaria between the two groups of children. These findings imply that the protective effect of ITBNs continued to have a beneficial impact if their use was sustained for a period of ≥3 years from infancy.

### 4.2 PREVALENCE AND AGE DISTRIBUTION OF MODERATE TO SEVERE MALARIAL ANAEMIA AMONG STUDY SUBJECTS FOLLOWING THE SUSTAINED USE OF ITBNS FOR A PERIOD OF ≤1 YEAR OR ≥3 YEARS

The study found that there was a significant reduction in the prevalence of moderate to severe malarial anaemia among the study subjects. These findings agree with those of a 2 year study carried out under similar conditions of intense perennial malaria transmission in Tanzania. The study reported that the prevalence of malarial anaemia had decreased from 49% to 26%. It also, showed that the use of ITBNs by children under 2 years old had a substantial positive impact on malaria specific morbidity (Abdulla et al., 2001). Another study in the same area, Kilombero District in Tanzania, showed that the use of ITBNs for a period of 6 months reduced the risk of malarial anaemia in highly exposed young children (Fraser-Hurt et al., 1999). A study in the coastal region of Tanzania, which is an area of intense malaria transmission with marked seasonal variations, found a 54% reduction in
the prevalence of malarial anaemia among young children (Premji et al., 1995). Similar findings were reported in Ghana (Binka et al., 1996), and Burkina Faso (Habluetzel et al., 1997), where malaria transmission was highly seasonal. This impact is of great importance because in endemic areas with high perennial transmission, like the study area, many children die from severe malarial anaemia. It becomes extremely important that infants and children <2 years of age are protected by using ITBNs because as the study showed, these children bear the greatest burden of the disease. Though, age adjusted ORs did not show any significant difference in the prevalence and age distribution of moderate to severe malarial anaemia between the two groups of children.

4.3 HAEMOGLOBIN LEVELS OVER A PERIOD OF 1 YEAR IN STUDY SUBJECTS WHO SUSTAINED THE USE OF ITBNS FOR A PERIOD OF ≤1 YEAR OR ≥3 YEARS

In the follow-up survey, it was noted that the observed increase in haemoglobin levels within the study subjects was more significant for the <2 year olds who used ITBNs for a period of ≤1 year. Similar findings were reported by a study in Tanzania, which investigated the first 6 months of ITBN use under comparable transmission settings (Fraser-Hurt et al., 1999). A 2 year study in the same region of Tanzania also found that the use of ITBNs by children <2 years of age resulted in a significant increase in haemoglobin levels (Abdulla et al.,
2001). Another study in The Gambia, under intense seasonal malaria transmission reported similar findings (D'Alessandro et al., 1995).

It was possible that the higher levels of haemoglobin observed among those children could have been a consequence of their better developed immunity, due to high exposure to infective mosquito bites before they started to use bednets. Such children may have responded more rapidly to the protective effect of using bednets, than children who had continued to use ITBNs for a period of ≥3 years since infancy and had been less exposed to the malaria parasite. These significant increases in haemoglobin levels are an important finding because they show evidence of the positive impact of the continued use of ITBNs on malaria specific morbidity (Snow et al., 1997; Nevill et al., 1996).

Although, all the children who participated in the study used ITBNs regularly, 20% were reported as having had clinical malaria. This shows that the continued use of ITBNs greatly reduced transmission but did not eliminate it completely. This observation is important, as it has implications for the development of partial immunity to malaria, which depends on exposure to the parasite. One of the questions that need further investigation, is whether the persistent level of malaria transmission observed would be sufficient to allow the timely development of naturally acquired immunity to the disease.

In summary, the findings of this study provide evidence of the beneficial effects of the continued use of ITBNs from infancy up to a period of at least 3 years, and more importantly the study did not find significant
evidence to suggest any increase in malaria specific morbidity in the older age groups of children due to the sustained use of ITBNs.
CHAPTER 5: SUMMARY OF CONCLUSIONS

a) There was an overall decline in the prevalence of clinical malaria for the children who had used ITBNs for a period of ≤1 year.

b) There was an overall decrease in the prevalence of moderate to severe malarial anaemia with the reduction being more significant for the children who had sustained the use of ITBNs for a period of ≥3 years, than for those children who had used ITBNs for a period of ≤1 year.

c) The study showed that there was an overall increase in the levels of haemoglobin, that the increase was more significant for the children who had used ITBNs for a period of ≤1 year, than for those children who had sustained the use of ITBNs for a period of ≥3 years, and that the most substantial increment of haemoglobin levels was noted among the <2 years age groups.

d) There was no compelling evidence of a shift of the burden of clinical malaria towards older children, for those who had used ITBNs for a period of ≥3 years.

e) The study also found that despite the sustained use of ITBNs, there was a certain level of malaria transmission that persisted.
6.1 RECOMMENDATIONS

a) The sustained use of ITBNs for periods of ≥3 years should be encouraged as an effective method for malaria control in childhood in endemic areas of intense perennial transmission.

b) The sustained use of ITBNs from birth should be encouraged in order to boost child survival among children <2 years of age in endemic areas of intense perennial transmission.

6.2 SUGGESTIONS FOR FUTURE RESEARCH WORK

Clinic-based cohort studies should be undertaken in order to determine the prevalence of severe malarial anaemia (Hb <5g/dl) and cerebral malaria among children who have sustained the use of ITBNs for periods of ≥3 years.
REFERENCES


Fraser-Hurt, N.; Felger I.; Edoh D.; Steiger S.; Mashaka M.; Masanja H.; Smith T.; Mbenza F. and Beck H.P. (1999). Effect of insecticide-


vectors of the Kenyan coast. *Medical and Veterinary Entomology, 10*: 251-259.


APPENDIX I

Written informed consent form

KEMRI and CDC are doing research to learn how insecticide treated bednets improve the health of young children in Asembo. The first part of the bednet study has ended and houses in round 2 villages have also been given bednets. For the next two years CDC/KEMRI will continue to study the health of children sleeping under bednets. As part of this study, we conducted a study in June 1999 to find out how much bed nets impact on the health of children under five years of age. We will conduct two more surveys in your village to look at how the impact of bed nets changes over time. The follow-up survey will be done in May/June of 2000. We will conduct a physical exam and ask questions about your child’s health. The exam will last approximately one half hour. Your child previously participated in the first survey; we are now asking him or her to participate in the next health survey.

If you agree to take part in the survey, we will ask about your child’s health and vaccination status. A staff member will also look at your child’s health and measure his or her height, weight and arm size and see if he or she has fever. We will also take a few drops of blood by pricking the child's finger or heel. We will take approximately 1/4 teaspoon (about 1 ml) of blood. The amount of blood we will take is very small and so no harm will come to anyone who agrees to be in the study. We will also ask you to provide a little bit of stool from your child.

We will test your child’s blood sample for malaria and lack of blood. If your child has malaria or lack of blood, we will treat your child free of charge. The blood sample will also be used in lab studies to see how your body fights against malaria, and we will test for genes that can affect how well your body does this, like sickle cell genes. We want to know if bednets change the parasites that cause malaria. We also want to know if your child has sickle cell trait as it can protect your child against malaria. If your child has sickle cell trait, we will inform you. We will not test any samples for HIV/AIDS. We will test your child’s stool for worms that can cause low blood or affect how your body fights malaria. If your child has worms in his/her stool, we will treat your child. We would also like to test your child’s stool at CDC to learn about the kinds of bacteria that are found in the stools of residents in this area.

There may be a small bruise or temporary mild pain on the finger or heel where the blood is taken. There is also a small chance of infection when blood is drawn. However, our careful procedures make this very unlikely. If there is any problem from the finger prick or a severe reaction to the malaria drug treatment, we will provide transport to the Hospital. In the hospital we will treat you free of charge. No such incident has occurred to any child since the beginning of the study in June 1992.

Your children will likely benefit from taken part in this study. First, your child will be given a health check by a clinical officer. All lab tests, and treatments are free of charge.

You are free to choose for you and your child to be part of this study. You have the right to refuse. If anyone does not want to go on with this study they can stop at any time. They will still get any benefits they would have gotten otherwise, such as treatment at the clinics. The facts we collect in the study and the result of the lab tests will be kept private to the extent allowed by law. Your name and your child's name will not be used on any of the study reports or study samples. If you do not want your child to participate in this study, your child can still be tested and treated for malaria or lack of blood at a hospital or dispensary. However, these facilities will charge you for the tests and any medication.
Should any questions arise, or if you want to quit the study, please contact Dr. Kim or Mr. Frank Odhiambo, in the CDC office in Asembo. If you have any questions about your rights as a study patient, or if you want to talk about the study with someone who is not part of this research project, please contact Dr. Margaret Oloo. Dr. Oloo is a special doctor for children and is not part of the study. You can also contact Dr. Margaret Oloo if you think your child has been injured because of this study. She works in the Aga Khan Hospital in Kisumu and can be reached by phone. The phone number is 035 41031.

**Today's study:** The above has been explained to me and I agree for my child to take part in the study. I understand that I am free to choose for my child to be in this study and that saying "NO" will have no effects for me or my child. I agree for my child's blood to be tested for malaria, lack of blood and factors which may protect against malaria or lack of blood. This includes inborn factors like sickle cell trait.

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<thead>
<tr>
<th>If you agree, circle “YES,” if you do not agree, circle ‘NO’.</th>
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<tbody>
<tr>
<td><strong>YES</strong></td>
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<tr>
<td><strong>NO</strong></td>
</tr>
</tbody>
</table>

We also would like to send your child's blood to the CDC in the US and store the blood for several years. We would like to use this blood to do additional studies on how your child's body protects itself against malaria. We would like to test your child's blood for genes other than sickle cell trait that affect malaria. We will only test for genes that are known to affect malaria. If we get any results from these lab studies that may affect the health of your child, we will inform you. We may also test for other infections.

If you do not agree to have your child's blood stored for genetic testing, we will destroy the sample after we have tested it in Kenya. If, at any time, you wish to withdraw your agreement, please contact Mr. Frank Odhiambo and we will destroy the sample. If you do not wish to have your child's blood stored for genetic testing, your child may still participate in our cross sectional survey. Your child will still be examined for malaria and lack of blood. If your child has malaria or lack of blood, we will still treat your child.

**Long term storage and future studies:** I agree for CDC-KEMRI to store my child's blood for future studies of factors which may protect against malaria and lack of blood. I understand that if any test results are found that are important for my child's health, CDC/KEMRI will try to report this to me, if possible. I understand that I have the right to withdraw my agreement to use my child's blood for future research anytime and for any reason. I may also ask that my child's blood not be used for certain types of testing. To do this, I may tell Mr. Frank Odhiambo of my request and he will tell the study people at CDC/KEMRI.

<table>
<thead>
<tr>
<th>If you agree, circle “YES,” if you do not agree, circle ‘NO’.</th>
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<tbody>
<tr>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
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</tbody>
</table>

**Genetic test:** I agree to have testing on my child's blood for inborn factors like sickle cell trait.

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<thead>
<tr>
<th>If you agree, circle “YES,” if you do not agree, circle ‘NO’.</th>
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<tbody>
<tr>
<td><strong>YES</strong></td>
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<tr>
<td><strong>NO</strong></td>
</tr>
</tbody>
</table>

**Parent/Guardian**

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
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<tr>
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</table>

**Witness**

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
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</table>

*A parent can sign, or verbally state his/her consent in the presence of a witness who will then sign.*
APPENDIX II
Questionnaire

Bednet Cross-Sectional Survey May-June 2000
Registration and Clinical Form

Part 1: Registration

1.01 Today's date (day/month/year)

1.02 Village/Comp, House

1.03 Relationship of person accompanying the child today (1= mother, 2= father, 3= grandparent, 4= aunt, 5= co-wife, 6= sibling, 7= other)

1.04 Is the birth mother of this child alive now? Y/N

1.05 If no, did she die within the last year? Y/N

1.06 Is the father of this child alive now? Y/N

1.07 If no, did he die within the last year? Y/N

1.08 Mother's name (natural mother)

Christian name

Juok name

Mother's clan

Clan name

Date of birth

Mother's age (years)

1.09 Husbands juok name

1.10 Husband's clan name

1.11 Child's name

Christian name

Juok name

Child's OOB

1.12 Mother's date of birth

1.13 Father's date of birth

1.14 Child's age

1.15 Child's sex

1.16 Father's sex

1.17 Child's DOB (If not known, copy from the list)

1.18/1.19 Child's age

1.20 Sex of child (M/F)

1.21 Where does child normally sleep?

(1= bedroom 2= kitchen 3= sitting room 4= other 5= DK)

1.22 Do you have a net in the house? Y/N

1.23 If yes; is it the green bednet supplied by CDC/KEMRI project? Y/N

Part 2: Vaccinations

If child is 24 months or older, go to 3.01

2.01 Has this child been vaccinated against childhood diseases? Bende nyatho oseypudo chanjo?

2.02 Where did the child go for his/her last vaccination?

(1= Abidha 2= Ong'ielo 3= Lwak 4= Saradidi 5= Ndori 6= Gobei 7= Nyagok 10= Rarieda 11= Masala 12= Komolo 13= Bondo 14= Rakoyo 15= Mahaya 16= Other 17= NA)

2.03 Do you have the vaccination card/booklet? Y/N

2.04 BCG vaccine (at birth)

Date (day/month/year) if the exact dates are not known fill in the year and if possible the month

2.05 Polio vaccine (at birth)

2.06 DPT 1/OPV1 (Polio) (at around 6 weeks)

2.07 DPT 2/OPV2 (Polio) (at around 10 weeks)

2.08 DPT 3/OPV3 (Polio) (at around 14 weeks)

2.09 Measles (at around 9 months)
Part 3: Symptoms of illness of survey child reported by caretaker

Is this child ill now? (If yes: continue with 3.02. If no: go to 3.03)

Does this child have a fever now? (Let the caretaker feel the child)

Including today has the child been ill during the past two weeks? (If no: go to 3.09)

How does caretaker consider the severity of that illness? (1=none, 2=mild, 3=moderate, 4=life threatening, 5=don't know)

Self reported symptoms over the past 2 weeks

Only write in Dholuo - do not translate into English

Probe for symptoms in past 2 weeks

During the past two months (not weeks) ago did the child have any of the following illness? (Y/N/D)
### Part 4: Health Care Seeking and Treatment

#### If child has not been ill in the last 2 weeks, go to 5.01

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No/Don't Know</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.01 Was the child taken anywhere to seek health care or get medicine in the last 2 weeks?</td>
<td>Y/N</td>
<td>D/K</td>
</tr>
<tr>
<td>4.02 Where was child taken first? (1=private clinic 2=health centre/dispensary 3=hospital IPD [admitted] 4=hospital OPD 5=traditional healer/herbalist 6=bush doctor 7=shop/duka/chemist 8=CHW/nyamrerwas 9=market vendors/hawkers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.04 Was the child given any traditional medicine or any western/conventional medicine from this visit? (1=traditional medicine 2=western medicine 3=no medicine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.06 Medicine 1</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>4.08 Medicine 3</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>4.10 Where was child taken next? (1=private clinic 2=health centre/dispensary 3=hospital IPD [admitted] 4=hospital OPD 5=traditional healer/herbalist 6=bush doctor 7=shop/duka/chemist 8=CHW/nyamrerwas 9=market vendors/hawkers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.12 Was the child given any traditional medicine or any western/conventional medicine from this visit? (1=traditional medicine 2=western medicine 3=no medicine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.14 Medicine 1</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>4.16 Medicine 3</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

#### Part 5: Clinical Examination (Village Monitors)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No/Don't Know</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.01 Breathing frequency / 60 sec (count for one full minute)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>5.02 Increased work of breathing? (N=none, M=mild, S=severe)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>5.03 Palm pallor (N=none, M=mild/moderate, S=severe)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>5.04 Eyelid pallor (N=none, M=mild/moderate, S=severe)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>5.05 Tongue pallor (N=none, M=mild/moderate, S=severe)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>5.06 Nail pallor (N=none, M=mild/moderate, S=severe)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
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</table>

#### Part 6: Clinical measurements (Gestational Age Nyamrerwas)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No/Don't Know</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.01 Weighing scale number</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.02 Height board number</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.03 Weight I (kg)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.04 Length/height I (cm)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.05 Weight II (kg)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.06 Length/height II (cm)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.07 MUAC I (cm)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.08 Axillary temperature I (°C) (under the arm-pit)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.09 MUAC II (cm)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>6.10 Axillary temperature II (°C) (under the arm-pit)</td>
<td>✔️</td>
<td>✔️</td>
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</table>
### Part 7: Clinical Examination (Clinical Officer)

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<tbody>
<tr>
<td>7.01</td>
<td>Does the child seem ill? (1=no, 2=mild, 3=moderate, 4=life-threatening)</td>
<td></td>
<td></td>
<td>Del maroumho/gwonyo (evidence of insect bite rash/scabies on lower arms or legs?)</td>
</tr>
<tr>
<td>7.02</td>
<td></td>
<td></td>
<td></td>
<td>Y/N/D</td>
</tr>
<tr>
<td>7.03</td>
<td>Skin (1=normal, 2=thin)</td>
<td></td>
<td></td>
<td>Visible severe wasting? (Wasted buttocks or bony thorax structure)</td>
</tr>
<tr>
<td>7.04</td>
<td></td>
<td></td>
<td></td>
<td>Y/N/D</td>
</tr>
<tr>
<td>7.05</td>
<td>Evidence of BCG scar</td>
<td>Y/N/D</td>
<td></td>
<td>Hair colour (1=normal, 2=light)</td>
</tr>
<tr>
<td>7.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.07</td>
<td>Hair texture (1=normal, 2=thin)</td>
<td></td>
<td></td>
<td>Oedema in both feet? (1=none, 2=mild, 3=severe)</td>
</tr>
<tr>
<td>7.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.09</td>
<td>Spleen (Hacket score) (0,1,2,3,4)</td>
<td></td>
<td></td>
<td>Any handicaps? (1=no 2=congenital malformation 3=blind 4=deaf 5=crippled 6=mental handicap)</td>
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<tr>
<td>7.10</td>
<td></td>
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Please indicate all diagnoses requiring treatment, other than malaria and anaemia.

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<tbody>
<tr>
<td>7.11</td>
<td>Other diagnosis 1</td>
<td></td>
<td></td>
<td>Other diagnosis 2</td>
</tr>
<tr>
<td>7.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.13</td>
<td>Other diagnosis 3</td>
<td></td>
<td></td>
<td>Other diagnosis 4</td>
</tr>
<tr>
<td>7.14</td>
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### Part 8: Hb and Medication given by Clinical Officer

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</thead>
<tbody>
<tr>
<td>8.01</td>
<td>Hb result field</td>
<td></td>
<td></td>
<td>Fansidar</td>
</tr>
<tr>
<td>8.02</td>
<td></td>
<td></td>
<td></td>
<td>Y/N</td>
</tr>
<tr>
<td>8.03</td>
<td>Amodiaquine</td>
<td></td>
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### Quality Control

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</thead>
<tbody>
<tr>
<td>Supervisor</td>
<td>Date</td>
<td></td>
<td>Name</td>
</tr>
<tr>
<td>Data Entry Clerk</td>
<td></td>
<td></td>
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</tbody>
</table>
Title: Effects of sustained use of insecticide-treated bednets on malaria specific morbidity in childhood in Asembo, Rarieda Division, Bondo District western Kenya.

By

Frank Ouma Odhiambo (BSc.Hons)
156/8778/99

Supervisors: Prof. Alloys S.S. Orago, Kenyatta University and Dr. Kim Lindblade, CDC/KEMRI, Kisumu.

ABSTRACT
Malaria is a major global public health problem. Around 300-500 million cases of clinical malaria are reported annually with 1.4-2.6 million deaths, mainly among African children. Insecticide treated bed nets (ITBNs) have proven effective in reducing exposure to malaria parasites. There is concern that sustained reduction in exposure from birth in endemic areas may result in a shift in the age and disease spectrum from severe anaemia in younger children towards cerebral malaria in older ones. Such a shift may lead to a paradoxical rise in disease risk throughout childhood. The objective of the study was to determine whether the sustained use of ITBNs in an area of intense perennial transmission results in a shift in the age and disease spectrum of malaria with reference to parasite densities and haemoglobin levels. The study area included 60 villages in Asembo, Rarieda Division, Bondo District, western Kenya. A follow-up cross-sectional survey was conducted in May 2000. The study subjects included 1,055 children <6 years old who were traced from a total of 1,347 children who participated in the baseline survey done in June 1999. Signs and symptoms of malaria were recorded and blood samples assessed. The mean value of haemoglobin levels rose from 10.1g/dl to 10.4g/dl, whereas the geometric mean of parasite densities declined from 4,759par/µl to 4,267 par/µl, prevalence of clinical malaria (23.5% to 20.3%) and moderate to severe malarial anaemia (6.0% to 2.7%) also declined. The results of the study demonstrated that the effects of the sustained use of ITBNs in childhood, in a holoendemic area of intense perennial transmission were significantly beneficial and did not increase malaria specific morbidity.