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AN OPEN LABEL, RANDOMISED AND PARALLEL-GROUP CLINICAL TRIAL ON ASSESSMENT OF ANTI-MALARIA EFFICACY AND SAFETY OF COTECXIN® (DIHYDROARTEMISININ) SUSPENSION COMPARED TO AMODIAQUINE SUSPENSION IN THE TREATMENT OF CHILDREN WITH ACUTE, UNCOMPLICATED MALARIA IN KENYA

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# AN OPEN LABEL, RANDOMISED AND PARALLEL-GROUP CLINICAL TRIAL ON ASSESSMENT OF ANTI-MALARIA EFFICACY AND SAFETY OF COTECXIN® (DIHYDROARTEMISININ) SUSPENSION COMPARED TO AMODIAQUINE SUSPENSION IN THE TREATMENT OF CHILDREN WITH ACUTE, UNCOMPLICATED MALARIA IN KENYA

A.O. ANISA

## ABSTRACT

*Background:* This was a clinical trial conducted in the period between January 23rd 2005 and February 27th 2006 at Malindi District Hospital.
*Objectives:* To assess the anti-malaria efficacy and safety of Cotecxin® (dihydroartemisinin) in comparison with amodiaquine equivalent study. The main study variables were treatment of malaria by using Cotecxin® (dihydroartemisinin) and amodiaquine suspensions.
*Subjects:* Children equal to or less than six years with clinical symptoms of malaria: falciparum parasite asexual form more than or equal to 1000/ ml with high fever.
*Design:* Multicentre randomised open-label study in two parallel groups.
*Methods:* Patients complying with inclusion criteria were randomised and received either Cotecxin® (dihydroartemisinin) or amodiaquine suspension. The dose was determined by the weight of the child, which was given between three to seven days. A total of 120 children were sampled from the entire population of malaria cases. The tools used in the study were case report form in which all treatment episodes of malaria was recorded by the clinicians treating the malaria patients as they came. Patient treatment was closely monitored using laboratory tests of ASAT/ALAT. Patient's temperature was taken before and after the treatment. Drug safety was closely monitored. All the 120 (100%) patients gave written consent to participate in the study. All the patients met the criteria as indicated in the methodology and study protocol. The mean age was 36.3 months, standard deviation 16.8704. Male participants were 57.5% and females 42.5%.
*Results:* None of the patients had taken anti-malarial drugs before the study began. The study also found out that no patient presented with malaria on concomitant diseases. There was no relationship between abnormalities detected during physical examination and the drug taking at $P<0.05$ c 9.230 df 8. After one day of taking the drugs, one or 1.67% of the patients treated with amodiaquine developed skin rash. No patient had rash after taking Cotecxin® (dihydroartemisinin). There was decrease in appetite and episodes of vomiting after taking both drugs. Nausea was observed more among patients who took amodiaquine 36.7% than those who took Cotecxin® (dihydroartemisinin) 15.3%. Twenty out of a hundred and twenty patients (16.7%) were discontinued from the study due to drug resistance, re-infection and follow-up problems. In conclusion, both drugs treated malaria but amodiaquine had more side effects than Cotecxin® (dihydroartemisinin). The study revealed that Cotecxin® (dihydroartemisinin) was more safe and effective than amodiaquine. It is therefore recommended that Cotecxin® dihydroartemisinin) be used as a first line drug for the treatment of acute, uncomplicated malaria in children aged six years and below.

## INTRODUCTION

Malaria is a febrile disease caused by infection of red blood cells (RBCs) by protozoal organism of the genus *Plasmodium*. Infection causes acute and chronic types of fever, anaemia and spleen enlargement. Infection sometimes causes severe disorders of the brain, kidneys, liver and other parts of the body (1,2).

Malaria is a life-threatening disease transmitted from person to person. Human malaria is a parasitic disease caused by infection with one or more of some four *Plasmodial* species namely *P.falciparum*, *P. vivax*, *P. malariae* and *P. ovale* (2,3). The parasite is transmitted to human beings by the bite of an infected female mosquito of the genus *Anopheles* (4), which inoculates *plasmodium* at the time of feeding (2). However induced malaria may be transmitted by inoculation of fresh blood contaminated with malaria parasite or by transfusion of contaminated blood or blood products (5).

The disease exerts its heaviest toll in Africa, where around 90% of the more than one million deaths from malaria worldwide occur each year; this constitutes 10% of the continent's overall disease burden. It is the leading cause of deaths in young children. Pregnant women are the main adult risk group in most endemic areas of the world (6).

In Kenya approximately 20 million people are exposed to stable malaria transmission regular parasite exposure every year. Since the 1980s epidemic unstable malaria has been increasing in frequency and severity among densely populated and economically important areas of Kenya's Western Highlands of Kisii, Kericho, Nyamira, Trans-Mara, Uasin Gishu and Nandi (7). Malindi District is an evenly populated district in Kenya, which falls within the unstable transmission regions. Being a coastal district in Kenya, it is characterised by high temperatures and therefore subject to malaria epidemics when climate conditions are optimal for localised transmission (7). Malaria is currently the major disease and it accounts for over 40% of the outpatient cases in the health facilities in the district (8). Malindi District Hospital and a few other private clinics serve Malindi residents. Both in and out patient data in these health facilities show malaria as a leading cause of morbidity and mortality.

*Malindi District profile*

Malindi; hitherto an administrative division under Kilifi District was made a district in December 1996; to become the seventh district in Coast Province of the Republic of Kenya. It borders Kilifi to the south Taita-Taveta to the west, Tana River district and the Indian ocean to the north and east respectively; lying between latitude 2.20° and 4.5° and longitude 39°E and 4.14°E. It covers a geographical area of 7605km$^2$ equivalent to 1.3 of Kenya's total area; the total area includes 2958 km$^2$ of game reserve.

*Topography and climate*

The district can be divided into four topographical features as follows:- (i) the coastal plain, (ii) the foot plain, (iii) the coastal range, and (iv) the Nyika plateau. The foot plain mainly consists of sand stones and impervious clays supporting grassland and stunted vegetation while the coastal range consists of low range sand stones hills of 150 - 420 metres high. The rest of the hinterland forms the Nyika plateau with an altitude ranging between 130 - 300 metres. The entire zone is marginally semi arid and suitable for extensive livestock development.

*Rainfall pattern*

The district experiences two rain seasons in a year; long rains between March and June while short rains comes between October and November. The annual average rainfall ranges from 400mm in the hinterland to 1200mm in coastal belt. It is during the long rain season that Malaria cases increase; because of the conducive climatic conditions.

**Table 1**

*Population distribution 2006*

| Division | Area (Km²) | Population | | Total Population | Population Density | % of Total Population |
|---|---|---|---|---|---|---|
| | | Males | Females | | | |
| Malindi * | 5,259 | 112,321 | 109,473 | 221,794 | 93/km² | 60 |
| Magarini | 729 | 43,526 | 46,612 | 90,137 | 124/km² | 24 |
| Marafa | 1,617 | 27,232 | 30,768 | 57,999 | 36/km² | 16 |
| Total | 7,605 | 183,079 | 186,852 | 396,931 | 84/km² | 100 |

*Includes 2,958km² of Game Reserve

**Table 2**

*Important population segments*

| Division | Population <1 Year 2006 | Population <5 Years 2006 | Women in child bearing age (15-49 years) |
|---|---|---|---|
| Malindi | 11,090 | 39,923 | 39,923 |
| Magarini | 4,507 | 16,225 | 16,225 |
| Marafa | 2,900 | 10,440 | 10,440 |
| Total | 18,497 | 66,588 | 66,588 |

CBS projections – 2006

**Table 3**

*Important indicators*

- Infant mortality Rate: - 74 / 1000
- Sex ratio: - 98 males per 100 females
- Population Growth Rate: - 3.9 % p.a
- Total Fertility Rate: - 6 children / woman
- Dependence ratio: - 95 / 100
- Literacy rate: - above 60% Estimated
- Population under 1 year: - 5 % total

**Figure 1**

*Malindi District rainfall pattern 2000*

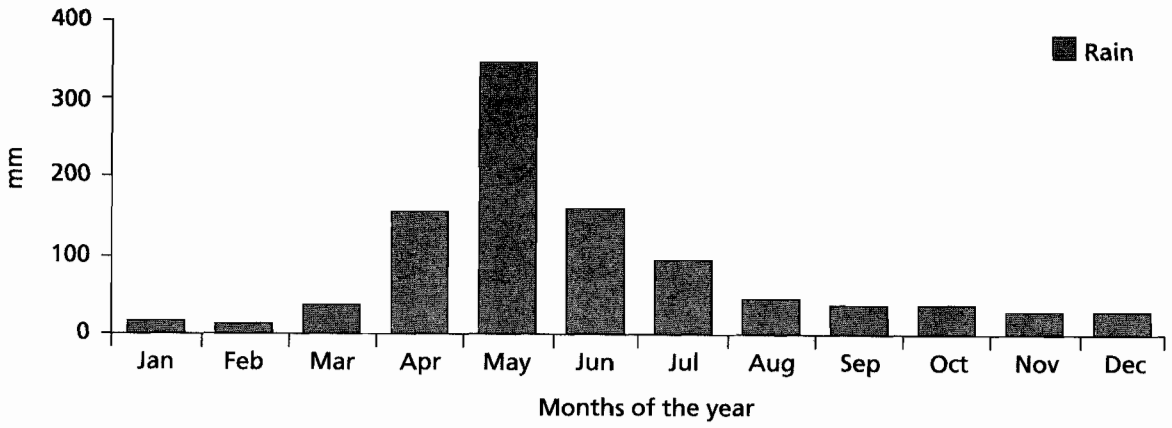
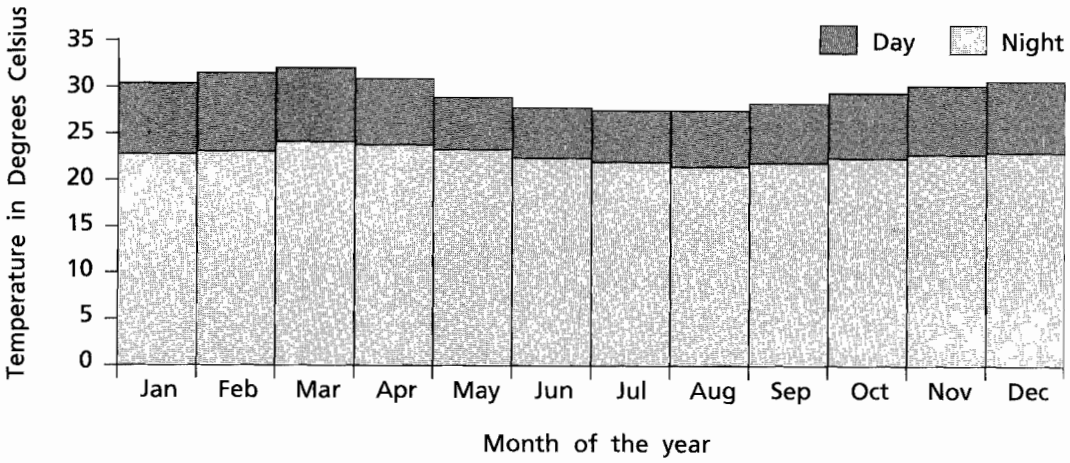


**Figure 2**

*Average temperature, Malindi Airport (Met. Stat.)*




It is generally hot and humid all the year round. The mean daily temperature ranges between 22.0°Celsius minimum and 29.5° Celsius maximum. Average relative humidity along the coastal belt is 65% but decreases as one moves to the hinterland. The lowest temperature is experienced during the long rainy seasons (Figure 2).

*Economic activities*

Tourism is a major source of employment directly or in-directly; given that Malindi is a popular tourist destination internationally. Tourism activities are mainly concentrated along the coastline in Watamu; Malindi town and Mambrui/Ngomeni. Other employment sources are the salt manufacturing companies namely:- Mombasa salt; Crystalline; Kensalt; Tana salt and Kurawa salt. Major agricultural activities deal with seasonal fruits e.g Pineapples and mangoes; otherwise over 50% ofthe indigenous people in the district are peasant farmers. Fishing is also a major economic activity along the Coastline.

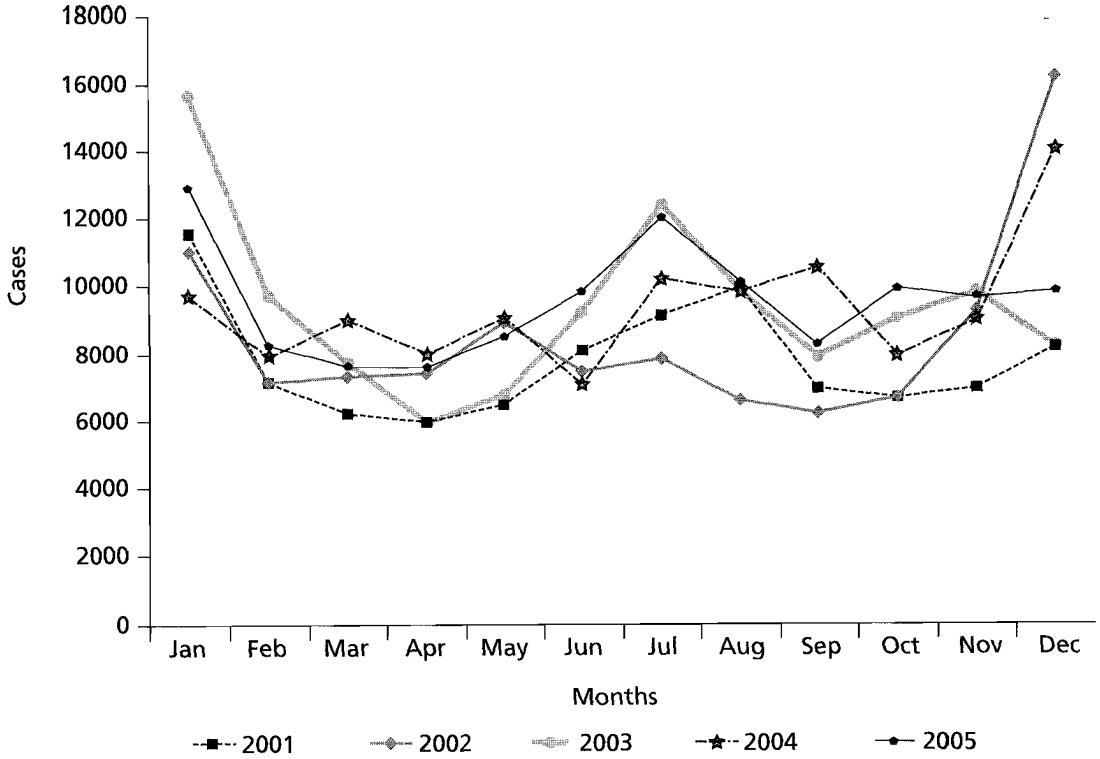
*Statement of the problem*

Globally malaria has a wider distribution (9). Malaria is one of the major public health challenges eroding development in the poorest countries in the world. Today malaria is found throughout the tropical and subtropical regions of the world and causes more than 300 million acute illnesses and at least one million deaths annually. Malaria is currently responsible for 1.4% of global disease burden (10).

In Africa, malaria has increased and spread to areas previously free from the disease for various reasons. It is today one of the two top killer diseases in sub-Saharan Africa (11). About 90% of all malaria deaths in the world today occur in Africa most of which are children under five years old (10). Conditions necessary for malaria transmission explain why malaria burden is high and difficult to control in Africa. With children under five years of age forming over 20% of the population and these children getting six to eight episodes of malaria per year, and with many asymptomatic carriers of malaria parasites in adults, Africa has plenty of gametocyte carriers. This means almost every *Anopheline* mosquito vector gets infected with gametocytes during its blood meal (12). The malaria situation in most of tropical Africa is worsened by man-made environmental changes (13, 14). The disease affects millions of Kenyans each year and fatal to many thousands. Malaria has increased in frequency and severity in some of the Kenyan regions among them Malindi District (7).

Malindi District Hospital, the study area has records showing malaria as number one among the top 10 diseases for the last 10 years. In the year 2002 the mean proportion of malaria to other diseases was 34%. Despite incomplete reporting, Malindi District recorded monthly average of 8,522 malaria cases in the year 2002. End year statistics for the same year put malaria as top of the list with 102,265 cases for the months beginning January to December. These exclude unreported cases from certain reporting centers of the district (15). In 2004, the case fatality rate for malaria at Malindi District Hospital was 9.4%. An average of 1100 new cases are reported monthly in the hospital.

**Figure 3**
*Malaria trends in Malindi*




*Research question*

What is the efficacy and safety of Cotecxin® (dihydroartemisinin) suspension compared to amodiaquine suspension in the treatment of acute uncomplicated malaria among children in Malindi?

*Justification of the study*

The Ministry of Health (MOH) through Division of Outbreak Management Unit (DOMU)/Malaria Control programme has ongoing massive nation-wide campaigns using mass media print and electronic, school health, workshops, seminars, and other avenues to educate the Kenyan masses on the prevention and control of malaria. The informal sector and the Non-Governmental Organisations (NGOs) have also their share in the campaigns. Despite all these efforts malaria morbidity has remained high in many parts of Kenya. Malindi District is one such area that has continued being characterised by high malaria morbidity.

This raises the question why malaria morbidity continues to be high and therefore this study assessed the anti-malaria efficacy and safety of Cotecxin® (dihydroartemisinin) and amodiaquine suspensions in the treatment of malaria. The study will also assess the safety of Cotecxin® (dihydroartemisinin) in comparison with amodiaquine. The findings shall be useful in the treatment of malaria in Malindi and any other part of Kenya by using Cotecxin® (dihydroartemisinin) and amodiaquine suspensions. Other stakeholders may also use the findings to plan for treatment/interventions towards the malaria problem affecting their areas. Future researchers with interest in malaria treatment and its related problems, particularly in Malindi will also find the results of this study useful reference material. Finally, the research will come up with recommendations to the MOH on the treatment of malaria by using Cotecxin® (dihydroartemisinin) and amodiaquine suspensions.

*Study objectives*

*Broad objective*

- To assess the anti-malaria efficacy of Cotecxin® (dihydroartemisinin) suspension by comparison with amodiaquine suspension in Malindi District.

*Specific objective*

- To assess the safety of Cotecxin® (dihydroartemisinin) suspension in comparison with amodiaquine suspension.

## LITERATURE REVIEW

This section presents relevant excerpts from various publications reviewed during this trial.

*Malaria as a disease*

Malaria begins as an influenza-like illness (16). The only consistent features of malaria are fever and rigors. Patients present initially with a chaotic swinging fever; rigors occur when the temperature rises. The fever becomes periodic when synchronous release of parasites is established after seven to fourteen days. Many nonspecific signs and symptoms may present (17) including general malaise, profuse sweating, feeling cold/shivering, headache, dysuria and pains in the back, joints and all over the body. There may be also loss of appetite, vomiting, abdominal pain and diarrhoea (18,19).

*Recommended malaria case definition*

MOH/DOMU-Kenya (20) recommends the use of case definitions for priority diseases, among them being malaria. In its guidelines for Integrated Disease Surveillance and Response (IDS/R), uncomplicated malaria is any person with fever or fever with headache, back pain, chills, sweats, myalgia, nausea, and vomiting and with laboratory confirmation of diagnosis by malaria blood film or other diagnostic test for malaria.

*Epidemiology of malaria: Malaria parasites and their life cycle*

The first biological process of malaria involves malaria parasites (17). The four species plasmodium responsible for human malaria have similar life cycles which, consists of phases in the human blood and liver – schizogony, and in the mosquito vector – sporogony (21).

*Populations at risk*

Young children and pregnant women are most at risk from severe infection with malaria in these areas. In areas of unstable malaria transmission, the whole population may have low levels of immunity and outbreaks of malaria may occur on a regular or infrequent basis, affecting all ages and population groups (22).

*Malaria transmission*

The female *Anopheles* mosquito is the vector for malaria parasites. *Anopheles* mosquitoes must bite a human and feed on blood to transmit malaria parasite. There are about 400 different species of anophelines. Most areas have multiple species of *Anopheles* and different ones occur in different parts of the world (11).

*Vectoral efficiency*

Given the necessary conditions the most efficient vectors are those, which are more anthropophilic, endophilic and endophagic than those, which are zoophilic, exophilic and exophagic (23).

*Distribution of malaria*

Malaria affects many people living between the latitudes of approximately 60°N and 40°S. Mosquito based transmission does not occur at temperatures below 16°C or above 33°C and at latitudes greater than 2000 metres because sporogony cannot take place. The optimum conditions for transmission are high humidity and an ambient temperature between 20°C and 30°C (2).

***Overview of the malaria situation***

*Malaria situation in the world*

Malaria is a public health problem in over 100 countries worldwide, inhabited by some 40% of the world's population (11). A study found that the global death toll from malaria is more than twice as high as has been previously reported. The study from the Multilateral Initiative on Malaria (MIM) found that deaths may be as high as 2.7 million annually, contrasted with the figure of 1 million that has been widely cited for decades (24). In any given year, nearly 10% of the Global population will suffer from malaria – 500million clinical cases (25).

*Malaria in Africa*

Malaria continues to be a major impediment to health in Africa south of Sahara where it frequently takes its greatest toll on very young children and pregnant women. The latest available data on outpatient visits and hospital admissions and deaths due to malaria confirm that this disease makes substantial demands on Africa's fragile health infrastructure (11). In endemic countries, as many as one third of all clinic visits and at least a quarter

of all hospital admissions are for malaria. In some countries, this data suggest that illness due to malaria has increased over the past decade; in others, the size of the problem has remained constant, no country in Africa south of Sahara for which data are available shows a substantial decline (6).

*Malaria in Kenya*

In Kenya malaria continues to be an important public health problem. Pregnant women are at a particular risk of infection and its harmful effects (26). Some 26,000 children aged five years and below die each year from malaria related causes. The greatest burden is borne by children and pregnant women especially in areas where malaria is transmitted throughout the year (27). Previous efforts to combat the malaria scourge have had mixed outcomes. Currently the incidence and impact of the disease are getting worse. Today, malaria is so invidious, its consequences so debilitating and its scale so great, that no national plan or aspiration, social or economic, can be divorced from it (28).

Almost every Kenyan household is afflicted by the human suffering and financial hardship caused by malarial illness. An estimated 170 million working days are lost each year as a result of the disease. The toll it exerts on individual families is viewed in terms of the physical, financial and emotional pain. It kills 26,000 children per year in Kenya (7). Malaria accounts for 30% of all outpatient attendance and 19% of all admissions to Kenyan health facilities. An estimated 170 million working days are lost to the disease each year (28). The cumulative human suffering and economic damage caused by malaria is immense. The economy in general and the health sector in particular are heavily burdened by the cost of drugs and treatment. Malaria accounts for more than eight million outpatient treatments at Government of Kenya (GoK) health facilities each year (7).

## DETERMINANTS OF MALARIA MORBIDITY

### *Social, economic and demographic determinants*

*Economic determinants*

In Africa the main challenges in malaria control include unfavourable socio-economic conditions and lack of adequate health infrastructure (21). A complex interaction between social, demographic and economic factors determines who actually applies malaria control measures (29). For example, bed nets are expensive (30) and there is difficulty in affording bed nets a number commensurate with the household needs. For example in Tanzanian studies, the number of nets required by each household was a major practical obstacle because people were only able to purchase only one net and leave other members unprotected. Further, the number of nets required will be affected by family size and sleeping patterns. Documentation from Insecticide Treated material (ITM) projects have shown that when families do not have sufficient resources to cover all the household members with nets, children are most likely to be left without (31). A study in Kisumu district found that only 12% of the local population used mosquito nets for protection, principally because of prohibitive costs of buying nets locally (32), while in Namibia 68% of people questioned said they did not use Insectcide Treated Material and Nets (IMNs) because of cost (33).

*Age determinants*

Prevalence of malaria was found to decrease with older age (34). Changes in risk of malaria with age are conveniently explained by the development of antimalarial immunity as individuals accumulate infection experiences with the antigenic repertoire of wild parasites (35). In Buenaventura, Colombia, behavioural factors were associated with risk to malaria infection and mobility to forests was identified as a main determinant of risk. In these situations children and older individuals were less exposed and, subsequently, the incidence of disease was higher in adults aged twenty to thirty nine years (36). In another study, individual exposure to the forest, measured by rural occupation, was associated with a higher risk of malaria; the adults aged 20 – 39 years assumed to be exposed to the forest had an odds ratio of 2:95 against the non-exposed (34).

*Literacy*

In The Gambia, as in Senegal and in most other countries of the Sudan and Sahel regions of West Africa, many illiterate families consider that severe neurological sign and symptoms are within the competence of traditional medicine; *Marabous*, and not doctors or nurses treat most cases of severe

malaria. Children from families with the best education and socio-economic status were much more likely to be hospitalised than children from other families not because they were most at risk but due to the fact that families with good educational backgrounds and better social status saw modern medicine offered at the hospital as the first choice (35).

*Knowledge on malaria*

In order to reduce malaria related mortality and morbidity, knowledge of malaria, its causation, preventive/protective methods and control; and also its health and economic implications are paramount at the household level. Health seeking and malaria prevention behaviour and its relationship with economic costs and degree of community identification must be considered (36).

People's knowledge and understanding of disease causation affect their health seeking behaviour. There is considerable variation in people's understanding of the relationship between malaria and mosquitoes. For most people, the major concern is the nuisance value of mosquitoes rather than the risk. In a study in Zimbabwe, bed nets were found useful for the prevention against the nuisance bites of mosquitoes, other debris and a form of privacy in overcrowded rooms (37). In Tanzania, communities were found to be more concerned about the nuisance value of mosquitoes and to appreciate IMNs for reducing this (38).

A Knowledge, attitude and practice (KAP) study in Moshona land, Zimbabwe, showed very limited knowledge of means of protection against malaria either at a personal level or community level (39). In Ghana only 21 – 47% of the population in four districts believed malaria is caused by mosquito bites, while in Zambia, a KAP survey showed that 50% of population in three communities knew that malaria is transmitted by mosquitoes (40).

In a Malawi's national KAP study 55% of the population identified mosquitoes as the cause of malaria and 52% used some kind of preventive measure, mainly commercial products. Mosquito coils were used by 16%, insecticide sprays by 11% and nets by 7%. In Kisumu District of Kenya 85% of a local population knew that malaria was caused by the bite of a mosquito but only 12% used mosquito nets for protection (37). A Kenyan study in Kisii District-Keumbu Division, 99% of the respondents knew what malaria was and 91% of them knew that malaria was caused by the mosquito bite; however they did not have adequate knowledge on the current treatment and prevention of malaria. At least above 50% of the respondents knew more than three types of mosquito breeding sites (41). In Beletwein town of Somalia, 97% knew what malaria was, while 91% had knowledge on the signs and symptoms of malaria. Among the respondents 92% mentioned mosquito bite as the cause of malaria and various preventive measures were mentioned by the respondents namely early treatment 37%, spraying 36%, net 32%, repellents 28% and bush clearing 20% (41).

People in Benin believed that malaria is associated with the sun and excess use of peanut and red palm oil, while a study in Zimbabwe revealed that in areas with altitude below 600 metres, people were aware of malaria, but the role of mosquito was not well known and people were not really aware that mosquito transmits malaria. Use of repellents as preventive means against malaria was non-existent (42).

A KAP study in Utengule Irrigation Scheme – Tanzania, 99% of the study population recognised malaria as the leading health problem, while 81% knew the use of nets as a preventive strategy, 63% and 62% knew the use of insecticides and drainage respectively as preventive measures (43). A Colombian study revealed most of the population 85% as knowledgeable about aetiology of malaria and a protective effect was statistically important. A significant association was detected with knowledge about elimination of breeding sites as an effective measure to prevent the disease, but a non-significant association was found with knowledge about use of bed nets (34).

*Malaria control practices*

The current measures for malaria control can be classified into vector control, chemotherapy, chemoprophylaxis and personal protection (21).

*Vector control*

Malaria control programmes directed against the mosquito vector remains the most effective means of limiting the malaria problem. However, vector control strategies to reduce mosquito populations, modify human-mosquito contact, or affect vector competence have all come under review in response to the double threat of insecticide resistance in the

mosquito and drug resistance in the parasite (44).

The reduction of the number of mosquito vectors can be achieved using several methods. There is the elimination of mosquito breeding habitats in which aquatic stage of the mosquitoes are destroyed. This is called environmental control or environmental management. This method involves finding and characterising all breeding habitats then altering them through permanent or recurrent changes on land, water or vegetation (45). This method prevents breeding of mosquitoes when they are resistant to the available insecticides. It is aptly called larval control by environmental modification; thus altering or eliminating the breeding places (source reduction). Such control methods include covering or screening water containers, draining ponds and marshes, filling ditches, pools, etc. Semi permanent measures that have to be repeated include clearing up refuse and containers serving as breeding sites, clearing vegetation from shores of ponds and creeks, changing water levels in lakes and reservoirs, flushing streams and repairing drains and gutters. Eucalyptus trees are used to dry up marshy areas (16). Environmental management can reduce or eliminate mosquito-breeding sites. It should be more often applied by local communities for collective protection from vectors and be incorporated into the planning of development projects. Its incorporation into development activities requires collaboration between the health sector and those involved in development, agriculture, water supply and other relevant activities (46).

There are the chemical and physical measures used to directly kill the aquatic or the adult stages of mosquitoes. The chief measure has been the use of DDT for house spraying (21). Larvicides suffocate or poison the surface-feeding/breathing larvae and pupae. Where larvicides are applied vegetation must be cleared. Furthermore, larviciding operations are cumbersome, costly (47) and usually temporarily effective (22).

*Vector control practices in various places*

In Sagana, Kenya various practices were demonstrated namely draining stagnant water 92%, land filling 18%, destruction of empty cans 87%, clearing vegetation 84% and spraying of houses 1.5% (48). In Kilgoris, Kenya 27% of the population applied house spraying and Insecticide Treated Nets (ITNs) use was 23.5% (60). In the Somalian town of Beletwein house spraying 35.5%, repellents 27.6%, clearing of bushes 20.3% were used to control mosquitoes (41).

*Reliance on home use products for vector control*

Home-use products include coils, insecticide aerosols, mosquito repellents and vaporizing mats. These products may be of some use in areas where mosquitoes bite early in the evening. However, they are needed every evening and may therefore be too costly and this was demonstrated in Afghanistan where efforts to socially market mosquito repellents had limited success (19). However these home-use products are not very effective preventive measures (41). Smoke from cooking was observed to be capable to repel mosquitoes but since cooking is done during the early evening, the smoke may not deter mosquitoes coming to the house in the late evening after cooking activities terminate (49). Actually *An. arabiensis* actively seek hosts throughout the night with several peaks and the highest biting time just before dawn. Thus smoke may be effective in repelling mosquitoes only in the early hours of the evening while cooking activities are underway. During the rest of the evening and throughout the night houses especially with open eaves will be well ventilated and the repellent effect of the smoke significantly reduced, allowing mosquitoes to enter freely (50). However, the use of repellents or insecticides appeared protective from malaria infection in an urban area of Columbia Pacific (51) and a good section of the populations living in malarious zone resort to them. A study in Rukanga, Kirinyaga District of Kenya found out that 58% of the study population used mosquito coil in mosquito bite prevention. In the same study cow dung smoke, repellent gel, herbal smoke and mosquito repellent spray were used to repel mosquitoes in the proportions of 40%, 40%, 11% and 25% respectively (48).

Salah (41) in a Somalian study found that 28% of the population used repellants. Mixed proportions were reported by Mutero *et al.* (52) in Suba District where 25.2% used coils in Rusinga and 31.2% in Mbita; plant smoke was also used; Rusinga 19.1% and Mbita 8.7%. A fairly large proportion of the homesteads did not use any method to protect themselves against the mosquitoes.

*Bed net utilisation*

In malarious areas mosquito-proof bed nets offer important protection, which is much increased by impregnation with permethrin (17). It was only recently appreciated that a net treated with insecticide offers much greater protection against malaria, not only does the net act as a barrier to prevent mosquitoes biting, but also the insecticide repels, inhibits, or kills any mosquitoes attracted to feed. Thus ITNs provide protection both to individuals sleeping under them and other community members. The effect is so significant that use of ITNs is considered to be one of the most effective preventive measures for malaria (6,19).

ITNs have shown in a number of studies to reduce morbidity and morbidity and mortality in young children (53). Also randomised controlled trials in African settings of different transmission intensities have shown that ITNs can reduce the number of under five-year old children by around 1/5$^{th}$ (54), saving about six lives for every 1000 children aged one to 59 months protected each year (6). Recent data from a highly malarious area in western Kenya indicate that pregnant women sleeping under ITNs experienced a significant reduction in episodes of anaemia, low birth weight and premature delivery (53).

*Practicability of bed nets*

Sleeping under a mosquito net provides an effective barrier against mosquito biting, but mosquitoes can still bite if there is a small hole or tear in the net or if any part of the body is touching the net. Treating nets with a suitable insecticide increases protection against mosquito biting. This is because the insecticide kills or repels mosquitoes before they enter the net or bite the person sleeping under the net. High coverage of net can reduce the adult mosquito population, and may therefore also protect people who do not use a net (11) even though it has been assumed that Insecticide treated Bed Nets (IBNs) work mainly through personal protection. The mass insecticidal effect of IBNs may be more important in some context. Thus the protection afforded by sleeping without a net in a village where IBNs are used extensively may be greater than sleeping under an IBN in a village where no one else uses them (55). Even a low coverage has some health benefits, for example, even limited distribution of ITNs has reduced malaria mortality and morbidity in Afghan refugee camps (56).

Although ITNs have been shown to provide protection in many settings and there is increasing evidence of their effectiveness, they are not effective in every epidemiological context (3,57). Practicability of ITNs may be influenced by local conditions of transmission (34), thus local human and mosquito behaviour (3,21). All night observations found that bed nets could not have prevented 10.5% of all bites because householders went to bed at around 23:00 hours while biting by mosquitoes began at 20:00 hours. Thirty five per cent of the study subjects left their bed at night to check disturbances in the compound or to urinate (27), while some mosquitoes bite early in the evening before people go to bed (57) and in the morning the householders get out of bed while biting still continued (27). Other studies done in Buenaventura, Pacific Coast of Colombia demonstrated that *An. albimanus*, the most important vector in the area has a greater predomiciliar activity with a peak biting-hour between 18:00 and 22:00 (58) and it was observed that this was the time for social activities (children playing and adults meeting) outside the house in the community and the more likely time for acquiring malaria. Therefore, the use of bed nets during the night could not be a very effective protective measure and environmental interventions may be needed to decrease the risk of infection (34).

*Low bed-net coverage*

Most African households in malaria risk areas do not possess any net (40) and current rates of net coverage are generally low (6). Reported bed net ownership and use is variable and may be less than 20% in most of tropical Africa (21). In nine countries surveyed between 1997 and 2001 a range of 1.1 – 54% of households were found to possess one or more nets and 0.2 – 4.9% of households surveyed in three countries owned at least one ITN (59).

Only 50% of the studied population in Kilgoris, Transmara district of Kenya, was found to be using nets as a control measure of malaria (60) and the rural areas of Tanzania had a rate of 29% compared to the 63% in towns (59). Another Kenyan study in Makueni district showed a bed net utilization for malaria prevention of 20% (61) and a study in Keumbu Kisii District of Kenya 11.5% of the studied population used simple bed nets while 9.3% of them used ITNs (41).

Even with an efficacious control measure, a low coverage of the target population might render the measure ineffective in tropical Africa where there is a very efficient vectoral system for malaria transmission. This implies that substantial efforts and financial investment will be needed to raise bed net coverage (21).

*Practice of animal keeping in the households*

Many mosquito species prefer to feed on animals rather than humans. Relocation or the introduction of cattle or other domestic animals may divert many mosquitoes from humans to animals. Differences between villages in the same area in the mosquito biting rates or in the number of malaria cases can sometimes be explained by the presence or absence of domestic animals (16). An Ethiopian study found that a higher proportion of mosquitoes collected from mixed dwellings feed on cattle compared to those who fed on humans suggesting cattle may protect humans from mosquito bites (62).

In contrast studies in the Gambia and Pakistan, respectively, showed that children of families with cattle had a higher risk compared to those who did not (63, 64). Similarly malaria incidence was significantly higher in children of families who kept animals in their houses compared to those who had a separate shelter for animals. However it should be noted that some areas have vectors which are more anthropophilic like The Gambia while other areas have those that are more zoophilic like Ethiopia (49).

The findings in Ethiopia indicated that animals may not act as zoo prophylactic agents, at least if large animals sleep in houses where humans sleep. When livestock are kept in the same house with humans, more mosquitoes could be attracted to the house but once inside the house the mosquitoes could preferably feed on humans (49). Also reported was increased prevalence of malaria in families who keep their animals closer to their dwellings. Moreover, having a separate shelter for animals helped reduce vivax malaria in Britain and Holland (65).

*Housing conditions*

Measures to make houses and shelters insect-proof work against species that enter houses to feed and rest. Many mosquitoes attack people at night inside houses. Methods that restrict or prevent the entry of mosquitoes into houses offer significant protection to inhabitants (16).

House design is one important factor in this aspect. Fewer and smaller openings in a house also mean that fewer mosquitoes enter. In tropical areas, ventilation openings such as windows and eaves provide easy access to flying insects (65). Blocking the eaves may be unacceptable because of the restriction of ventilation. However screening the eaves is a good idea. Door and windows should fit and close properly. If eaves cannot easily be blocked or screened a ceiling may be constructed to stop mosquitoes entering the living quarters (65).

Anti-mosquito screening of doors, windows and other openings in houses prevents insects from entry into buildings (17), while maintaining some ventilation. To stop most mosquito species the meshing should be 1.5 $mm^2$ or less. Screening is often unacceptable because of the restriction on ventilation (16).

High malaria incidence has been associated with poor housing conditions (66). In Sri Lanka individuals living in houses with an incomplete roof, windows without shutters and doors with holes were subjected to repeated malaria infections while others in houses without those characteristics experienced little infection (67-69). In another study in The Gambia a significantly higher number of mosquitoes were collected from bedrooms without ceilings compared to those with ceilings. In Guinea Bissau a significantly higher number of mosquitoes were collected from houses with open eaves compared to those with closed ones (70) and in The Gambia children living in houses with closed eaves had less frequent malaria attacks compared to those living in houses with open eaves (71). In Ethiopia open eaves were strongly associated with a higher incidence of malaria. Therefore open eaves, a gap between the wall and roof of a house, may be an important factor in the transmission of malaria, serving as a major route by which mosquitoes enter houses (49).

Another open space that can allow free entry of mosquitoes is a window. Higher malaria incidence was found in houses with windows compared to houses without windows (49). This was also observed in Sri Lanka that window and door spaces can allow easy access to mosquitoes (69). Windows may allow more mosquitoes into a house if they are not fitted with a shutter or if the shutter has open spaces for mosquito access (49).

It has also been reported that a corrugated roof was more protective than a traditional roof because the latter may provide a favourable environment by enabling mosquitoes to rest and stay closer to their blood sources. The traditional roof may provide a favorable microhabitat for mosquito resting. Such a conducive environment could even increase the survival chance of the mosquito (65).

Families with single sleeping room had a higher risk of malaria compared to those who have more (49). In the Sudan, children from houses with two or less rooms had more malaria compared to those from larger houses, and that children from families with six or more members had higher risk of malaria (72). Similarly overcrowding was associated with higher risk of malaria in The Gambia and Cameroon (66, 73). First this may be because more people result in a higher production of carbon dioxide and other volatiles host-related odours attractive to mosquitoes (74). Mosquitoes are attracted by odours emanating from vertebrate host. The blood-feeding behaviour is initiated in response to host body heat (75). Secondly, infective mosquitoes among those that enter a house may infect more than one person on the same night because infected mosquitoes tend to bite with higher frequency (49) and crowding may make life easier for probing mosquito (49).

*House siting*

Many people prefer to place their houses close to rivers, creeks, or ponds so as to be close to a supply of water. Depending on the breeding and resting habits of the local mosquito species, this may increase the risk of being bitten (16).

Mosquitoes cannot fly far; most anophelines cannot fly more than 4 Kilometres (Km), and in general they remain within 2Km of their breeding sites (19). Usually the mosquitoes that bite breed in collections of water within 2Km of the dwelling place. So malaria can be avoided by siting homes away from breeding sites (19). If humans do no live near breeding sites the chances of infection are reduced because many vectors bite inside houses and the siting of the dwelling is an important determinant of malaria risk (2).

Proximity of breeding sites increases risk of malaria infection (19). A higher prevalence of malaria was reported in villages near irrigated highland rice in Ruzizi valley in Burundi. Villages close to dams had a seven-fold increase in malaria incidence compared to villages away from dams. Proximity to a microdam is one of the risk factors for higher malaria incidence in Ethiopia. This was consistent with the finding of a clustering of cases in houses located downstream from the dam and closer to irrigation canals (49).

*Chemoprophylaxis against malaria*

This is an anti-plasmodial strategy, which involves regular medication with anti-malarial drugs to prevent the development of disease in susceptible individuals. It is recommended for selected groups of individuals in whom there is demonstrable and beneficial protection against malaria such as non-immune travelers to endemic areas (76), but anti-mosquito bite measures should always be used to enhance the effect of chemoprophylaxis (17). Obviously if mosquito bite can be prevented, no other form of prophylaxis is necessary (4).

Antimalarial prophylaxis must be taken regularly to ensure therapeutic antimalarial concentrations are maintained, however prophylactic drugs can no longer be relied upon, particularly in areas of multiple drug resistance such as Southeast Asia and South America. When prescribing antimalarial prophylaxis it is important to emphasise that no antimalarial is completely effective. The use of antimalarial prophylaxis by the inhabitants of malarious areas remains controversial. It is generally agreed that pregnant women should take antimalarial prophylaxis if there is a significant risk of malaria, but that other adults should not (77).

Daily or weekly chemoprophylaxis is theoretically an ideal way of preventing malaria in the vulnerable group, but it is often very difficult to achieve. Adherence to treatment regimens has been poor (78, 79). Children in malaria endemic areas may benefit from prophylaxis, an intervention that reduces the incidence of clinical attacks of malaria, increases haemoglobin levels and also reduces infant mortality rates. In primigravidae chemoprophylaxis reduces the incidence of malaria and leads to delivery of babies with higher birth weights. However, chemoprophylaxis has problems associated with supply of drugs and other logistical aspects. These lead to low coverage of the selected groups and poor compliance (80). More so even if prophylaxis is properly used, there is a small risk of malaria (17).

A KAP study in Malawi found out that while women uniformly considered malaria to be a

problem in pregnancy and most believed that antimalarials are effective in curing malaria, and significantly less believed they are effective in preventing malaria. In contrast individuals in survey, without medication in the previous month appeared to have lower prevalence of malaria infection at the survey. The prevalence of malaria infection in individuals who received a prescribed treatment chloroquine and/or SP was higher -twice the risk of being infected (34).

Lumiti (63) found that prophylaxis was practised by 55.5% in Kilgoris Division, Transmara District, Kenya.

*Malaria treatment*

This is another anti-plasmodial measure involving the treatment of episodes of malaria to eliminate human stages of the malaria parasites. It is the main strategy for preventing death and shortening duration of malarial illness. For this reason it is presently the main strategy for malaria control in tropical Africa (46). However chemotherapy has been hampered by the emergence of drug-resistant parasite strains and a lack of cheap alternative drugs (Werndosfer, 1994). Antimalarial drug resistance has become one of the greatest challenges in malaria treatment. Chloroquine, the cheapest and most widely available antimalarial drug has lost its chemical effectiveness in most parts of Africa. Resistance of *P. falciparum* to the most affordable alternative drugs, notably SP, is also emerging problem in eastern and south eastern Asia (6).

Prompt and effective treatment of malaria is a critical element of malaria control (46) but due to inadequate health infrastructure and other reasons, chemotherapy is usually underutilised. For example, only 10 to 25% of the malaria cases seek competent treatment in Africa (81).

In Africa, most cases of malaria are diagnosed on the basis of clinical symptoms and treatment is presumptive, rather than based on laboratory confirmation. Moreover malaria parasitaemia is common among clinic attendees in many endemic areas, so that a positive laboratory result does not necessarily mean the patient is ill with malaria – fever and general weakness are nonspecific and may well be due to other common infections (6). Survey findings indicate that 70% of the patients treated with antimalarial drugs are found to be negative. This has led to flourishing of drug resistant strains of *plasmodium*, thus rendering cheap drugs like chloroquine ineffective and imposing a serious drawback in the global eradication campaign of this disease (82).

*Treatment seeking behaviour*

Malaria control strategies should consider treatment-seeking behaviour of populations (37). It has also been shown to be affected by a number of factors, including access, attitudes toward providers and beliefs about disease (83).

The components of treatment-seeking behaviour include traditional medicine (34). The effectiveness of case management depends to some extent on community understanding and action – one of the reasons for high malaria mortality in both emergency and non-emergency situations is late presentation of cases to, or failure to seek treatment from health facilities (19).

*Treatment of malaria outside public health facilities*

Treatment decisions taken in the first stages of onset of malaria can be critical to the outcome of malaria infection. There is a high proportion of cases, which are self-treated, and increasing role of commercial outlets in the home malaria treatment, and lack of easy access to public health facilities in some parts of Africa (37). The role of the private sector, particularly small shops and street traders in self-treatment for malaria is clearly very important and cannot be disregarded. Strategies to educate the providers are greatly needed, particularly in correct dosage. In Zimbabwe shopkeepers were requested to sell only complete doses of chloroquine, but they felt that their sales had decreased as result of complying (83).

Drug use practices in African countries show that the vast majority of people presenting with malaria symptoms receive treatment from outside the public health system, most preferring to buy antimalarial drugs from private outlets such as pharmacies and retailers in the market place. Home treatment of fever in the African region can account for up to 75% of all cases (84). In Kilifi District, Kenya, a study found that mothers of young children treated their children by purchasing drugs from the nearest shop (85).

In Ghana, self-medication is spreading rapidly, using either drugs or traditional herbs. Use of drug store operators (trained or untrained) for advice on

what drugs to purchase is also becoming very common, as it is cheaper than going to health centers. While self-medication is the most popular choice for treating both mild and severe forms of malaria in adults, for children aged two to seventeen years, slightly more than 50% of severe cases are reported first in hospitals or clinics. In almost all severe cases, if the first choice fails, the second choice is a hospital or clinic. There is also increasing use of contraindicated drugs left over from previous episodes which may not be appropriate or which may have expired. Chloroquine use was also reported by Wabomba (41) where 60% of the studied population used chloroquine in Keumbu, Kisii-District, Kenya

A Ghanaian study found that the majority (83%) of the population was initially treated at home against 12% who were first treated at a health facility. Those first treated at home were treated after an average of one and a half days whiles those at health facility – 4.7 days (37).

While comparing the advantages and disadvantages of treatment it was found that the frequent tendency to administer antimalarial drugs to children at home when they manifest febrile illnesses means that many are being treated unnecessarily, and with consequences of increasing drug resistance. On the other hand it undoubtedly decreases children's mortality from malaria. The increase in home treatment of fever with chloroquine is thought to be responsible for some leveling off in the cases of malaria in Ghana, but there is some tendency towards under dosing both because of inadequate knowledge by the caretakers and the cost of the drugs (37).

Munguti (86) in Baringo District demonstrated that various health measures were utilised which included public health facilities, over the counter medications, private clinics and herbal medicines. He noted that majority of households (73.5%) used public health facilities as a first choice of care. Using shop-bought drugs has been demonstrated elsewhere. Snow *et al* (85) found out in the Kenyan Coast that the preferred choice for treatment for childhood febrile illness was with proprietary drugs bought over the counter at shops and kiosks (72%). Salah (41) also found out that the sources of drugs in Beletwein Somalia are the shops (95.5%) and peddlers (4.1%), while 83.1% of the population seeked treatment from health facilities.

In Utengule Tanzania, Ntomola (43) found out that 33.8% of the population seeked traditional medicine and only 69.6% went to hospital. Dlamini (48) found that only 1% of the studied population in Sagana, Kirinyaga-Kenya used traditional medicine, while 96.3% and 2% went to health facility and drug shops respectively. Chiumia (87) demonstrated (3%) use of herbal medicine in Sagana while 89% of the population went to hospital, 4% bought drugs and 2% went to private clinics. Chloroquine use was also reported by Wabomba (41) where 60% of the studied population used chloroquine in Keumbu, Kisii-District, Kenya.

*Traditional medicine in malaria treatment*

Western medicine is still unavailable to perhaps as many as a billion people in developing countries. That does not mean that people simply wait for illness to follow its natural course. Their own traditional forms of medical care systems still remain. It has been observed that most malaria illnesses and deaths occur at home, without contact with the formal health systems. Approximately 70% - 80% of cases are managed at the community level where management is inadequate (88, 89). In Kilifi District, Kenya, severe form of malaria was referred to traditional healers (85).

In Ghana, many people used traditional herbs. Households were found to have considerable knowledge of herbal preparations effective against malaria (37). A recent study in a town in Somalia found herbal medicine as a choice in malaria treatment. Three percent of the studied population was found to be using herbal medicine (41) and same finding was reported in a study done in Sagana, Kenya (87). In Entasopia, Kajiado District of Kenya, 8% of the study population resorted to traditional healing (90), while 34% of the population in a Tanzanian rural community used traditional healers (43).

## MATERIALS AND METHODS

The study was a clinical trial conducted between January 23rd 2005 and 27th February 2006. The study area was Malindi District. The study population was the children attending Malindi District Hospital with malaria. The major variables of the study were categorised into two, namely, independent and dependent variables: independent variables were patient presenting with malaria and dependent

variables were treatment of malaria with Cotecxin® (dihydroartemisinin) suspension and amodiaquine suspension.

The study was a randomised open label in two parallel groups. Children aged six years and below with clinical symptoms of malaria.

*Sampling technique*

Patients complying with inclusion criteria were randomised and received either Cotecxin® (dihydroartemisinin) or amodiaquine suspensions.

*Sample size determination*

The desired sample size was determined using the following formulae of Fisher *et al* (91).

$$n = \frac{Z^2 pq}{d^2}$$

Where:

n = the desired sample size [when population is greater than 10,000.]

Z = the standard normal deviate, set at 1.96, which corresponds to 95% Confidence level.

p = prevalence of malaria in the study area in a proportion, in this study 0.47 was used as this was the mean proportion of malaria to other diseases in the Public health facility serving the study area.

q = 1.0 – p

d = degree of accuracy desired, here set at 0.05 corresponding to the 1.96

z = Statistic used in the numerator.

In substitution,

$$n = \frac{1.96^2 \infty 0.34\ (1 - 0.34)}{0.05^2}$$

$$= 345$$

The total number of new cases per month in the study area (N) = 1200 and because N was less than 10,000 the second formula was applied in determining the sample size thus:

$$nf = \frac{n}{1 + \frac{n}{N}}$$

Where:

nf = desired sample size for a population less than 10,000.

n = desired sample size for population more than 10,000 which was found to be 383.

N = New cases per month 1,200.

In substitution,

$$nf = \frac{345}{1 + \frac{345}{1200}}$$

$$= 268$$

Therefore the desired n = 268 and actual n = 120

*Data collection tools*

Case report forms-the researcher administered these with the assistance of clinicians treating the patients.

*Data collection procedure*

Validated data collection tools case report forms were completed as the patients were given treatment. This was done up to the time the patients received complete dose. Patients were monitored for any allergy or drug reaction. The case report forms were completed using standard medical terminologies as patients were interviewed in *Kiswahili* language.

***Inclusion criteria***

*The study included:-*

(i) Infants and children (- 6 years) with clinical symptoms of malaria.

(ii) Falciparum parasites asexual form ž 1000/ ml or large ring form ž 300ml with high fever.

***Non inclusion (exclusion) criteria***

*The study excluded any person with:-*

(i) Over the age of seven years

(ii) Any patient with severe vomiting

(iii) Severe complication, abnormalities in laboratory blood test

(iv) Patients presenting with conditions requiring hospital admission

(v) Treatment within the past seven days with any antimalarial

(vi) Using of an investigational drug within past 30 days

(vii) History of allergy or hypersensitivity to amodiaquine or *dihydroartemisinin.*

(viii) Unreliable parents or guardians (opinion judged by investigator)

*Statistical analysis of data*

Analysis of raw data was done using Ms Excel, EPI Info 2000 computer software. Evaluation of interaction between a treatment results was done by $c^2$ test and by constructing multiple comparative bar graphs.

*Presentation of findings*

Findings of this study have been presented in text, tables and charts. The presentation has been divided into two sections namely; descriptive and inferential.

*Validity and reliability of data*

(i) The researchers approved the case report forms.

(ii) The researchers at the end of every day's data collection studied and edited the used tools.

*Ethical consideration*

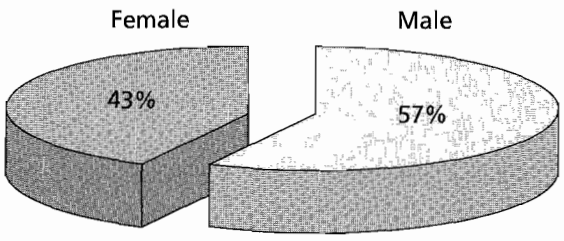
The Ministry of Health and Ministry of Education, Science and Technology and Malindi District Health Ethics and Research Committee gave ethical approval for this study. Voluntary written consents were also obtained from patients recruited for the study.

## RESULTS

This section presents the findings of the study. The findings have been presented in quantitative terms such as in percentages, frequencies, the means, the modes, the minimums, the maximums and the standard deviations.

**Figure 4**

*Gender of respondents*




The males 57.5% were more than the females 42.5%.

*Consent to participate in the study*

All the 120 patients had given consent to participate in the study. No patient was included in the study without written consent.

*Inclusion criteria*

All the patients who participated met the study criteria of being - 6 years with malaria or symptoms of malaria. All the patients were malaria patients with plasmodium falciparum form ž1000/ml, or large rings form ž 300/ ml. They were symptomatic of malaria infection. Exclusion criteria included children with > 7 years with severe vomiting and complication, serum creatinine >150 mmol/L. All patients did not have signs or symptoms indicative of severe malaria.

*Socio-demographic characteristics of the respondents*

**Table 4**

*Age of the Respondent*

| Variable | Value |
|---|---|
| Mean age (months) | 36.3 |
| Standard Deviation | 16.9 |
| Standard Error | 1.5 |

The mean age for the patients was 36.3 months. Standard deviation was 16.9 and Standard Error of 1.5. The Standard error of 1.5 indicates a very insignificant degree of error.

**Table 5**

*Gender of respondents*

| Gender | Frequency | (%) |
|---|---|---|
| Male | 69 | 57.5 |
| Female | 51 | 42.5 |
| Total | 120 | 100 |

**Table 6**

*Mean weight and height of respondents*

| Gender | Weight (kgs) | Height (cms) |
|---|---|---|
| Male | 12.5 | 113.0 |
| Female | 11.0 | 90.5 |

**Table 7**

*Age in months*

| Gender | Weight (kgs) | Height (cms) | Mean (age) |
|---|---|---|---|
| Male | 6 | 72 | 37.5 |
| Female | 7 | 66 | 36.5 |

**Figure 5**

*Mean weight and height*

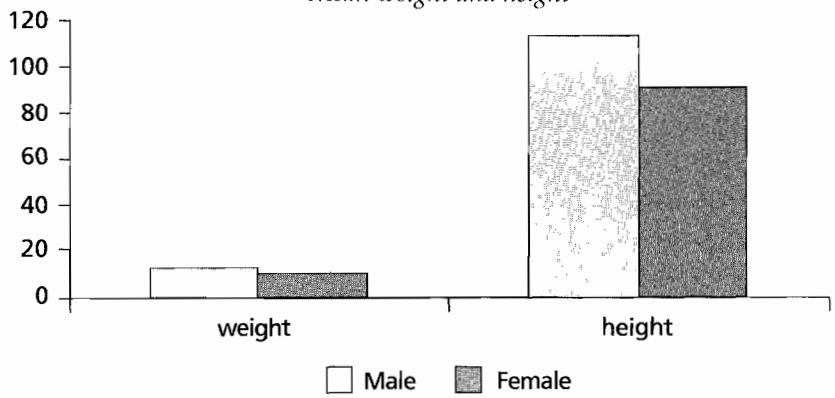



**Table 8**

*Drugs taken previous seven days before study*

| GenderY | es | No | Total |
|---|---|---|---|
| Male | 24 | 45 | 69 |
| Female | 13 | 38 | 51 |
| Total | 37 | 83 | 120 |

**Table 9**

*Types of drugs taken before study*

| Drugs | Male | Female | Total |
|---|---|---|---|
| Antibiotic | 1 | 1 | 2 |
| Actal | 1 | 0 | 1 |
| Aspirin | 3 | 2 | 5 |
| Iron Sulphate + Vitamin B | 0 | 1 | 1 |
| Analgesics | 18 | 8 | 26 |
| Trihistamine | 2 | 0 | 2 |
| Total | 25 | 12 | 37 |

None of the drugs taken before study were anti-malarial drug.

**Table 10**

*Patients with concomitant diseases*

| Sex | Yes | No | Total |
|---|---|---|---|
| Male | 9 | 60 | 69 |
| Female | 5 | 46 | 51 |
| Total | 14 | 106 | 120 |

**Table 11**

*Concomitant diseases by sex*

| Diseases | Male | Female | Total |
|---|---|---|---|
| Anaemia | 1 | 1 | 2 |
| Bronchospasm | 1 | 0 | 1 |
| LRTI | 2 | 0 | 2 |
| URTI | 4 | 3 | 7 |
| Scabies | 1 | 1 | 2 |
| Total | 9 | 5 | 14 |

**Table 12**

*Physical examination of body systems*

| System | Normal (No. of pts) | Abnormal (No. of pts) | Total (No. of pts) |
|---|---|---|---|
| Cardiovascular | 113 (94.17%) | 7 (5.83%) | 120 (100%) |
| Respiratory | 118 (98.33%) | 2 (1.67%) | 120 (100%) |
| Central nervous | 119 (99.17%) | 1 (0.83%) | 120 (100%) |
| Gastroenteritis | 115 (95.83%) | 5 (4.17%) | 120 (100%) |
| Skin | 119 (99.17%) | 1 (0.83%) | 120 (100%) |

**Table 13**

*Treatment drugs taken*

| Drug | Frequency | (%) | Cum % |
|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 60 | 50 | 50 |
| Amodiaquine | 60 | 50 | 100 |
| Total | 120 | 100 | 100 |

Test drug taking was 60/120 (50%) for Cotecxin® (dihydroartemisinin) with a dose of between 10ml and 25ml depending on body weight and 60/120 (50%) for amodiaquine with a dose between 5ml and 20ml depending on weight of child.

**Figure 6**

*Drugs taken seven days previously*

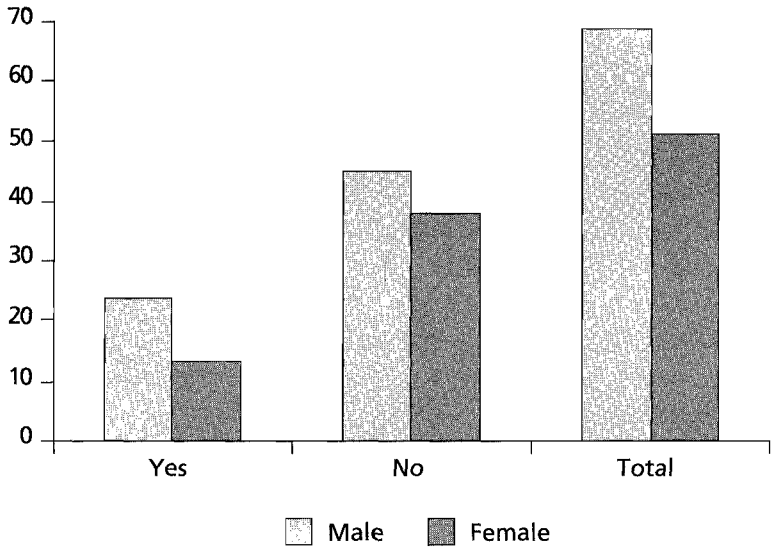
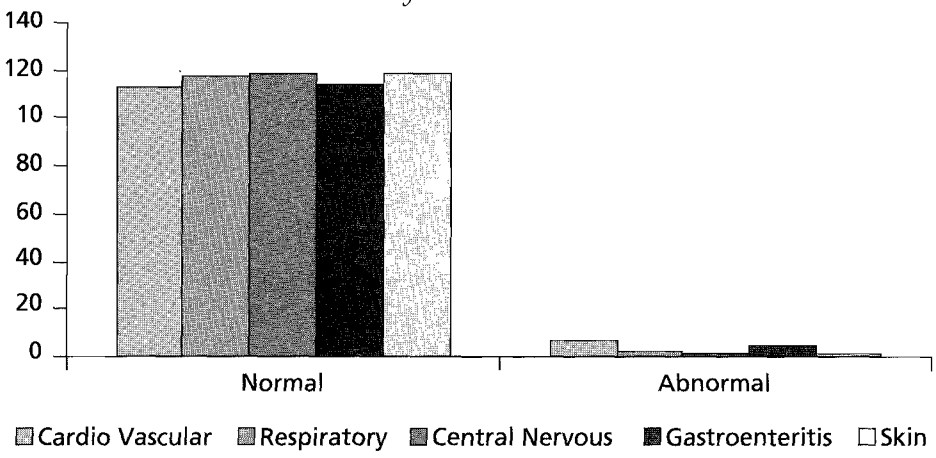



**Figure 7**

*Patients with system abnormalities detected*




The Chi-square test at df 8 was 9.230 at $P < 0.05$ indicating no significance. This shows that the abnormalities detected before the study did not influence the treatment outcome.

**Table 14**

*Treatment by sex*

| Drugs | Male | Female | Total |
|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 36 (60%) | 24 (40%) | 60 (100%) |
| Amodiaquine | 33 (55%) | 27 (45%) | 60 (100%) |
| Total | 69 (57.5%) | 51 (42.5%) | 120 (100%) |

**Table 15**

*Vomiting within one hour/dose replacement*

| Drugs | Yes | No | Total |
|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 0 (0%) | 60 (100%) | 60 (100%) |
| Amodiaquine | 0 (0%) | 60 (100%) | 60 (100%) |
| Total | 0 (0%) | 120 (100%) | 120 (100%) |

No patient vomited within one hour of taking any of the drugs.

**Table 16**

*Patients dropped from study (day 2 onwards)*

| Discontinued | Patients | (%) |
|---|---|---|
| Amodiaquine | 19 | 68 |
| Cotecxin® (dihydroartemisinin) | 7 | 25 |
| Follow up problem | 2 | 7 |
| Total | 28 | 100 |

28/120 (23.3%) patients were discontinued from the study due to treatment failure. 19/28 (68%) of those who discontinued were from the amodiaquine group. 7/28 (25%) were from Cotecxin® (dihydroartemisinin). This indicates that amodiaquine had more cases of failure than Cotecxin® (dihydroartemisinin) suspension.

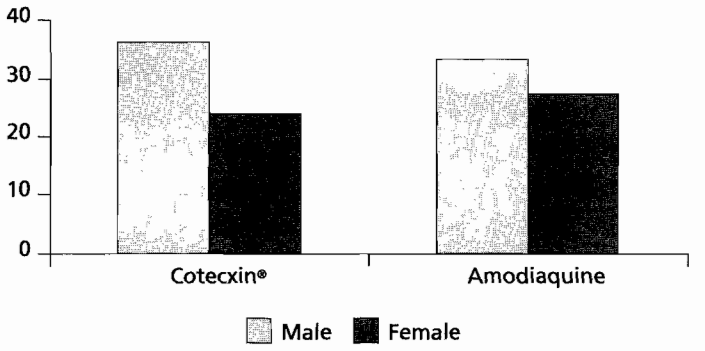
**Table 17**

*Parasite Clearance Time*

| Drug Taken/ Patients with parasites | D1 | D2 | D7 | D14 | D28 |
|---|---|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 60 | 36 | 11 | 3 | 0 |
| Amodiaquine | 60 | 44 | 6 | 6 | 0 |
| Total | 120 | 80 | 17 | 9 | 0 |

**Figure 8**

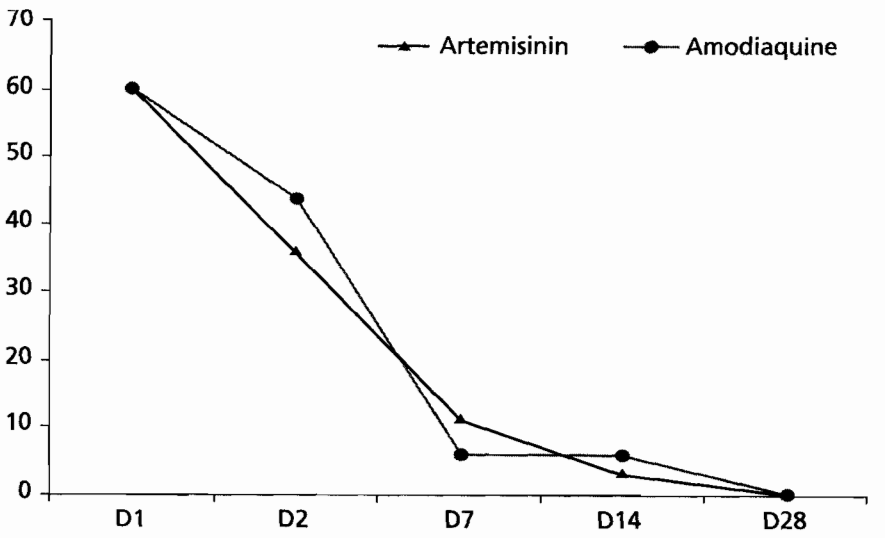
*Treatment by sex*




Cotecxin® (dihydroartemisinin) was taken by 36/120 (60%) male and 24/120 (40%) females. Amodiaquine was taken by 33/ 120 (55%) male compared to 27/120 (45%) females. In both drugs, the study took more males than females.

**Figure 9**

*Parasite clearance time*




Parasite clearance time is the time it takes a drug to reduce the parasites density (asexual forms) in the circulatory system to zero.

From Table 17 and Figure 9, Cotecxin® (dihydroartemisinin) demonstrated rapid parasite clearance than amodiaquine.

*Fever clearance time*

**(a) Table 18**

*Cotecxin® (dihydroartemisinin)*

| Day | Temp Minimum | Temp Maximum |
|---|---|---|
| 1 | 37.3 | 40.8 |
| 2 | 35.5 | 38.0 |
| 7 | 35.8 | 38.2 |
| 14 | 35.0 | 37.5 |
| 28 | 35.0 | 36.5 |

**(b) Table 19**

*Amodiaquine*

| Day | Temp Minimum | Temp Maximum |
|---|---|---|
| 1 | 30.0 | 40.4 |
| 2 | 35.7 | 39.7 |
| 7 | 35.0 | 39.0 |
| 14 | 35.6 | 39.0 |
| 28 | 35.0 | 37.1 |

From Tables 18 and 19 above it can be observed that patients treated with Cotecxin® (dihydroartemisinin) took shorter time for their temperature to return to normal than those on amodiaquine. During the study, the temperature results at P=0.0001 and P< 0.05 indicated that there was strong relationship between body temperature and drug taking; the temperature normalised after starting the treatment.

**Table 20**

*Presence of rash after follow up day one*

| Drugs | Yes | No | Total |
|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 0 (0%) | 55 (100%) | 55 (100%) |
| Amodiaquine | 1 (2.2%) | 44 (97.8%) | 45 (100%) |
| Total | 1 (1.0%) | 99 (99.0%) | 100 (100%) |

After day one, rash was observed in one (2.2%) patient treated with amodiaquine. No rash was observed with Cotecxin® (dihydroartemisinin) suspension.

**Table 21**

*Decrease in appetite after day one of taking drugs*

| Drug | Yes | No | Total |
|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 25 (45.5%) | 30 (54.5%) | 55 (100%) |
| Amodiaquine | 32 (71.1%) | 13 (28.9%) | 45 (100%) |
| Total | 57 (57.0%) | 43 (43.0%) | 100 (100%) |

There were fewer patients (45.5%)) with decreased appetite in day one on Cotecxin® (dihydroartemisinin) treatment than in amodiaquine (71.1%) as shown in Table 21.

**Table 22**

*Episodes of vomiting on subsequent follow ups*

| Drug | D1 | D2 | D7 | D14 | D28 |
|---|---|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 21 | 3 | 2 | 1 | 0 |
| Amodiaquine | 11 | 3 | 3 | 1 | 0 |
| Total | 32 | 6 | 5 | 2 | 0 |

Though vomiting episodes were observed in both groups of patients, there was evidence of improvement among patients who were treated with Cotecxin® (dihydroartemisinin).

**Table 23**

*Nausea episodes after taking Cotecxin® (dihydroartemisinin)*

| Day | Yes | No | Cum total |
|---|---|---|---|
| Day 1 | 26 | 34 | 60 |
| Day 2 | 9 | 51 | 60 |
| Day 7 | 7 | 48 | 55 |
| Day 14 | 3 | 52 | 55 |
| Day 28 | 1 | 54 | 55 |
| Total | 46 (16.1%) | 239 (83.9%) | 285 (100%) |

**Table 24**

*Nausea episodes after taking amodiaquine*

| Day | Yes | No | Total |
|---|---|---|---|
| Day 1 | 37 | 23 | 60 |
| Day 2 | 22 | 38 | 60 |
| Day 7 | 17 | 28 | 45 |
| Day 14 | 15 | 30 | 45 |
| Day 28 | 19 | 26 | 45 |
| Total | 110 (43.1%) | 145 (56.7%) | 255 (100%) |

**Table 25**

*Numbers of stools passed in the last 24 hours*

| Treatment/Patients | D1 | D2 | D7 | D14 | D28 |
|---|---|---|---|---|---|
| Cotecxin® (dihydroartemisinin) | 50 | 6 | 2 | 0 | 0 |
| Amodiaquine | 42 | 7 | 3 | 1 | 0 |
| Total | 92 | 13 | 5 | 1 | 0 |

*Laboratory examination of ASAT / ALAT*

**Table 26**

*ASAT*

| Variable | Value |
|---|---|
| Mean | 24.28 |
| SD | 16.73 |
| Standard error | 1.710 |
| STD test | 15.75 |
| P-value was | 0.001 at P<0.05 |
| Mode | 20.67 |

**Table 27**

*ALAT*

| Variable | Value |
|---|---|
| Mean | 32.54 |
| SD | 18.09 |
| Standard error | 41.87 |
| STD test | 15.75 |
| P-value was | 0.001 at P<0.05 |
| Mode | 24.00 |

Liver function tests assessed by alanine transaminase (ALAT) and aspartate transaminase (ASAT) were within normal ranges as observed in the investigation.

**Figure 10**

*Nausea after taking drugs (%)*

The episodes of nausea were more observed in patients who were treated with amodiaquine (43.1%) than those treated with Cotecxin® (dihydroartemisinin) (16.1%.)

## DISCUSSION

The research involved children between one and six years with symptoms of malaria at Malindi District Hospital during the period of study. The objective of the study was to assess the anti-malaria efficacy and safety of Cotecxin® (dihydroartemisinin) in comparison to amodiaquine suspension between January 23rd 2005 and February 27th, 2006.

To attain this, the following study objectives and sub-objectives were formulated.

(i) To assess the anti-malaria efficacy of Cotecxin® (dihydroartemisinin) suspension by comparison with amodiaquine suspension equivalent study.

(ii) To assess the safety of Cotecxin® (dihydroartemisinin) in comparison with amodiaquine. Research variables were:
(iii) Infant and children up to six years with clinical symptoms of malaria, falciparum parasite asexual form more or equal to 1000ml or large ring form more/equal to 300ml with high fever.

Chi-test and percentages were computed to measure relationships between various variables.

The respondent's ages from six to 72 months and the mean age was 36.33 months with a standard deviation of 16.87. For males, the mean age was 37.5 months and females 36.5 months and a standard error of 1.5401. All the study subjects met the inclusion criteria. The age was predetermined as part of the criteria. On gender, 51/120 (42.5%) of the respondents were females while 69/120 (57.5%) were males. Drugs taken seven days previously before the study were all non-malaria drugs. Those patients who took such drugs were 37/120 (30.83%.) This did not affect the study subjects, as there was no relationship between the drugs taken and the malaria treatment during the study.

On the test drug taken, Cotecxin® (dihydroartemisinin) and amodiaquine suspensions were given on 50/50 basis i.e. 60/120 (50%) for each. No significant amounts of side effects were noted after the study. The study realised remarkable improvement in patients on Cotecxin® (dihydroartemisinin) suspension compared with those who took amodiaquine.

There was nausea, decrease in appetite and episodes of vomiting among patients on amodiaquine suspension. The body systems abnormalities detected among some patients during the study did not have any influence on the results. This was tested at $P<0.05$ with c of 9.230 at 8 = df. The fact that no drug was replaced is a clear indication that both the two drugs treated malaria.

Some patients were discontinued from the study due to various reasons. Most of those who discontinued were those treated with amodiaquine; thus 21/60 (35%) while 5/60 (11%) were on Cotecxin® dihydroartemisinin). Reasons attributable to the discontinuation include: drug resistance, re-infections, and admission to hospital and lost to follow-up.

There was marked lowered temperatures among the patients put on Cotecxin® (dihydroartemisinin) compared with patients on amodiaquine. This was tested at $P<0.05$ and a strong relationship was established between drop in temperature and drugs taking.

The significant efficacy noted with Cotecxin® (dihydroartemisinin) in this study agrees with various studies done way back from 1972 in China and Vietnam; where the drug was confirmed to be highly effective with close to 100% cure rate for malaria. It has the ability to destroy the malaria parasites by releasing high doses of free radicals that attack the cell membrane of the parasite in the presence of high iron concentration. Over one million malaria patients have been cured via this method. Their symptoms also subsided in a matter of days.

Laboratory tests for safety and efficacy were done and though both drugs proved to be generally safe; Cotecxin® (dihydroartemisinin) proved to be much safer. amodiaquine had more side effects of nausea and vomiting. There is therefore significant evidence that Cotecxin® (dihydroartemisinin) is a more effective and safe drug that can be used as a first line drug for the treatment of malaria.

This is in tandem with the World Health Organisation (WHO) recommendation that a switch to artemisinin combination therapy (ACT) should be made in all countries where the malaria parasite has developed resistance to chloroquine. Artemisinin and its derivatives are now standard components of malaria treatment in China, Vietnam and other countries in Asia and Africa and other malarious areas of the world, where they have proved to be the best ever anti-malarial drugs. To date there is no evidence of drug resistance with artemisinin based compounds.

## CONCLUSIONS

The following are the generalised conclusions about treatment of malaria in children using Cotecxin® (dihydroartemisinin) and amodiaquine suspensions at Malindi District Hospital: (i)The efficacy and safety of Cotecxin® (dihydroartemisinin) was better than that of amodiaquine (ii) There were more treatment failures in patients treated with amodiaquine compared to patients on Cotecxin® (dihydroartemisinin), (iii) parasites clearance time was shorter in patients on Cotecxin® (dihydroartemisinin) than those on amodiaquine

(iv) fever clearance time was shorter in patients on Cotecxin® (dihydroartemisinin) than those on amodiaquine, (v) nausea episodes were observed more on patients who took amodiaquine than those who took Cotecxin® (dihydroartemisinin), hence Cotecxin® (dihydroartemisinin) is much safer than amodiaquine suspension, and (vi) reduced appetite was more on patients who took amodiaquine than those who took Cotecxin® (dihydroartemisinin).

## RECOMMENDATION

Based on the findings of this study, the following recommendation was made, namely that Cotecxin® (dihydroartemisinin) suspension should be used as a first line drug for the treatment of acute, uncomplicated malaria in children aged six years and below.

## REFERENCES


1. Janet E.J.L and Melvrick E.A. Review of medical microbiology. 14th Ed. Alder berg. 1980; 548.
2. Schull R.C. 1999. Common medical problems in the tropics. **55(2):** 1091, 1150.
3. White N.J. Malaria epidemiology. In: Cook G.C. and Alimuddin Z. Manson's Tropical Diseases. W. B. Saunders. 2003; 1205-1271.
4. Cook G.C. Communicable and tropical diseases. Heinemann, London. 1988; 63-64.
5. Bruce-Chwatt L.J. Transfusion malaria revisited. *Trop. Dis. Bull.* 1982; **79:** 827-884.
6. WHO and UNICEF. The Africa Malaria Report, 2003. 19, 32 and 56.
7. GoK/MOH. Malaria: Situation analysis for Kenya. 1998; 9-24.
8. GoK. District Development Plan-Nyamira. GPK. Nairobi. 1997; 10-15.
9. WHO. 2000a. Malaria Homepage: *http://www.who.int/cmcupload/0/000/016/327/MADpr.pdf*
10. WHO. 2002a. Malaria Homepage: *http://mosquito.who.int/cmcupload/0/000/015/370/RBMinfosheet-3.htm*
11. Samba M.E. Statement on the African Summit on RBM. Africa Health Monitor. Vol. 1. WHO Regional Office for Africa. 2000; 2.
12. Bruce-Chwatt L.J. Essential Malariology. W. Heineman Medical Books London. 1985
13. Gilles H.M. and Warrel D.A. Environmental factors in malaria spread. In: Bruce-Chwatt L.J. Essential Malariology. Edward Arnold. London. 1993.
14. Colluzi M. Malaria and the Afrotropical ecosystem: Impact of man-made environmental changes. *Parasitologia.* 1994; **36:** 223-227.
15. MOH/DOMC. Malaria Information System Database: Malaria outpatient morbidity cases by health facility (unpublished). 2003.
16. Rozendaal J.A. Vector control: Methods for use by individuals and communities. WHO, Geneva. 1997; 27, 52, 58, 99,105.
17. Bannister A.B., Begg T.N. and Gillespie H.S. Travel Associated Diseases. 2nd Ed. Blackwell Science. London UK. 2000; **436, 447:** 449-4450.
18. Kouznetsov R.L. Malaria: A manual for community health workers. WHO, Geneva Electronically accessed through: *http://www.who.int/enl/* 1996.
19. WHO, 2000b. Management of severe malaria. A practical handbook. 2nd Ed. WHO. Geneva. 1, 64.
20. GoK/MOH/DOMU. Integrated Disease Surveillance and Response: Technical guidelines (First Draft). 2001; 199.
21. Some E.S. Optimizing the community effectiveness of Insecticide Impregnated Bed Nets used for malaria control in Coastal Kenya: Implications of perceptions, programme organization, compliance and costs. PhD Thesis. 1999; 26-30, 40-47.
22. WHO. 2002b. Malaria control in complex emergencies – an inter-agencies handbook. Geneva, Switzerland. 7, 69, 97,106, 111,123.
23. Coosemans M., Wery M., Mouchet J. and Camevale P. Transmission factors in malaria epidemiology and control in Africa. Mem Institute. Oswaso. Cruz. 87. Suppl. 1992; **3:** 385-391.
24. Malaria Consortium. Malaria update electronic access: (*http://www.malariaconsortium.org*) 2001.
25. AMREF. Amref homepage. 2003. *http://www.amref.org/malaria.htm*
26. GoK/MoH, 2002. Focused Antenatal Care in Pregnancy: Baseline survey report of Few Malaria Endemic Districts of Kenya. V.
27. Snow R.W., Phillips A., Lindsay S.W. and Greenwood B.M. How best to treat bed nets with insecticide in the field. *Trans. Royal Soc. Trop. Med. Hyg.* 1988; **82:** 647-648.
28. MOH. 2001. National Malaria Strategy. 2001–2010.
29. d'Alessandro U., Olaleye B.O., McGuirew, *et al.* Mortality and morbidity from malaria in Gambian children after introduction of impregnated bed net programme. *Lancet.* 1995; **345:** 479-483.
30. Hargreaves K. Anopheles funestus resistant pyrethroid insecticide in S. Africa. *Med. Vet. Entomol.* 2000; **14:** 181-189.

31. Chavasse D., Reed C. and Attawel K. Insecticide Treated Nets projects: A handbook for managers. Malaria Consortium. London. Electronic access. 1999 (*http://www.malariaconsortium.org*).
32. Hill J. KAP survey on malaria prevention and control in Kabar West, Kisumu, Kenya. UNICEF Report. 1989.
33. Meek S. A survey of the KAP of the population of Ovamboland, Northeast Namibia related to malaria and of the effectiveness of the residual spraying programme. Draft. Quoted in Hill J. Approaches to malaria control in Africa. Part I: A malaria Consortium Initiative 1996. Consortium Initiative, Liverpool School of Tropical Medicine. 1999.
34. Mendez F., Carrasquilla G. and Munoz A. Risk factors associated with malaria in an urban setting. *Trans. Royal Soc. Trop. Med. Hyg.* 2000; **94:** 367-371.
35. Baird J.K. Host age as a determinant of acquired immunity to *Plasmodium falciparum. Parasitol. Today.* 1995; **11:** 105-111.
36. Carme B., Rogier C. and Trape J.F. Risk factors for severe malaria: Importance of careful study design: A correspondence in *Trans. Royal Soc. Trop. Med. Hyg.* 1999; **94:** 89.
37. Aranha L.M., Duccini G.M., Urbano M., *et al.* Hypoendemic malaria in Rondania (Brazil, Western Amazon Region): Seasonal variation and risk groups in an urban locality. *Amer. J. Trop. Med. Hyg.* 1996; **55:** 32-38.
38. Standing H. A situation analysis and opportunities for malaria control support in selected countries in Africa I: social development. Malaria consortium report Electronic access: (*http://www.malariaconsortium.org*) 1996.
39. Hill J. Approaches to malaria control in Africa. Part I: A malaria consortium initiative. Malaria consortium, Liverpool School of Tropical Medicine, London. 1996; **12, 43:**
40. Terney A. A situation analysis and opportunities for malaria control support in Tanzania III: Social Development. Malaria Consortium Report. (*http://www.malariaconsortium.org*) 1993.
41. Geldermalsen A.A. and Munochiveyi R. Knowledge, attitude and practice relating to malaria in Mashonaland, Central Zimbabwe. *Central Afr. J. Med.* 1995 ; **41:** 10-14.
42. Chimumbwa J. A community-based programme in Zambia. Luapula community-based malaria prevention and control programme. Presentation at second international conference on ITNs, Dar es Saalam, United Republic of Tanzania. In WHO & UNICEF, 2003. Africa Malaria Report: ITNs. Geneva. 27, 1999.
43. Salah A.O. Study of factors associated with malaria and its effects on the population in the Republic of Somalia (a case of Beletwein Town). A dissertation presented to AMREF School of Community Health. 2001; 37-44.
44. Wabomba F.M. Factors contributing to increased malaria incidence in Keumbu Division, Kisii, Kenya. A dissertation presented to AMREF School of Community Health. 1999; 39.
45. Massong A. Research for development review. Quoted in Bokuma M., 2001. Use of antimalarial treatment during pregnancy in an area of low transmission (a case of Entasopia, Kajiado District-Kenya). 1997.
46. Ntomola S. Knowledge, attitude and practice among the rural community in Utengule Irrigation Scheme – a case of Mbeya Rural District, Tanzania. A dissertation presented to AMREF School of Community Health. 2001; 29.
47. Gwadz W.R. Development of the malaria parasite in the mosquito. In: Lopez-Antunano F.J. and Schmunis G. (Eds). Diagnosis of malaria. *Pan Amer. Hlth. Org.* 2000; 19.
48. Rajagopalan P.K., Das P.K., Panicker K.N, Reuben R., Rao D.R., Self F.S. and Lines J.D. Environmental and water management of mosquito control. 1991; 34-40.
49. WHO. A global strategy for malaria control. Malaria Control Unit. Division of Tropical Diseases. WHO. Geneva. 1993; 1-3.
50. Zahar A.R. Vector control operations in the African context. *Bull. WHO.* 1984; **62:** 89-100.
51. Dlamini B.G. Knowledge, attitude and practice on malaria control in Sagana, Kirinyaga, Rukanga sub-location. A dissertation presented to AMREF School of Community Health. 1999; 51.
52. Ghebreyesus T.A., Haile M.,Witten H.K, *et al.* Household risk factors for malaria among the children in the Ethiopian Highlands. *Trans. Royal Soc. Trop. Med. Hyg.* 2000; **94:** 17-21.
53. Braack L.E., Coetzee M., Hunt R.H., Biggs H., Cornel A. and Gericke A. Biting pattern and host-seeking behaviour of *Anopheles arabiensis* (Diptera: Culicidae) in Northeastern South Africa. *J. Med. Epidemiol.* 1994; **31:** 333-339.
54. Nieto T., Mendez F., and Carrasquilla G. Knowledge, beliefs and practices relevant for malaria control in endemic area of the Colombia Pacific. *Social Sci. Med.* 1999; **49:** 601-609.
55. Mutero C.M., Ouma J.H., Agak B.K., Wanderi J.A. and Copeland R.S. Malaria prevalence and use of self-

protection measures against mosquitoes in Suba District, Kenya. *East Afr. Med. J.* 1998 **75:** 11-15.

56. Dolan G. Bed nets for the prevention of malaria and anaemia in pregnancy. *Trans. Royal Soc. Trop. Med. Hyg.* 1991; **87:** 620-626.
57. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochcrane Review, 2001; Issue 4.
58. Curtis C.F. and Mnzava A.E. Comparison of house spraying and ITNs for malaria control. *Bull. WHO.* 2000; **27:** 1389-1400.
59. Rowland M. Transmission and control of vivax malaria in Afghanistan refugee villages in Pakistan. *Trans. Royal Soc. Trop. Med. Hyg.* 1997; **91:** 255-257.
60. Luxemburger C. Permethrin-impregnated bed nets for the prevention of malaria in school children on the Thai-Burmese border. *Trans. Royal Soc. Trop. Med. Hyg.* 1994; **88:** 155-159.
61. Olano V., Carrasquilla G. and Mendez F. Urban malaria transmission in Buenaventura, Columbia: entomological aspects. *Pan Amer. J. Public Hlth.* 1997; **2:** 378-385.
62. Demographic and Health surveys (DHS). Calverton, MD, DRS Marco. (Electronic access – *http://www.measuredhs.com*).
63. Lumiti C.L. Factors contributing to increased incidence of malaria in Kilgoris Division, Transmara, District, Kenya. A dissertation presented to AMREF School of Community Health. 2000; 23-34.
64. Kasungi J.M. Factors influencing use of insecticide treated nets as a strategy for malaria prevention at household level. A case of Muusini sub-location, Makueni District. Dissertation submitted to Kenya Medical Training College. 2002; 46-47.
65. Hadis M., Lulu M., Makonnen Y. and Asfaw T. Host choice by indoor-resting Anopheles arabiensis in Ethiopia. *Trans. Royal Soc. Trop. Med. Hyg.* 1997; **91:** 376-378.
66. Adiamah J.H., Koram K.A., Thomson M.C., Lindsay S.W., Todd J. and Greenwood B.M. Entomological risk factors for severe malaria in a peri-urban area of the Gambia. *Annals Trop. Med. Parasitol.* 1993; **99:** 1-10.
67. Bowma M. and Rowland M. Failure of passive zooprophylaxis: cattle ownership in Pakistan associated with higher prevalence of malaria. *Trans. Royal Soc. Trop. Med. Hyg.* 1995; **89:** 351-353.
68. Schofield C.J. and White G.B. Engineering against insect-borne diseases in the domestic environment: house design and domestic vectors of disease. *Trans. Royal Soc. Trop. Med. Hyg.* 1984; **78:** 285-292.
69. Koram K.A., Bennet S., Adiamah J. H. and Greenwood B.M. Socio-economic risk factors for malaria in a peri-urban area of the Gambia. *Trans. Royal Soc. Trop. Med. Hyg.* 1995; **89:** 146-150.
70. Mendis C., Gamage-Mendis A.C. and de Zoysa A.P.K. Characteristics of malaria transmission in Kataragama, Sri Lanka: a focus for immunoepidemiological studies. *Amer. J. Trop. Med. Hyg.* **42:** 298-308.
71. Gamage-Mendis A.C., Carter R., Mendis C. de Zoysa A.P.K., Herath P.R.J. and Mendis K.N. Clustering of malaria infections within an endemic population: risk of malaria associated with the type of housing construction. *Amer. J. Trop. Med. Hyg.* 1991; **45:** 77-85.
72. Gunawardena D.M., Wickremasinghe A.R., Muthuwatta L., *et al.* Malaria risk factors in an endemic region of Sri Lanka, and the impact and cost implications of risk-factor interventions. *Amer. J. Trop. Med. Hyg.*1998; **58:** 533-542.
73. Palsson K. 1999. Ecology and control of Anopheles mosquitoes and human malaria in Guinea Bissau, West Africa. PhD Thesis, Uppsala University, Sweden. Quoted in Mendez *et al.* Household risk factors for malaria among children in the Ethiopian Highlands. *Trans. Royal Soc. Trop. Med. Hyg.* 2000; **94:** 17-21.
74. Lindsay S.W. and Snow R.W. The trouble with eaves; house entry by vectors of malaria. *Trans. Royal Soc. Trop. Med. Hyg.* 1988; **84:** 553-562.
75. El Samani F.Z., Willet W.C. and Ware J.H. Nutritional and socio-demographic risk indicators of malaria in children under five: a cross sectional study in a Sudanese rural community. *J. Trop. Med. Hyg.* 1987; **90:** 69-78.
76. Kuate-Defo B. Epidemiology and control of infant and early childhood malaria: a competing risk analysis. *Int. J. Epidemiol.* 1995; **24:** 204-217.
77. Gillies M.T. Anopheline mosquitoes: vector behaviour and bionomics. In: principles and practice of malariology, Wernsdorfer W.H. and Mc Gregor I. (Eds). Churchill-Livingstone. 1988; 453-500.
78. Galun R., Koontz L.C., Gwadz R.W. and Ribeiro J.P. M. Effect of ATP androgus on the gorging response of Aedes agypti. *Physiol. Entomol.* 1985; **10:** 275-281.
80. Steffen R., Fuchs E., Schindknecht J., *et al.* Mefloquine compared with other malaria chemoprophilactic regimens in tourists visiting East Africa. *Lancet.* 1993; **341:** 1299-1303.
81. Greenwood B.M., Greewood A.M. and Bradley A.K. Comparison of two strategies for control of malaria within primary health care programme in The Gambia. *Lancet.* 1988; **1:** 1121-1128.
82. White N. and Nosten F. Advances in chemotherapy and prophylaxis of malaria. *Current options in infectious Disease.* 1993; **6:** 323-330.

83. Lobel H.O. and Kozarky P.E. Update on prevention of malaria for travelers. *JAMA*. 1997; **278:** 1767-1771.
84. Kaseje D.C., Sepembwa E.K. and Spencer HC. Malaria chemoprophylaxis to pregnant women provided by CHW in Saradidi, Kenya. Reasons for non-acceptance. *Ann. Trop. Med. Parasitol.* 81: Suppl. 1987; **1:** 17-82.
85. Brinkman U. and Brinkman A. Malaria and health in Africa: The present situation and epidemiological trends. *Trop. Med. Parasitol.* 1991
86. AMREF. Malaria Data Sheet. 1. 1997
87. Mc Combie S.C. Treatment seeking for malaria: A review and suggestions for future research. Papers for social and economic research in tropical diseases. No.2 UNDP/WORLD BANK/WHO. 1994.
88. Foster S. Treatment of malaria outside formal health services. *J. Trop. Med. Hyg.* 1995; **19:** 29-34.
89. Snow R.W., Peshu N., Foster P., Mwenesi H. and Marsh K. The role of shops in the treatment and prevention of childhood malaria on the Kenyan Coast. *Trans. Royal Soc. Trop. Med. Hyg.* 1992; **86:** 237-339.
90. Munguti K.J. Community perception and treatment seeking of malaria in Baringo District, Kenya: Implications for disease control. *East Afr. Med. J.* 1998; **86:** 687-691.
91. Chiumia G. Evaluation of the Sagana malaria control programme. A dissertation presented to AMREF School of Community Health. 38. 2002
92. Mwenesi H., Harphan T. and Snow R.W. Child malaria treatment practices among mothers in Kenya. *Soc. Sci. Med.* 1995; **40:** 1271-1277.
93. Nyamongo I.K. Home case management of malaria: an ethnographic study of lay people's classification of drugs in Suneka Division, Kisii District, Kenya. *Trop. Med. Hyg.* 1999; **4:** 736-743.
94. Bokuma M. Use of antimalarial treatment during pregnancy in an area of low transmission (a case of Entasopia, Kajiado District-Kenya). 2001
95. Fisher A.A., Lang J.E., Stoeckel J.E. and Townsend J.W. Handbook for Family Planning Operations Research Design. 1991; **2:** 45-46.