Malaria in children at Haydom Hospital in Tanzania

A fifth year project by:

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Summary

Background:

Malaria is a parasitic disease which kills somewhere between 0.5 to 3.0 million people each year, 75% of these are children under the age of five. The most affected region is sub-Saharan Africa. Our aim was to study malaria in children admitted at Haydom Lutheran Hospital (HLH), which is remotely situated in the Mbulu district in northern Tanzania. The hospital covers an area with around 440 000 people and malaria is endemic in this area.

Material and methods:

We conducted a follow up study in a period from 27.06.06 to 17.07.06 where we registered all patients below five years of age who were admitted with fever or other possible symptoms of malaria, and all children treated with quinine. The following data were registered: age, sex, length of admission, blood slide, fever, Hb, treatment and symptoms and outcome.

Results/Discussion:

191 patients were included during the 3 week study period. The median age of the patients was 8 months and median admission length was 5 days. 12 of 191 patients died (6% mortality).

72 children received a final clinical diagnosis of malaria, before considering the results of the blood slide. However, only 14 of 72 (19 %) had a positive malaria blood slide. 119 patients received different non-malaria diagnoses, but 7 (6 %) of these also had positive blood slide.

There are significantly more positive blood slides in the group with the final clinical diagnosis of malaria compared to the rest of the patients ($p < 0.001$), indicating that clinicians may recognize malaria clinically in 2/3 of all blood slide positive cases. 1/3 of the patients with positive blood slide did not receive a malaria diagnosis, still all of them received antimalaria treatment. In total 21 out of 185 patients had positive blood slide, which is lower than expected in an endemic area. However the registration was done in the dry season when the prevalence malaria in this area is fairly low. Many of the children were very young, and because of immunity due to maternal transfer of malaria antibodies they are not highly susceptible to get malaria.

Despite the outcome of the lab results, the clinical state of the child was the most important criteria for starting treatment. The time from admission and start of treatment to the lab results arriving at the ward varied much and did not influence the anti malaria treatment. Since the decision was made to treat with antimalaria based on the clinical state of the child, it is correct to finish the treatment even if lab results later could not confirm the malaria diagnose.

29 patients without the malaria diagnose got antimalaria treatment. This suggests that the use of quinine was liberal at HLH. Over treatment with antimalarias can cause drug resistance and it is considered a major problem in Africa.

History

The characteristic symptoms of malaria were described as early as in 2700 BC in China. Hippocrates made detailed accounts on the principal symptoms of malaria 500 BC (1). The Roman, Assyrian, Indian, Arabic and European physicians have recorded the disease up to the 19th century (2). In a Sanskrit medical treatise called Susruta, malaria was associated with bites of insects. Romans thought the "mal aria" (bad air) came from the miasmas rising from the swamps.

The plant which artemisinin is extracted from was first described in China more than 2200 years ago in the work "52 remidies". Artemisinin was isolated in 1971 by Chinese scientists (1).

Spanish missionaries learned from South America's natives that the bark of a special tree cured fever. The Countess of Chinchon (married to the viceroy of Peru) was cured by this bark in the 17th century, and the bark was named Peruvian bark and the tree Cinchona. The modern name of the medicine extracted from the bark is quinine (1).

A French army surgeon named Charles Louis Alphonse Laveran discovered parasites in the blood from a patient suffering from malaria. He made his discovery in 1880 and was awarded the Nobel Prize of medicine in 1907 (1).

An Italian neurophysiologist called Cammilo Golgi discovered that there were at least two forms of the disease. He also found that the rupture of red blood cells and release of merozoites caused fever. He made his discoveries in 1886 and was awarded the Nobel Prize of medicine in 1906 (1).

In 1890 Giovanni Batista Grassi and Raimondo Filetti introduced the names P. vivax and P. malariae. Grassi also demonstrated a few years later malaria transmission (1899) by letting Anopheles mosquitoes feed on a patient in Rome, thereby transporting the mosquitoes to London and let them feed on two healthy volunteers who developed malaria. Two years earlier in 1897 Ronald Ross demonstrated that malaria was transmitted by mosquitoes. For this discovery Ronald Ross was awarded the Nobel Prize of medicine in 1902 (1).

In 1897 William H. Welch named the malignant form of the parasite P. falciparum.

Chloroquine was discovered in 1934 by Hans Andersag. Chloroquine was established as a safe anti-malaria remedy in 1946 by British and US scientists (1).

The World Health Organization (WHO) ambitiously made a proposal for the eradication of malaria worldwide in 1955. The strategies were based insecticides, anti-malaria drugs treatment and surveillance. They had a four step plan; preparation, attack, consolidation and maintenance. In some nations malaria was eradicated, but in most countries the eradication goal had to be given up. Most of Sub-Saharan Africa was never even in the eradication program. Many factors made the campaign against malaria difficult; drug resistance, resistance to insecticides, wars, population movements, lack of funding and lack of community participation (1).

Roll Back Malaria is an international alliance of more than 90 organizations including WHO, UNICEF and the World Bank. It was initiated in 1998 and their goal was to halve malaria mortality by the year 2010 (3). The tools to achieve this goal are bed nets, effective combination treatments based on artemisinin and insecticides (4). WHO plays a key role in the way this alliance is organized. WHO coordinate the economy, knowledge, research, supervision etc (5). In 2005, seven years after the RBM was formed, the malaria rates have

increased. The RBM has been a dysfunctional organization which have had trouble making decisions and therefore losing credibility from the international community, this and lack of proper funding from the donors are the main reasons why RBM has been a failure so far (3).

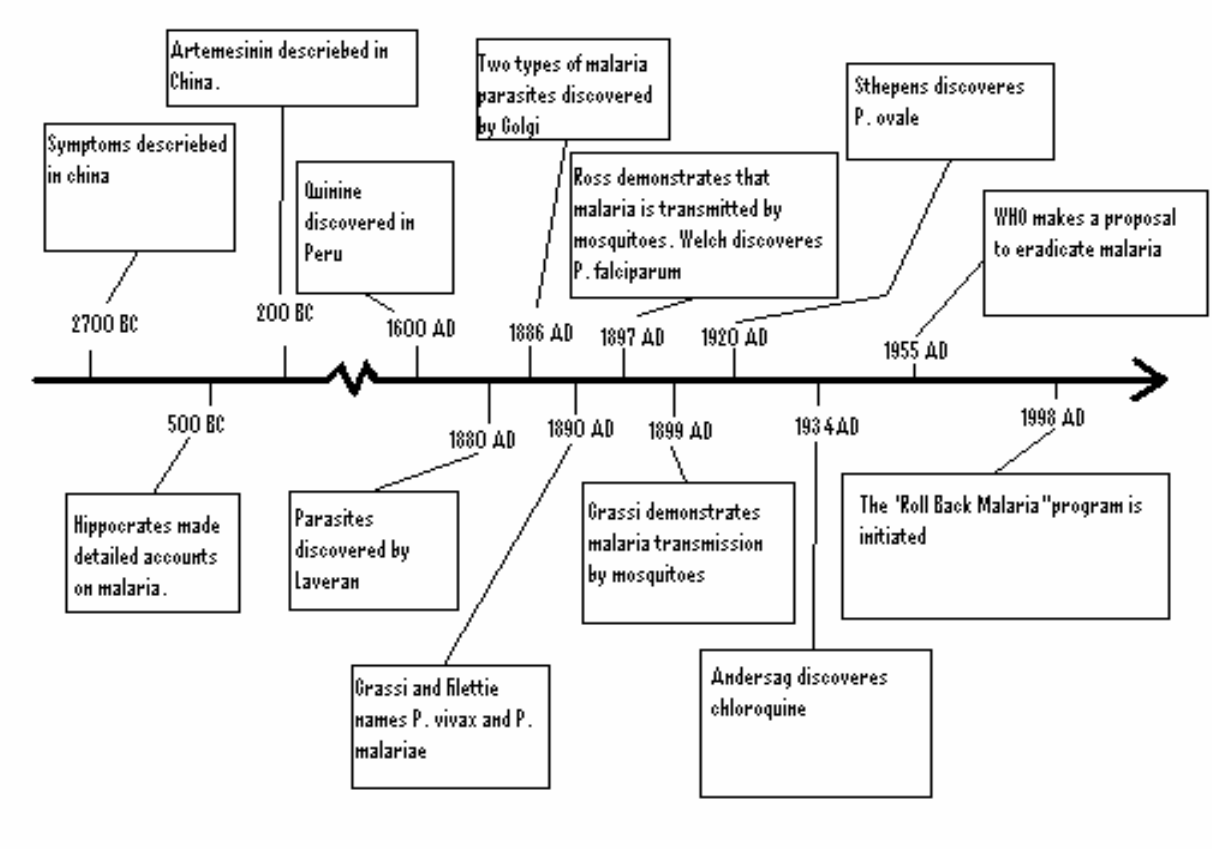

Fig. 1. Timeline of historic events.

Evolution of malaria

Malaria parasites

Genetic evidence suggests that the ancestor of the malaria parasite arise more than 500 million years ago. These “pre-malaria parasites” acquired at an early stage in their evolution an asexual form of reproduction called schizogony. Schizogony is a form of reproduction where the parasite forms a number of daughter cells within one host cell. This “technique” greatly enhanced the growth rate of the parasite. About 150 million years ago the “pre-malaria parasite” adapted to Diptera insects, which is the ancestor to today’s Anopheles mosquito. There are today more than 25 named plasmodium species which infect primates. Four of the species are human parasites; P. falciparum, P. vivax, P. malaria and P. ovale. P. falciparum’s lineage separated from the other human malaria species more than 130 million years ago. P.vivax, P. malaria and P. ovale diverged over 100 million years ago (6).

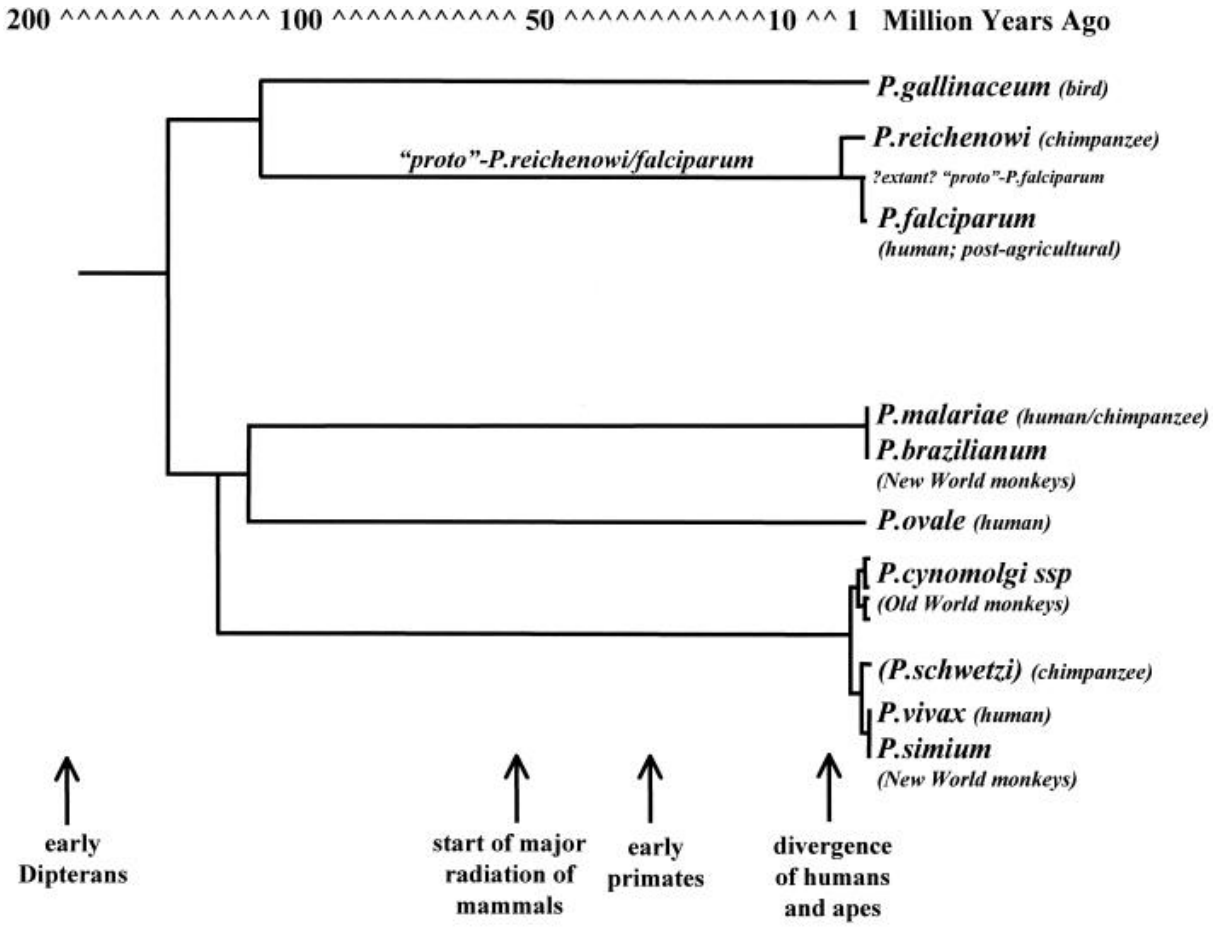

Fig. 2. Phylogeny of the malaria parasites of humans and some other related malaria parasite species (3).

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P. ovale is known to solely infect humans. P. malaria on the other hand has been found in an indistinguishable form to infect other primates, and P. vivax has close related malaria parasites which infect monkeys in south-southeast Asia. Evidence from human genetic data suggests that the origin of P. falciparum is in West Africa within a thousand years ago, due to the agrarian revolution (6).

The vector

The mosquitoes of the anopheles genus are the vector which carries the parasite. Of the approximately 400 anopheles species, 30-40 transmit malaria. Anopheles gambiae is the best known, because it is an important vector of P. falciparum (7).

Outside of Africa mosquito vectors prefer to feed on animals rather than on humans. In most parts of the world the probability of the vectors blood meal being human is less than 10-20%. In Sub-Saharan Africa the probability is 80-100%. If a vector takes 1/10 of their blood meal from humans they will transmit the disease 100 times less frequently than mosquitoes taking all their blood from humans. This might be the single most important reason for the high intensity and stability of malaria transmission in Sub-Saharan Africa (6). Entomological inoculation rate (infective bites per year) is high in Africa, especially in sub-Saharan Africa. This contributes to higher incidence in general and very high incidence among children (8).

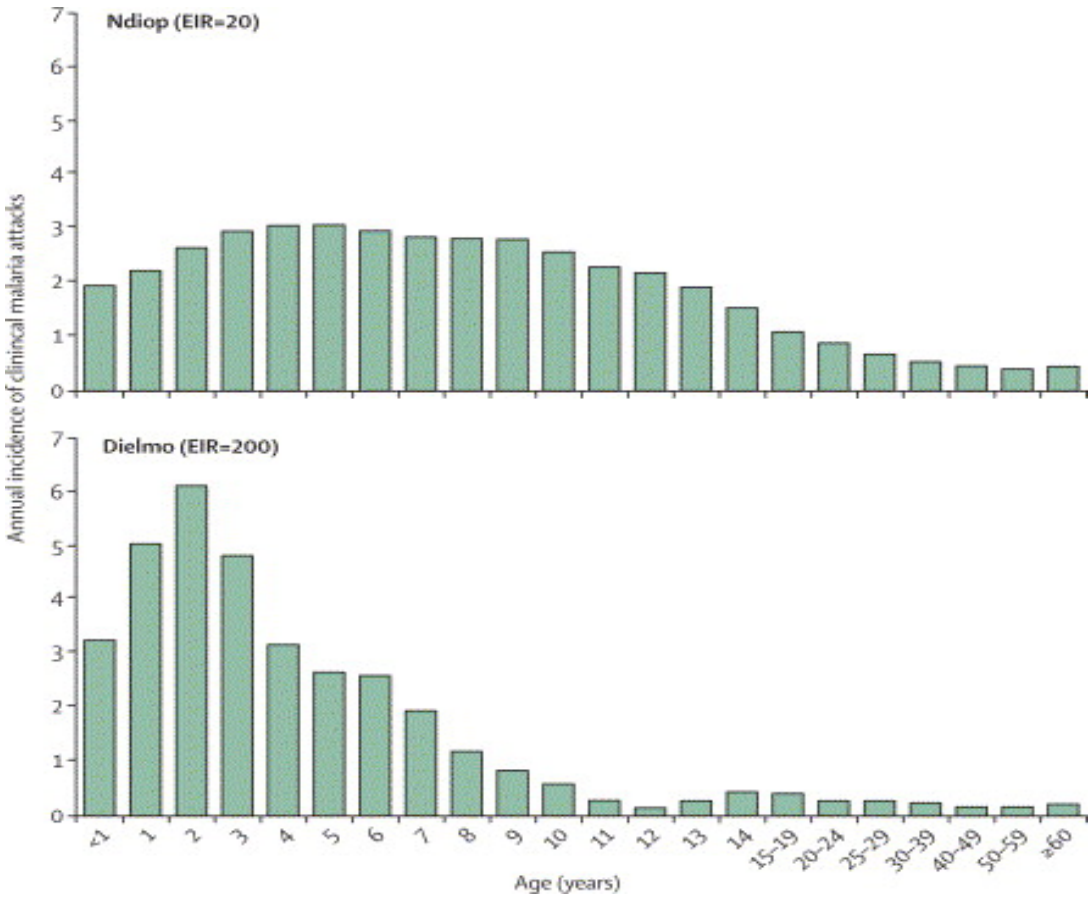

Fig. 3. Annual incidence of malaria attacks in residents of two Senegalese villages with different P falciparum transmission (8).

EIR = entomological inoculation rate

Epidemiology

It is estimated that more than a third of the world's population live in malaria-endemic areas. Estimates suggest that one billion people are infected with the parasite at any given time (9). Plasmodium falciparum is the most dangerous specie; it is responsible for most of the deaths caused by malaria (10). 95% of the malaria cases are caused by either falciparum or vivax.

Malaria causes 0.5 – 3.0 million deaths each year. 75% of these deaths occur in African children under the age of five (11). 20% of the total deaths in children under five years of age in Africa is due to malaria, and malaria constitutes 10% of the total disease burden in Africa (12). It is estimated 200-450 million cases of fever in children infected by malaria parasites each year in Africa (9). The most affected regions in the world are Sub-Saharan Africa and Southeast Asia.

Malaria in pregnancy is believed to account for up to 25% of the severe maternal anemia cases, and could account for 10-20% of neonatal and infant deaths based on effects of low birth weight (10).

The estimates are imprecise because little investment has been put into documentation. The mortality of malaria is especially difficult to measure because most deaths occur at home, and the symptoms are non-specific (9).

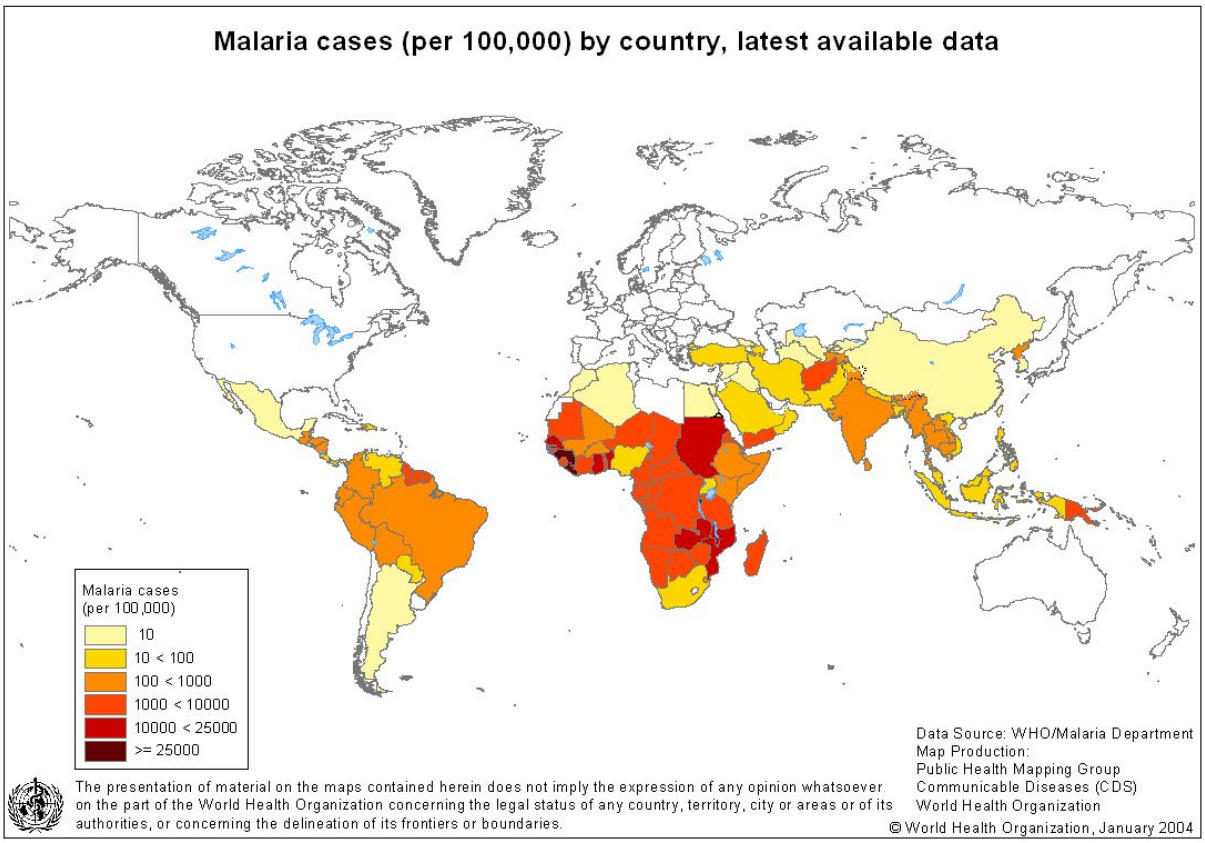

Fig. 4. Malaria cases worldwide

Pathophysiology

The female Anopheles mosquito requires blood as nutrition for reproduction, and this blood is drawn from people (13). When one mosquito bites a malaria-infected person, the mosquito becomes a carrier for the parasite and is able to transmit the disease to the next person on the mosquito's menu. Normally it takes a number of bites from different carrier mosquitoes for a person to get infected, depending on the mosquito and the immunity of the victim.

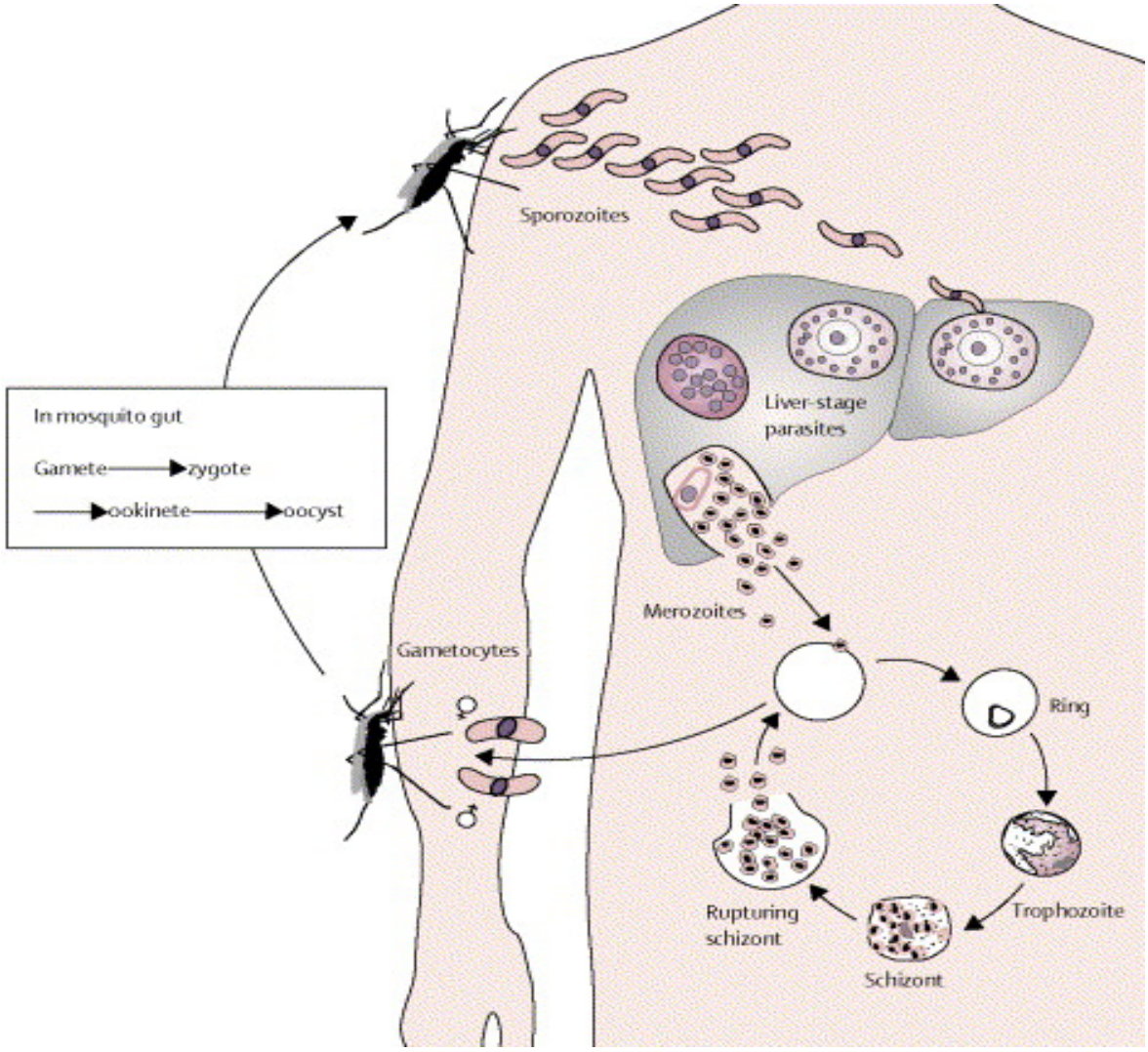

Fig. 5. Life cycle of the malaria parasite (10)

1. The infected anopheles mosquito feed on a human being. The parasite is injected into the blood of the human host. The infectious stage of the parasite is called sporozoites.

2. The sporozoites go with the blood to the liver where they enter the liver cells. They multiply inside the liver cells and the daughter cells of the sporozoite are called merozoites. The infected liver cells rupture and thousands of merozoites are released into the blood.

3. The merozoites invade red blood cells where they multiply until the red blood cell rupture and release more merozoites. These merozoites invade more red blood cells.

4. Some merozoites develop into sexual stages, the male and female gametocyte. These gametocytes can be transmitted to a feeding mosquito.

5. In the gut of the mosquito the gametocytes goes through different stages to form an oocyst. Inside the oocyst, sporozoites develop and these sporozoites infect the salivary glands of the mosquito.

Symptoms and signs of malaria in children

The main symptom of uncomplicated malaria in children is fever. The fever is normally recurrent and irregular. Other symptoms in infants are irritability, poor feeding, vomiting, jaundice and splenomegaly. Older children may present with headache, backache, chills, myalgia and fatigue. Between attacks, the patient may look quite well (14). The clinical manifestations vary according to strain and host immunity.

In areas with stable transmission anemia is a common sign in young children. Enlargement of the spleen and slight enlargement of the liver is common (15).

The symptoms and signs of severe malaria are coma, acidosis, severe anemia, renal failure, pulmonary edema, hypoglycemia, hypotension, bleeding, convulsions, hemoglobinuria, impaired consciousness, extreme weakness, hyperparasitemia and jaundice. In children anemia, convulsions, hypoglycemia, coma and metabolic acidosis are the most common signs of severe malaria, in adults jaundice, renal failure and pulmonary edema are most often present (15).

When a malaria parasite invades a red blood cell it consumes and degrades intracellular proteins, including hemoglobin. This can cause anemia. The membrane of the erythrocyte is altered by the P falciparum parasite. Protuberances (“knobs”) appear on the red blood cell surface and these extrude an adhesive protein that cause cytoadherence to venular and

capillary endothelium. Infected red blood cells may also attach to uninfected red blood cells. Cytoadherence and agglutination result in sequestering of red blood cells in vital organs (15).

Because of interfered microcirculatory flow, lactate production of the parasite, hypovolemia and a failure of hepatic and renal lactate clearance, lactic acidosis may occur (15).

Hypoglycemia is common complication in malaria patients, especially in children. The reason for the hypoglycemia is impaired hepatic gluconeogenesis and increased consumption of glucose in the host (15).

Anemia is a result of increased destruction of red blood cells by the spleen and ineffective erythropoiesis. Anemia can develop rapid and blood transfusion is often required. Anemia is a common sign of severe malaria in children (15).

Mild thrombocytopenia is common and some with severe malaria experience disseminated intravascular coagulation (15).

Convulsion is a common severe complication in children with falciparum malaria. Convulsions may lead to aspiration pneumonia which is an important cause of death in cerebral malaria (15).

Jaundice is more common in adults than in children and is due to hemolysis, hepatocyte injury and cholestasis. If the liver is severely damaged it contributes to hypoglycemia, lactic acidosis and impaired drug metabolism (15).

Renal impairment is rare among children with severe falciparum malaria, but common in adults. The syndrome manifests as acute tubular necrosis and may be related to erythrocyte sequestration interfering with microcirculatory flow and metabolism (15).

Pulmonary edema may develop in adults after several days of antimalarial treatment (15).

The definition of cerebral malaria is unrousable coma and no other cause of encephalopathy in the presence of P falciparum infection (15).

Diagnosis

The signs and symptoms of malaria are non-specific. The main symptom is fever. WHO guidelines have the following recommendations:

- In general, in settings where the risk of malaria is low, clinical diagnosis of uncomplicated malaria should be based on the degree of exposure to malaria and a history of fever in the previous 3 days with no features of other severe diseases.
- In settings where the risk of malaria is high, clinical diagnosis should be based on a history of fever in the previous 24 h and/or the presence of anaemia, for which pallor of the palms appears to be the most reliable sign in young children (16).

Parasitological diagnosis is important because over-diagnosis has become a major issue. Drug combinations are the preferred form of first-line treatment and these drugs are expensive and in a relatively short supply (10).

Microscopy

Light microscopy has high sensitivity and specificity depending on the quality of equipment and personnel (16). The parasites asexual form is demonstrated on stained peripheral blood smears. The Giemsa stain is preferred, but Wright's, Field's or Leishman's stain can also be used. Thin and thick blood smear is examined. The thick smear has high sensitivity. Examination of the thin smear under oil immersion at x1000 magnification can reveal the plasmodium specie and determine the parasite density. The number of parasitized

erythrocytes is counted per 1000 red blood cells or per 200 white blood cells. This figure is converted to number of parasitized erythrocytes per microliter. In general more than 10000 parasites per microliter is related to poor prognosis, however non-immune patients may die at lower counts and semi-immune patients may tolerate higher counts. A predominance of more mature P. falciparum parasites indicates a bad prognosis in severe malaria (15).

Rapid Diagnostic Tests

Several rapid diagnostic tests based on antigen-capture techniques have high sensitivity and specificity. In endemic areas many healthy people have parasitaemia, and therefore will a negative test rule out malaria, but a positive test does not prove that malaria is the cause of the illness. Rapid diagnostic tests are relatively expensive. However, they are easy to use, give a fast result and is useful in areas where microscopy is not available (10).

Laboratory Findings

Laboratory findings are non-specific. Anaemia is usual. Leucocytes are usually normal. Erythrocyte sedimentation rate and levels of C-reactive protein are high. Platelet count is usually reduced. In severe malaria, metabolic acidosis may occur. Glucose, sodium, bicarbonate, calcium, phosphate and albumin may be lowered. Lactate, blood urea nitrogen, creatinine, urate, muscle and liver enzymes and bilirubin may be elevated (15).

Treatment

General

Previously a variety of drugs could be, and were used in the treatment of falciparum malaria. Because of the increased resistant to the drugs acquired by the parasite it is now a limited number of drugs that will treat the malaria effectively. WHO has developed guidelines that will secure sufficient treatment for the patient and prevent further drug resistance by the parasite. Constant development of new drugs, research and the still growing resistance of the drugs have resulted in big changes in the policy of the treatment. Chloroquine is maybe the best example of a drug that was effective, and widely used, only a few years ago, but today it is ineffective as treatment of falciparum malaria.

The use of monotherapies is still widely spread, but to prevent further resistance of P. Falciparum and to increase the effectiveness of the therapy WHO now recommend combinations of antimalarias. The treatment does not only become more effective, but in the rare cases of the parasite being immune to one of the drugs, it will be killed by the other (16).

After several different clinical studies conducted in both Asia and Africa the WHO has in its newest guidelines made some alterations in the treatment of uncomplicated and severe malaria. Artemisinin Combination Treatment (ACT) has now been added to the recommended treatment of uncomplicated and severe falciparum malaria for adults and children, in adults in addition to quinine (16).

Quinine

Quinine is an alkaloid extracted from the bark of the Cinchona tree and can be used in the treatment of both uncomplicated and severe falciparum malaria (17). It is believed that the mechanism for the drug is raising the pH of the endocytotic vesicles and inhibiting internal membrane fusion processes (target the asexual stages of all malaria parasites) (18) (19). Quinine can be administered intravenous, orally or intramuscular (16). Initially quinine is given i.v. (as Quinine dihydrochloride) or i.m. until the patient is healthy enough to take it orally. There is little resistance to quinine by falciparum malaria despite of the long use.

Side effects:

- nausea
- dysphoria
- blurred vision
- tinnitus
- hypoglycaemia

These side effects may be severe, but normally resolve with the end of the treatment (18). If administered rapidly quinine can cause hypotension, and overdose is associated with blindness and deafness. The dangers of these severe side effects is still much smaller than the health risks the patient can face if receiving insufficient treatment (16).

Artemisinin

Artemisinin was first described more than 2000 years ago in China. It is extracted from the leaves of Artemisia annua (sweet wormwood) and it was first isolated in 1971 by Chinese scientist. The different derivates of artemisinin like art artemether, artemotil, dihydroartemisinin and artesunate have been used in treatment of malaria resulting in rapid clearance of parasites and resolutions of symptoms. ACT reduce parasite number by a factor of 10.000 in each asexual cycle compared with 100- to 1000-fold per cycle with other current anti-malarias. Its activity is broad against all stages from young rings to schizonts in the asexual parasites. It is also shown that artemisinin kills the gametocytes (including the stage 4 gametocytes) in P. Falciparum malaria (16).

Side effects:

- mild gastric disturbance
- dizziness
- tinnitus
- reticulocytopenia
- neutropenia
- elevated liver enzyme values
- electrocardiographic abnormalities (including bradycardia and prolonges QT intervals)

Side effects are much less severe than quinine and usually these drugs are tolerated well.

Ways of administration:

	Rectal	Intravenous	Intramuscular	Orally
Artemisinin	X	-	-	X
Artemether	X	-	X	X
Artesunate	X	X	X	X
Artemotil	-	-	X	-
Dihydroartemisinin	X	-	-	X

Because of the more potent dihydroartemisinin (and its derivates, artemether, artemotil and artesunate), artemisinin is not so much used any more.

These ACTs are now recommended by the WHO (alphabetical order):

- arthemeter-lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- artesunate + sulfadoxine-pyrimethamine

For patients ≥5 kg kg arthemeter-lumafantrine is recommended, and it is indicated that therapeutic respons and safety profiles is the same for young children <10 kg and older children (16).

The length of treatment differs depending on what compounds the therapy consists of apart from Atremisinin. The rapid clearance of Artemisinin, and when given with other rapid clearing compounds like tetracyclines or clindamycin, results in the need of a 7-day course.

When given in combination with slow eliminated antimalaria drugs, the treatment course is shortened to 3 days (16).

Treatment of uncomplicated malaria

The ACT treatment mainly consist of two different tablets (exept artemether-lumefantrine), and is combined to get the wanted effect. Co-formulated tablets are being developed, and when arriving on the market it will make it easier to give the correct treatment to the patients.

A. Artemether-lumefantrine is currently available as a tablet containing 20 mg Artemether and 120 mg as a co-formulation. Dosing schedule is shown in the figure below.

Table 1. Dosing schedule for artemether-lumefantrine

Body weight in kg (age in years)		No. of tablets at approximate timing of dosing[a]					
		0 h	8 h	24 h	36 h	48 h	60 h
5–14	(< 3)	1	1	1	1	1	1
15–24	(≥ 3–8)	2	2	2	2	2	2
25–34	(≥ 9–14)	3	3	3	3	3	3
> 34	(> 14)	4	4	4	4	4	4

[a] The regimen can be expressed more simply for ease of use at the programme level as follows: the second dose on the first day should be given any time between 8 h and 12 h after the first dose. Dosage on the second and third days is twice a day (morning and evening).

Figure 6. Dosing schedule for artemether-lumefantrine (16).

These ACTs can also be used:

B. Artesunate + amodiaquine

C. Artesunate + sulfadoxine-pyrimethamine

D. Artesunate + mefloquine

Treatment of severe malaria

A randomized clinical trial with 103 children aged 6 months to 5 years in Uganda showed that rectal artemether could be used as treatment for cerebral malaria. Compared with the standard quinine regime it also had a lower mortality rate (20).

Trials in South-East Asia comparing artesunate and quinine showed a 35 % decrease in mortality in the artesunate group. Since the study was mainly with adults (only 202 of the 1461 patients were <15 years), it could only suggest the change in treatment for adults.

Artesunate (i.m./ i.v.), artemether (i.m.) or Quinine (i.m./ i.v.) are all recommended in the treatment of severe malaria. Despite different clinical trials made, rectally artemisinins should only be used when parenteral treatment is not available (16).

Quinine

In the treatment of severe malaria quinine is recommended given with an initial booster dose of 20 mg/kg bodyweight, and then 10 mg/kg bodyweight with 8 hours intervals for 7 days. The initial doses can be given either i.m. or i.v. until they can be taken orally. To avoid overdose patients with renal failure, hepatic dysfunction or in the case of no clinical improvement should have the doses reduced by 1/3 after 48 hours (16).

One important aspect in the treatment of malaria is the importance of finishing a started treatment when it's decided to treat, even if test made later does not support the diagnose (16).

Artesunate and artemether

Artesunate 2.4 mg/kg bw i.v. or i.m. given on admission

(time = 0), then at 12 h and 24 h, then once a day.

Artemether 3.2 mg/kg bw i.m. given on admission then

1.6 mg/kg bw per day.

Supportive treatment

Coma (cerebral malaria):

- Maintain airways
- Exclude other treatable causes for coma (hypoglycemia/meningitis)
- Avoid corticosteroids, heparin and adrenaline
- Intubate when necessary

Hyperpyrexia

- Keep body temperature below 38,5˚ Celsius
- Fanning/cooling blanket/sponging
- Paracetamol/Ibuprofen

Convulsions

- I.v. or rectal diazepam
- Or i.m. paraldehyde

Hypoglycemia

- Treating the underlying cause is the best cure, in acute face treat with i.v. glucose.

Anaemia

- Blood transfusions when <5 Hb. Apart from that the best treatment is to lower parasite number.

Acute pulmonary oedema

- Patient placed with upper body in a 45˚ angel
- O_2
- Diuretic and stop intravenous fluid
- BiPAP
- CPAP
- Intubate

Acute renal failure

- Exclude pre-renal causes
- Check fluid balance and urine electrolytes
- Established renal failure: haemodialysis or haemofiltration (or peritoneal dialyses)

Spontaneous bleeding and coagulopathy

- Blood transfusion with whole blood (if available cryoprecipitate, fresh frozen plasma and platelets)
- Vitamine K injections

Metabolic acidosis

- Treat or exclude hypoglycemia, hypovolemia or aepticaemia
- If necessary add heamofiltration or heamodialysis

Avoid bed sores

- Turn patient frequently

Prevention

Bed Nets

Widespread use of insecticide treated bed nets can reduce overall mortality by about 20% in Africa. If 1000 children aged 1 to 59 months are protected, 5.5 lives can be saved each year. If every child in Africa are protected, 370 000 lives could be spared. The number of clinical episodes of uncomplicated malaria is halved in high transmission areas with the use of insecticide treated bed nets. The Roll Back Malaria partnership endorses this view (21).

Insecticides

Dicophane (DDT) was successful in controlling malaria in the 50s and up to the 70s when it was banned in most countries due to increased health and environmental concerns. Research and testing has shown that well managed programmes of spraying DDT indoors pose no harm to humans or to wildlife. Countries that continued to use DDT have shown that correct and timely use of indoor spraying can reduce malaria transmission by up to 90%. WHO is now recommending the use of indoor residual spraying, not only in epidemic areas, but also in areas with constant and high rates of transmission of malaria, which include all of Africa (22).

The reasons why DDT is the preferred insecticide are; it is more effective than other insecticides, it lasts longer, is cheap, repel mosquitoes from indoor environments and kill mosquitoes that land on sprayed surfaces (23).

Agriculture exporters in some African countries are concerned that their products will be banned from the EU if DDT is used for indoor residual spraying. EU has said that they will not automatically ban imports from countries if DDT levels has exceed tolerated levels. EU says they will stop consignments containing residues above their maximum limits. How this will affect the economy of the African countries staring to use DDT in their anti-malaria campaign is hard to say (23).

Vaccine

Vaccine against malaria is an area of malaria prophylaxis with great potential. Estimates suggest that if a vaccine can give a child protection from malaria for three years, child mortality in endemic areas could be lowered by 30% (24).

There are three types of malaria vaccine; vaccines against the invading sporozoite or the parasite's development in the liver cells (pre-erythrocytic stage), vaccines directed against the parasite's invasion of and development in the red blood cells(blood stage) and vaccines directed at the fertilisation process in the mosquito(transmission blocking) (24).

Most efforts have been put into developing a pre-erythrocytic stage vaccine. The most advanced pre-erythrocytic vaccine, RTS,S/AS02A, has provided substantial short-lived protection in volunteers. There has been done a phase IIb trial in semi-immune adult men in The Gambia with disappointing results. However, more trials are ongoing (10).

Blood stage vaccines try to reduce or eliminate parasites in the blood stage. These kinds of vaccines are undergoing clinical trials.

Transmission-blocking vaccines try to block parasite development inside the vector. One vaccine shows promising results with long time protection. The research has so far been done only on mice, but the researchers are optimistic about the vaccine (25).

Even if one develops an effective vaccine against malaria, there are many challenges in regard to cost and distribution.

Prognosis and complications

Treated uncomplicated malaria has a mortality rate of around 0.1%. If the infection develops into severe malaria the mortality rises steeply. Untreated severe malaria has death rate of nearly 100%. Treated cerebral malaria has a death rate of 20% among adults and 15% in children (15). Severe malaria develops within 48 hours of fever onset in children (16).

Complications of the acute phase of malaria is hypoglycaemia, lactic acidosis, pulmonary oedema, renal impairment, anaemia, disseminated intravascular coagulation, liver dysfunction, aspiration pneumonia, septicaemia, convulsions and coma (15).

Chronic or repeated malaria infections may cause normocytic anaemia and splenomegaly. Some exhibit an abnormal immunologic response to repeated infections. This syndrome is called hyperreactive malarial splenomegaly. These patients usually presents with anaemia and some degree of pancytopenia. They have increased vulnerability to respiratory and skin infections (15).

24 % of children after cerebral malaria have evidence of some impairment. 11 % experience neurological sequelae such as ataxia, hemiparesis, quadriparesis, hearing, visual and speech impairment, behavioural difficulties and epilepsy. Recent studies reports that epilepsy is associated with cerebral malaria. This suggests that at least 250 000 children in sub-Saharan Africa each year will develop neurocognitive impairments from malaria (26).

Sickle cell disease, thalassemia and glucose-6-phosphate dehydrogenase deficiency are genetic orders that protect against death from falciparum malaria (15).

Haydom

Haydom Lutheran Hospital is remotely situated in the Mbulu district in northern Tanzania. The hospital was build by the Norwegian Lutheran Mission in 1953. Today the hospital has 350 beds and covers an area with around 440 000 people. The immediate catchments area has a population of around 100 000. The area around the hospital lies about 1500 to 2000 meter above sea level. The hospital has a medical and surgical ward, paediatric and obstetric department, eye clinic, laboratory and nursing school (27).

Children arriving at the hospital are first examined in the out patient department (OPD) where they either get medical treatment or being sent to the paediatric ward for admission. Patients arriving at the hospital in the afternoon or night will be examined in the reception. Depending on the clinical status they will be admitted or get drugs to administer at home. Each morning the newly admitted patients will be presented for the doctors at the morning meeting.

The treatment costs are partly paid by the hospital and partly by the patient's family depending on the income of the family.

Material and methods

We conducted a follow up study of all children below five years of age admitted to Haydom Lutheran Hospital in Tanzania diagnosed with malaria (either as main or differential diagnosis, and all children treated with quinine) in the period from 27.06.06 to 17.07.06. This period is in dry season, and hence the malaria transmission rate is fairly low. The whole patient file was studied and registered on a customized form. The files were controlled (almost) every afternoon in the ward.

On admission, symptoms and signs were registered. Age, sex and the diagnosis at both the OPD and the paediatric ward were recorded. The children were first examined at the OPD and given one or more diagnoses. At the paediatric ward the patient got a tentative diagnosis (or several) before test results were present. The tentative diagnose at the ward has been registered as the "final clinical diagnosis". In some files several diagnoses were set, in such cases the first diagnose is registered as the final clinical diagnosis. During the time the patient was admitted, treatment, blood slide result and new symptoms were recorded. Finally, outcome and/or discharge date was recorded.

A positive blood slide result from the laboratory was regarded as proven malaria.

To compare differences between groups, the Mann-Whitney test was used for continuous variables without normal distribution. All analyses were 2-tailed and $p<.05$ was considered to be significant. Statistical analysis was done with SPSS for Windows software version 14.0.

Results

General results

In total there were 191 admissions which fulfilled the inclusion criteria and were included in this study. This gives an average of 9 patients each day in the three week period.

Information on the patients treatment, diagnoses and general data can be found in *Table 1* and *Table 2.*

Diagnose

As shown in *Table 3,* 72 children received a final clinical diagnosis of malaria, before considering the results of the blood slide. 119 patients received different non-malaria diagnosis as their final clinical diagnose. If side diagnoses also is included, 162 of the patients got the malaria diagnose, leaving 29 patients without malaria diagnose. These 29 patients all got anti malaria treatment. 19 out of 72 patients with clinical malaria had severe (n=12) or cerebral malaria (n=7).

Blood slide

Blood slide was taken in 190 out of 191(99.5%) patients and analysed in 159(83.3%) of the cases. 21 of the patients had positive blood slide. There are significantly more positive blood slide in the group with the final clinical diagnosis of malaria compared to the rest of the patients. However 1/3 of the patients with positive blood slide did not receive malaria as their main diagnosis, but all of them received anti-malaria treatment. As shown in *Table 4,* the children with positive blood slide was a worse clinical condition than those with negative blood slide. Even though, the mortality in the two groups did not differ significantly.

Treatment

Of all the 191 children admitted 29 (15.2%) didn't get any malaria diagnose in the ward. 6 (3.1%) patients did not receive any quinine treatment at all. The children not receiving quinine did not have malaria as a main diagnose.

118 (67.8%) children got a 7 days treatment with quinine as recommended by the WHO. The treatment length spread from 0 till 15 days.

Blood transfusion demanding anaemia

In our study the children needing blood transfusion were significantly older than the children without anaemia. They also had a significantly higher number of positive blood slides

suggesting that the anaemia was caused by the malaria parasite. Specific data are shown in *Tabel 5.*

Mortality

12 of 191 patients (6%) died while admitted in the ward.

Discussion

There are significantly more positive blood slides in the group with the final clinical diagnosis of malaria compared to the rest of the patients, indicating that clinicians may recognize malaria clinically in 2/3 of all blood slide positive cases.

29 patients without the malaria diagnose got antimalaria treatment. This suggest that the use of quinine was liberal at HLH. Over treatment can cause drug resistance and it is considered a major problem in Africa (16).

Children receiving anti malaria treatment before coming to the hospital will have a decreased parasite number that may result in a negative blood slides even if the child was infected. After two days of effective antimalaria treatment the parasite count drops by 75%. This will make microscopy diagnostics more inaccurate.

The data was collected in July which is the low season for malaria transmission. The draught in this part of the year results in lower mosquito number, which results in fewer children being bitten and infected with malaria. This may have had an affect on our data. If the study was made in the rain season there might have been a higher number of patients with the diagnosis malaria and positive blood slide.

Diagnostic

The children were mainly examined twice before getting the main diagnose in the ward. The dominant diagnoses were malaria, gastroenteritis and pneumonia. These three diagnoses made out about 80-90% the total patient group. Because of the capacity of the lab, clinical examinations were the only tools used in the diagnostic of the children on arrival. The lab results were used to confirm diagnose or to decide if the children needed blood transfusion because of parasite induced anaemia. Stool sampling was also used in some cases of gastroenteritis.

Blood slide was the lab test made to support or dismiss the malaria diagnose set earlier. Despite the outcome of the lab results, the clinical state of the child was the most important criteria for starting treatment. The time from admission and start of treatment to the lab results arriving at the ward varied much and did not influence the anti malaria treatment. Since the decision was made to treat with antimalaria based on the clinical state of the child, it is correct to finish the treatment even if lab results later could not confirm the diagnose (16).

Treatment

The treatment given to anaemic children depends on the cause of the anaemia and the quality of the health service available. Children who are believed having malaria also run the risk of having anaemia because of the destruction of red blood cells by the parasite. Since malaria is the far most common reason for anaemia the treatment of malaria is normally enough to

reverse the anaemia. Children with Hb<5 should however get blood transfusion according to the WHO guidelines.

At HLH 9 out of 10 children with Hb<5 got blood transfusion

At HLH the quinine treatment didn't include an initially dose of 20 mg/kg as recommended by WHO. The treatment consisted of a 10 mg/kg dose from the initial dose till ended treatment. Most of the children (2/3) got the recommended length of treatment. Still the treatment length varied considerably mainly because of these criteria

- Previous admissions were not recorded in the new patient file, resulting in children getting more than one full course treatment with quinine in a short span of time.
- Some children didn't survive long enough to get a full course treatment.
- Children were discharged by the parents because of financial reasons before ended treatment.
- The i.m. or p.o. quinine treatment given at OPD was not recorded at the ward, and a full week treatment was given in the ward in addition to that treatment.
- Parents of the children could not always clearly reproduce what kind of, or how long, pre-treatment the child had received at home or at the different health stations.

Outcome

None of the 12 children who died had reported coma or convulsions, suggesting that they did not have severe or cerebral malaria at admission. 3 of the children had malaria as the main diagnose. Only one patient had positive blood slide, however we did not have the blood slide

results in 7 of these 12 patients. The test results arriving post mortem were not recorded in the patients file. This, and that the cause of death was not reported in the patient file, makes it difficult to exclude malaria as the cause of death.

Limitations with the study

The major problem was lack of data registrations in the patient files. There were no common standard for mentioning examination findings, both positive and negative, from the OPD or the ward. As mentioned earlier, the previous admissions were not taken into consideration when treating and parents had problems reproducing what kind of treatment the children had got at home or at the health stations.

The study was conducted over a short period of time, giving us a limited number of patients. In addition we had insufficient time to get to know all the routines used in the diagnostic and treatment of children with malaria at HLH.

Patient files were written in English. Still, the fact that we did not speak the native language may have had an influence on the accuracy in the collecting of the data.

Tables

Table 1: Background data

Patient in study	191
Age in months	
Median (IQR)	8 (6-14)
Sex	
Male	111 (58.1%)
Female	72 (37.7%)
Unknown	8 (4.2%)
Length of admission	
Median (IQR)	5 (4-7)
Initial diagnose OPD	
Malaria	58 (24.1%)
Cerebral malaria	5 (2.6%)
Severe malaria	2 (1%)
Gastroenteritis	75 (39.3%)
Pneumonia	29 (15.2%)
Other	22 (17.8%)
Final clinical diagnosis	
Malaria	53 (27.7%)
Cerebral malaria	7 (3.7%)
Severe malaria	12 (6.3%)
Gastroenteritis	80 (41.9%)
Pneumonia	25 (13.1%)
Other	14 (7.3%)

IQR = Interquartile range

Table 2. Treatment and lab results

Total days quinine	
Median (IQR)	7 (7-7)
Blood slide	
Numbers taken	190 (99.5%)
Positive result	21 (11.0%)
Negative result	138 (72.3%)
Unknown or no result	32 (16.7%)
Hb (g/dl)	
Numbers taken	148 (77.5%)
Median Hb (IQR)	11.4 (10.1-13.1)

IQR = Interquartile range

Table 3. Clinical symptoms, treatment and lab results in children with clinical malaria.

	Malaria **n= 72**	**Non-Malaria** **n=119**	**P value**
Median age in months (IQR)	10 (7-25)	7 (6-10)	<0.001
Positive blood slide	14 (19.4%)	7 (5.9%)	0.004
Clinical anemia	18 (25%)	12 (10.1%)	0.73
Hb, median (IQR)	10.9 (8.7-13.2)	11.9 (10.4-13)	0.15
Blood transfusion	6 (8.3%)	6 (5%)	0.37
Anti malaria treatment before admission	8 (11.1%)	33 (27.7%)	0.68
Convulsions	11 (15.3%)	4 (3.4%)	0.004
Coma	2 (2.8%)	2 (1.7%)	0.63
Dead	3 (4.2%)	9 (7.6%)	0.34

IQR = Interquartile range

Tabel 4. Clinical signs, treatment and outcome in children with positive blood slide.

	Positive Blood Slide **n = 21**	**Negative, unknown or no result blood slide** **n = 170**	**P value**
Median age in monmths (IQR)	25 (7.5-36)	8 (6-12)	0.002
Median Hb in g/dl (IQR)	8.1 (4.8-11.4)	11.8 (10.4-13.2)	0.004
Blood transfusion	5 (23.8%)	7 (4.1%)	0.05
Coma	4 (19%)	0	0.04
Convulsions	7 (33.3%)	8 (4.7%)	0.01
Temperature, median (IQR)	38 (37.5-38.8)	37.5 (37.1-38)	0.03
Dead	1 (4.8%)	11 (6.5%)	0.7

Tabel 5. Clinical symptoms, lab results and treatment of anemic patients

	Hb <5 **n=10**	**Hb ≥5 or unknown** **n=181**	**P value**
Age, median (IQR)	24.5 (11.5-27)	8 (6-12)	0.017
Clinical signs of anemia	9 (90%)	21 (11.6%)	<0.001
Positive blood slide	5 (50%)	16 (8.8%)	0.002
Blood transfusion	9 (90%)	3 (1.7%)	0.005

References

1. Centers for Disease Control and Prevention; http://www.cdc.gov/malaria/history
2. Cox FE. History of Human Parasitology. Clinical Microbiology Reviews, October 2002, p. 595-612, Vol. 15, No. 4
3. Editorial. Reversing the failures of Roll Back Malaria. The Lancet. 2005 April 23; 365: 1439
4. Yamey G. Editorial. Roll Back Malaria: a failing global health campaign. BMJ. 2004;328:1086-7
5. Myrvang B, Godal T. WHOs malariaprogram Roll Back Malaria. Tidskr Nor Lægeforen 2000;120:1661-4
6. Carter R, Mendis KN. Evolutionary and Historical Aspects of the Burden of Malaria. Clinical Microbiology Reviews. 2002 October;564-94.
7. Wikipedia. http://en.wikipedia.org/wiki/Anopheles
8. Lalloo DG, Olukoya P, Olliaro P. Malaria in adolescence: burden of disease, consequences, and opportunities for intervention. The Lancet Infectious Diseases. 2006 December;6:780-93
9. Guerin PJ, Olliaro P, Nosten F, Druilhe P, Laxminarayan R, Binka F, Kilama WL, Ford N, White NJ. Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. The Lancet Infectious Diseases. 2002 September;2:564-73
10. Greenwood BM, Bajang K, Whitty CJM, Targett GAT. Malaria. The Lancet. 2005 April 23; 365:1487-98

11. The Roll Back Malaria Partnership. Infosheet. Children and malaria. http://www.rbm.who.int
12. The Roll Back Malaria Partnership. Infosheet. Malaria in Africa. http://www.rbm.who.int
13. The Roll Back Malaria Partnership. Infosheet. What is Malaria?. http://www.rbm.who.int
14. Weinberg A, Levin MJ. Malaria. Current Pediatric Diagnosis and Treatment, 18th Edition. Chapter 39, Infections: Parasitic and Mycotic.
15. White NJ, Breman JG. Malaria. Harrison's Principles of Internal Medicine, 16th Edition. Chapter 195. Malaria and Babesiosis: Diseases Caused by Red Blood Cell Parasites.
16. World Health Organization. Guidelines for the treatment of malaria 2006. http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf
17. Centre for Cancer Education, University of Newcastle upon Tyne http://cancerweb.ncl.ac.uk/cgi-bin/omd?cinchona
18. Bloland PB, Williams HA. Malaria control during mass population movements and natural disasters, 2003.
19. Centre for Cancer Education, University of Newcastle upon Tyne http://cancerweb.ncl.ac.uk/cgi-bin/omd?quinine
20. Aceng JR, Byarugaba JS, Tumwine JK. Rectal artemether versus intravenous quinine for the treatment of cerebral malaria in children in Uganda: randomised clinical trial. BMJ. 2005 February 12;330:334-7
21. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews 2004, Issue 2. CD000363

22. Rehwagen C. WHO recommends DDT to control malaria. BMJ. 2006 September 23; 333:622

23. Editorial. DDT for malaria control: the issue of trade. The Lancet. 2007 January 27; 369:248

24. Jespen S. Malariavaksiner- hvilke vaksiner til hvem?. Tidsskr Nor Lægeforen 2000;120:1665-8

25. Kubler-Kielb J, Majadly F, Wu Y, Narum DL, Guo C, Miller LH, Shiloach J, Robbins JB, Schneerson. Long-lasting and transmission-blocking activity of antibodies to Plasmodium falciparum elicted in mice by protein conjugates of Pfs25. PNAS. 2007 January 2;104:293-8

26. Idro R, Jenkins NE, Newton CRJC. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. Lancet Neural. 2005;4:827-40

27. http://www.haydom.no