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Malaria in East Africa

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Historically, malaria has coloured the European view of East Africa since the days of early exploration. Victorian England regarded the African coast as a place where they were very likely to die from the disease, and with good reason. The protestant missionary, Rev. Dr Johann Ludwig Krapf, arriving in East Africa in early May 1844 before the rains started, established a mission station at Rabai, outside Mombasa. He was "attacked by the fever" on 1st July, and his pregnant wife became sick at the same time. She gave birth to a baby girl on 6th July, but died 3 days later. The baby died on 15th July. It was felt that no European could live long on the coast of East Africa without being attacked by *mkunguru* or fever of the country (Pavitt 1989).

Obviously, the major burden of malaria morbidity and mortality falls on the people of Africa; a disease which still kills approximately two million African children each year, despite the considerable resources which are directed against it. The Global Eradication Strategy for malaria, conceived as a practicable endeavour, has quietly been replaced by a policy of Malaria Control. Vector control has been largely abandoned as impracticable, drug resistance in the parasite continues to erode the small collection of effective treatment drugs and a malaria vaccine remains well below the horizon. Despite hopeful new initiatives (bed nets, improved drug availability to rural areas), malaria remains a scourge for the inhabitants of East Africa.

Malaria Epidemiology in East Africa

The pattern of malaria within the region varies considerably. All of the four species of *Plasmodium* which cause disease in man are found in East Africa: *P. falciparum*, *P. malaria*, *P. ovale*, and *P. vivax*. *P. vivax* is rare and found only in individuals whose red cells carry the Duffy factor, but does occur in coastal regions, where Arabic genetic influence is strongest. *P. falciparum* is the most important infection by far, and is responsible for most of the malaria morbidity, and virtually all the malaria mortality of the region.

In Kenya, there are areas of "stable" malaria, where the climate supports mosquito proliferation, and there is year-round transmission: the lake Victoria basin; the coast; and narrow strips of land along the major rivers. Over the rest of the country, malaria is often found where there is surface water (e.g. after the annual rains) and where the altitude is low enough to support an adequate mosquito population. In these areas, malaria tends to be "unstable". It is often highly seasonal, as is the case in Turkana, Northern Kenya, a semi-desert region where parasite rates are very low during the 10 months of the year when no rain falls. Epidemic malaria may arise in these areas. This is a particularly dangerous occurrence because the people have little immune protection and mortality can be high.

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The relationship between the malarial parasite, the human host and transmission by anopheline mosquitoes is well-established. Less well understood are the specific interactions between the host and the parasite, a major focus of research. Young children are the age group most often parasitized. Typically, parasite prevalence by age increases sharply as protective maternal immunity wanes (ca. 6 months), reaching a peak before the age of 5 and then declining. The peak itself is a function of the transmission characteristics of the area. In Kilifi, Kenya coast, (year-round transmission but with pronounced seasonality), this occurs later than in Ifakara, Tanzania which has year-round, high transmission. In Kilifi, the average young child has one or two clinical attacks of malaria each year, although there will be parasitaemic episodes which do not give rise to sickness. These asymptomatic parasitaemias become more common after childhood with increasing exposure to the local parasite strains. The outcome is a partial immunity against subsequent attacks, and few children over the age of five die from malaria. There is, therefore, a distinct difference between the parasitized but well child, and the parasitized sick child. By adulthood, while clinical malaria may still occur, it is rarely life-threatening, except in the pregnant woman, where lowered immunity leads to increased parasite densities and sometimes severe anaemia.

A very large number of African children die each year from malaria (estimates vary, but the number is of the order of 2 million deaths; 5617 each day, 234 each hour, 4 every minute). Most of these deaths are caused by *P. falciparum*. To address this major health problem, we need to know more about the factors which are responsible for the progression: uninfected, infected (well), infected (sick), very sick, death. We do not yet know whether the control of this progression is mainly due to host or parasite factors. This is a major research effort of the KEMRI-Wellcome Trust Research Programme, at Kilifi, a research unit on the Kenyan coast.

Clinical Malaria

Malaria is an illness occurring with parasitaemia (malaria parasites seen on microscopic observation of a finger-prick blood sample), which is often serious enough to make the child's mother seek health care. The diagnosis is not straightforward because in endemic areas many children will be parasitaemic, but well, or parasitaemic but sick due to a different condition (e.g. respiratory infection, or measles). At the health centre or hospital, cases are divided, on the basis of

clinical presentation, into non-severe or severe malaria. Clinically, the sick child with non-severe malaria usually has fever and general malaise, but without any of the attributes of severe malaria (high parasitaemia, anaemia, metabolic acidosis, seizures and sometimes cerebral complications, including coma). Non-severe malaria is generally managed by a treatment course of an effective antimalarial drug alone. However, because of the time-dependent kinetics of parasite sequestration, there is always the possibility of a non-severe case becoming severe over a short time period. A smaller proportion of malaria patients present to hospital with more serious, life-threatening disease, who require admission; this is 'severe malaria' by definition. In Kenya, life-threatening malaria can be subdivided into three overlapping clinical syndromes; malaria with impaired conciousness, malaria with severe respiratory distress, and malaria with severe anaemia. There is a complex interaction between these components, and the risk of death is proportional to the degree of overlap (Marsh et al 1995). Similarly, cerebral malaria, one of the most serious clinical manifestations, is no longer regarded as a homogenous clinical syndrome. Even strictly defined cerebral malaria, with unarousable coma, comprises several distinct syndromes: 'metabolic' coma, associated with severe metabolic acidosis; coma due to atypical status epilepticus; and a primary neurological syndrome (English et al 1996). Recovery from severe malaria may be complete in terms of easily recognizable defects. However, it is becoming clear that many children suffer from neurological sequelae which may have far-reaching implications for the mental development of the child and the acquisition of educational norms at school.

In other parts of the world, e.g. South East Asia, where falciparum malaria is of lower endemicity, and patchy, individuals are more likely to remain immunologically naive into later life, and adult malaria patients are much more common than in Africa. There is a remarkable difference in the clinical pattern of severe malaria between these two groups. In adults, acute renal failure and acute pulmonary oedema are frequent causes of death (WHO 1990) whereas children more often die of severe anaemia and metabolic acidosis although it is often difficult to ascribe an exact cause of death (White & Ho 1992). The pace of the disease is quicker in children than in adults; the child tends to deteriorate more rapidly, and also recover more quickly than the adult (Waller et al 1995). Another striking difference between these age groups is the rarity of neurological sequelae in adults who recover from cerebral malaria.

Parasitaemia and disease severity

The correlation between clinical severity and parasitaemia is weak in malaria; well children may have high peripheral parasitaemia, and occasional cases of cerebral malaria may be slide-negative. One of the problems in judging the relationship between peripheral parasitaemia and clinical condition is that the blood slide only provides information on the number of circulating (non-sequestered) parasites, and not on the total parasite load. As the parasite matures through the erythrocytic cycle, which is complete in 48 h for falciparum malaria, a stage is reached where parasites express adhesin proteins on the red blood cell (RBC) surface, which stick to specific binding sites on venule endothelium. The net effect is the removal from circulation of RBCs containing the more mature parasite stages. For this reason, patients with the same level of peripheral parasitaemia may differ by 62-fold in their sequestered parasite biomass (White & Krishna 1989). Post-mortem specimens from patients who have died from severe malaria may show venules in the brain which are packed with adherent parasitized erythrocytes (PRBCs). In-vivo, it is likely that PRBCs are loosely attached, and roll along the inner vessel wall in the direction of blood flow. The sequestration mechanism is advantageous to the parasite, since it effectively protects it from reticuloendothelial clearance. However, it follows that the peripheral parasitaemia is not a reliable measure of total (circulating plus sequestered) parasite load. This fact creates a problem in using parasitaemia per se as an indicator of disease severity. Although there are methods for estimating sequestered parasitaemia (White & Krishna 1989), none are yet appropriate to bed-side use.

The Treatment of Clinical Malaria

Treatment strategies differ for severe and non-severe malaria, which is the main reason for the two categories.

The treatment of severe falciparum malaria

The accepted rule for the chemotherapy of severe falciparum malaria is to start treatment with an effective drug, immediately the diagnosis is proved or suspected. The parenteral route should be used whenever possible because the absorption of drugs by the gastrointestinal route cannot be relied upon in severely ill patients who may be vomiting, or shocked, and in whom the blood flow to the gut may be reduced (Warrell 1993). The use of a loading dose to rapidly achieve inhibitory blood concentrations has been a contentious issue for quinine in the past, but is still the recommended method (Warrell 1993; Marsh et al 1995). Recent research in Kilifi has shown that the intramuscular route may be unreliable under certain conditions. Absorption of water-soluble drugs from intramuscular depot injections is altered by malaria infection (Winstanley et al 1992), and absorption of drugs having low water solubility from this site may be dangerously reduced in severe malaria because of reduced blood flow to skeletal muscle (Murphy & Watkins, unpublished data). An interesting possibility is the use of the rectal route to deliver drugs in severe cases, where the patient may be unconscious. The methodology is undemanding, and could be used by rural dispensaries (which lack the skills and equipment for intravenous administration). Artemisinin has been used in this way as an effective treatment for severe malaria in Vietnam (Arnold 1994).

In East Africa, quinine remains the standard treatment for severe malaria; a drug with high efficacy against the parasite at achievable in-vivo concentrations. Quinine does not prevent parasite sequestration or alter parasite clearance during the first 12 h of treatment. Against sensitive parasites, chloroquine was perhaps the ideal treatment for severe malaria when given by the parenteral route; inducing rapid clearance of parasites (White et al 1992). Unfortunately, this is no longer possible because of the high prevalence of chloroquine-resistant malaria in East Africa. Despite the use of effective treatment (quinine, together with appropriate supplementary clinical management—control of seizures, rehydration, control of metabolic acidosis), the mortality from severe disease remains high, at about 15%. Most of these deaths occur within 24 h of admission (Marsh et al 1995), which is a reflection of the rapid

course of the disease in children, and also results from late presentation. On the Kenyan coast the pattern of "health seeking behaviour", which principally involves the mother, is becoming better understood. For fever, the initial recourse is to shop-bought medicine (usually chloroquine because it is cheap, and therefore stocked by village shops). Other definable symptoms may involve a visit to the local herbalist. If the child remains sick, or worsens, then hospital or health centre care is sought. Under the new arrangements for cost sharing in many African countries, this can be an expensive option for people who are essentially outside the cash economy. For these reasons, many children in Africa die at home, before reaching hospital (Greenwood et al 1987), or are admitted to hospital in a serious condition where the outcome may already be irreversible.

The treatment of non-severe falciparum malaria

As for severe malaria, the prime requirement for the successful treatment of non-severe, or outpatient malaria, is an effective, cheap drug, with a dosage regimen lasting no longer than three days. This last point is particularly important; if the drug works, the child will be getting better 24 to 48 h after the start of treatment. The mother will tend to reserve any remaining medication, which has been paid for, to treat the next similar episode (Foster 1991).

Chloroquine was, for about 40 years, the mainstay of outpatient malaria treatment. In East Africa, chloroquine-resistant falciparum malaria (CRFM) is now common in the high transmission areas, although still comparatively rare in some isolated regions, especially those such as Northern Turkana, characterized by less efficient mosquito vectors and a highly seasonal pattern of malaria (Clarke et al 1996). Unfortunately, these areas are few, accounting for a very small proportion of the malaria cases in the region. The antifolate antimalarial combinations, represented by pyrimethamine–sulphadoxine (PSD), remain generally effective treatments, although there are indications (both from theoretical considerations and from field studies) that this may be temporary. PSD is comparatively cheap, which is a very important consideration for almost all African countries. Although CRFM is widespread, most malaria infections still respond partially to chloroquine, with a rapid initial fall in peripheral parasitaemia, and clinical improvement which may be due in part to the potent antipyretic action of chloroquine. For these reasons, rather than a complete change from chloroquine to PSD, some centres find that a combination of the two drugs provides optimal treatment.

Drug Resistance and New Therapeutic Approaches

Several reports from South East Asia have described advantages of the artemisinin derivatives over quinine in the treatment of severe malaria. Quinine efficacy has been decreasing steadily in South East Asia for several years as a result of parasite resistance, and this may in part account for this observation, although the mechanisms of action of the two drugs are also dissimilar. In the treatment of patients with artemisinin compounds, two particular differences are apparent: the parasite clearance time is much shorter than with quinine and there is specific activity directed against the early ring stages.

Until very recently, it was thought that quinine exerted broad-spectrum activity against all the developmental blood stages of the parasite. This was shown not to be the case in a study at Kilifi which measured the viability of parasites ex-vivo from patients with non-severe malaria treated with different drugs. While the viability of parasites from quinine-treated, or PSD-treated patients remained $>90\%$, and no different to the pre-treatment samples for at least the first 24 h of therapy, in-vivo exposure to halofantrine for 6 h was sufficient to arrest parasite development. (Watkins et al 1993). We have recently shown that artemether (an oil-soluble artemisinin derivative formulated as an intramuscular injection) has a similar effect (Murphy et al 1995). Clearly, if artemether or a similar artemisinin derivative can arrest the development of young parasites to the stage at which they sequester, while at the same time rapidly reducing peripheral parasitaemia, these effects may translate into reduced mortality.

This was the rationale behind a multi-centre comparative trial of intramuscular artemether vs parenteral quinine, recently completed in Kenya, Malawi and Nigeria, in strictly defined cases of severe malaria, and with death as the endpoint. In all studies, parasite clearance was more rapid with artemether, but there was no difference in mortality between treatment groups (Murphy et al 1996). However, in the Kenyan study the concentrations of artemether and the major metabolite dihydroartemisinin which were achieved in-vivo varied widely between patients, and were significantly lower in patients with respiratory distress, a marker for metabolic acidosis. These are the sickest children and are often hypovolaemic with cool extremities, an indication of poor muscle perfusion (Murphy & Watkins, unpublished data). Although confirmation is needed, it is very likely that these patients did not absorb artemether, a poorly water-soluble drug, in sufficient amounts from the intramuscular site. More appropriate derivatives might be the water-soluble compounds sodium artesunate or artelinic acid, although these drugs are not yet available in Africa.

For the treatment of non-severe malaria, there is an urgent need to find alternatives to PSD. The long elimination half-life of this combination, which in the past was seen as a benefit because it protected the host from early re-infection, provides a potent mechanism for the selection of pyrimethamine-resistant parasites. In an area of continuous malaria transmission, the treated child is soon re-infected; residual physiological drug kills sensitive, but not resistant parasites. In a trial at Kilifi, 90% of new infections in the period 15 to 52 days following PSD treatment were pyrimethamine-resistant in-vitro, in contrast to a wild-type resistance prevalence of 15% (Watkins & Mosobo 1993). Further, the mutations in the parasite dihydrofolate reductase gene which govern resistance to individual antifolate drugs are known, and drug-specific. Work in Kilifi and Nairobi is addressing the efficacy and utility of chlorproguanil–dapsone (CPG–DDS) as an alternative to PSD. The new combination has the potential advantages of a short elimination half-life, and thus reduced selective pressure for resistance, and greater efficacy against pyrimethamine-resistant infections.

Another potentially useful antimalarial under investigation in Kenya is the benzonaphthyridine drug pyronaridine, a drug related structurally to both the acridine mepacrine, and to amodiaquine. Pyronaridine, synthesized in China in 1970 and used widely as an antimalarial drug in that country, is new to

western medicine. Only one preliminary clinical trial has been conducted in Africa, but the results are encouraging. One hundred percent parasite clearance by day 7, with patients still parasite-free at 14 days, was achieved with pyronaridine, against infections which were mainly chloroquine-resistant (Ringwald et al1996). Work on pyronaridine is being actively pursued by WHO, since this drug may eventually present an effective and affordable replacement for chloroquine.

To ensure continued malaria control in East Africa there is an urgent need for new antimalarial drugs which will have a useful therapeutic life extending over at least 10 years, and which are affordable. If basic and operational research studies do not deliver effective new drugs in the near future, the outlook is bleak. Mefloquine, the drug which replaced PSD in South East Asia, is far too expensive to be purchased in adequate amounts in Africa, and the same consideration applies to all the current alternative treatments, even if demand forces price reductions. It is unlikely that the available alternative drugs will ever become cheap enough to ensure that all cases of malaria are treated. In this scenario, an alarming rise in malaria-related morbidity and mortality is likely to occur in the future. Ways must be found to address and solve this problem.

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