MALARIA CONTROL STRATEGIES IN THE KILOMBERO VALLEY, TANZANIA

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Prof. Dr. Andreas Zuberbühler
Dekan

Dedicated to my family

Table of contents

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Summary

Malaria is major public health problem in Tanzania and increasing trends have been observed in the last two decades. A significant consequence of repeated malaria infections in high transmission areas is anaemia in very young children. The control of malaria in Tanzania includes both preventive and curative strategies. On the preventive side insecticide treated bed nets (ITNs) are a promising tool. ITNs have been shown to be effective in reducing malaria morbidity and mortality in controlled trials. Large-scale implementation of the technology is currently being initiated in many African countries. We report the impact of a large social marketing programme of ITNs on malaria morbidity through a series of studies, in a population of about 55,000 people in Tanzania.

The ITNs social marketing programme resulted in a rapid increase in any net ownership (from 58 to 83%) and an increase in ITNs ownership (from 10 to 61%) in children under two years of age within 2 years of implementation. As a result the overall mean haemoglobin levels increased (from 8.0 to 8.9 g/dl) in the study children during the successive surveys. The prevalence of anaemia in the study population decreased from 49% to 26%. Comparison between children with ITNs and those without nets showed that ITNs had a protective efficacy of 63% (95% CI: 38 to 77) on the prevalence of parasitaemia, and 63% (95% CI: 27 to 82) on anaemia (haemoglobin $\leq$ 8 g/dl). These results endorse the wide scale implementation of ITNs in Tanzania.

ITNs can only reduce the risk of malaria disease but cannot eliminate it. Hence, appropriate effective treatment is required. Chloroquine is a cheap and safe antimalarial and it was until recently the first line drug of choice in the National Malaria Treatment Policy. Resistance to chloroquine has been reported with increasing frequency in Tanzania and has been linked to the increasing admissions with severe disease in hospitals. A comparative randomised, open clinical trial of chloroquine against Co-artem® (fixed combination of Artemether + Benflumetol) an alternative new antimalarial, showed seven-day parasitological cure rates of 94% for Co-artem® and only 35% for chloroquine. Generally, Co-artem® showed a superior clearance rate, successfully cleared higher parasite densities and suppressed new infections

over a longer period of time. Furthermore, Co-artem® suppressed more effectively gametocytes in these children, indicating a potential benefit for reducing malaria transmission. The unacceptably high chloroquine failure rates call for an urgent review of the National Malaria Treatment Guidelines.

The decision to change the first line antimalarial and the choice of a new drug depend on a number of factors that include the clinical, epidemiological and social-economical factors, as well as the health infrastructure. Considering all of these dimensions, sulphadoxine-pyrimenthamine (SP) was identified as a good interim replacement for chloroquine. Further Phase IV evaluation of Co-artem® and other combination therapy regimens are required before considering their inclusion in the national treatment policy. Much work is also needed to identify suitable compounds to be used for home management of malaria, within the national treatment guidelines.

Experience gained with these studies gives a description of the different methodologies and tools that can be used to evaluate different components of the National Malaria Control Programme. For example, it was difficult to assess the impact of the ITNs programme using the case-control approach. Repeated cross-sectional assessments were found to be more suitable for assessing the impact of ITNs under programme conditions, especially on malaria-related anaemia in this area of high transmission. Specific indicators for programme evaluation may need to be identified for specific interventions. These may be different from the ones used in randomised controlled trials. The use of molecular markers for monitoring and evaluation of antimalarial intervention programmes illustrate the need to develop and validate novel tools and approaches for programme evaluation.

Better malaria control is expected by combining ITNs and an effective antimalarial, especially combination therapy. The evaluation, implementation, and monitoring of all these control activities requires a partnership between researchers, policy makers, health managers, in close collaboration with other stakeholders in the public and private domain, including the beneficiaries - the community.

Zusammenfassung

Malaria ist ein schwerwiegendes öffentliches Gesundheitsproblem in Tansania. In den vergangenen 20 Jahren hat sich ein Trend zunehmender Ausbreitung der Krankheit beobachten lassen. Eine symptomatische Hauptfolge wiederholter Malariainfektionen in Gebieten mit hohen Übertragungsraten ist Anämie in Kleinkindern. Die Malariakontrolle in Tansania umfasst sowohl präventive als auch kurative Strategien. Auf der Seite der Prävention haben sich insektizidimprägnierte Bettnetze (IIB) als vielversprechendes Instrument erwiesen. In ‚kontrollierten Versuchen' zeigte die Verwendung von IIB eine effektive Reduzierung malariabedingter Morbidität und Mortalität . Ein erweiterter Einsatz dieser präventiven Massnahme findet derzeit in zahlreichen afrikanischen Ländern statt.
Die vorliegende Arbeit zeigt die Wirkung eines grossangelegten sozialen Marketingprogramms für IIB auf Malaria Morbidität auf. Eine Serie von Studien in einer Population von 55'000 Menschen wurden hierfür durchgeführt.

Das soziale Marketingprogramm in Tansania für imprägnierte Bettnetze hatte in einem Zeitraum von 2 Jahren eine rapide Steigerung des Besitzes von Mückennetzen bei Erwachsenen (von 58 % auf 83 %) und der Nutzung bei Kindern unter zwei Jahren Lebensalter zur Folge. Als Konsequenz hieraus stieg der Gesamtmittelwert des Hämoglobinlevels (von 8,0 g/dl auf 8,9 g/dl). Die Prävalenz für Anämie sank in der Untersuchungspopulation von 45 % auf 26 %. Vergleiche zwischen Kindern, die mit und ohne imprägnierte Netze schliefen, zeigten eine Schutzwirkung der imprägnierten Netze von 63 % (95 % CI: 38 bis 77) in bezug auf die Prävalenz von Parasitämie, und 63 % (95 % CI: 27 bis 82 %) bezüglich der Anämieprävalenz (Hämoglobin $\underline{\geq}$ 8 g/dl). Diese Ergebnisse unterstützen eine Befürwortung einer grossräumigen Einführung insektizidimprägnierter Bettnetze in Tansania.

Imprägnierte Bettnetze können jedoch das Risiko an Malaria zu erkranken nur reduzieren, nicht völlig aufheben. Folglich ist eine effektive Behandlung ebenso notwendig wie die Prävention. Chloroquine war lange Zeit ein kostengünstiges und sicher wirkendes Antimalariamedikament und es war bis vor kurzem das Medikament der Wahl in der nationalen Politik der Malariabehandlung. Es ist jedoch in Tansania mit zunehmender

Häufigkeit von Chloroquineresistenzen berichtet worden und es wurde ein Zusammenhang zwischen Spitalkonsultationen mit schwerer Malaria und Chloroquineresistenzen festgestellt. Ein vergleichender randomisierter klinischer Versuch zur Wirkung von Chloroquine und Co-artem®, einem neuartigen Antimalariamedikament (Kombination aus Arthemether und Benflumetol), zeigte nach siebentägiger Anwendung eine Effizienz von 94 % bei Co-artem® und nur 35 % bei Chloroquine. Insgesamt zeigte Co-artem® eine höhere '*clearance rate*', d.h. es beseitigte eine höhere Parasitendichte und verminderte Neuinfektionen über einen längeren Zeitraum als Chloroquine. Weiterhin unterdrückte Co-artem® die Gametocytenbildung in Kindern wirkungsvoller, woraus ein weiterer Nutzen in Form einer verminderten Malariaübertragung resultiert. Die nicht akzeptierbar hohe Ausfallrate von Chloroquine erfordert eine umgehende Aenderung der nationalen Richtlinien zur Malariabehandlung.

Die Entscheidung, ein etabliertes Antimalariamedikament durch ein neues zu ersetzen, hängt von vielerlei klinischen, epidemiologischen, sozio-ökonomischen Faktoren, als auch den infrastrukturellen Bedingungen ab. Unter in Betrachtziehung all dieser Komponenten wurde Sulphadoxine-Pyrimenthamine (SP) als adäquater interimistischer Ersatz für Chloroquine identifiziert. Es sind weitere *Phase IV* evaluationen von Co-artem® und anderen Kombinationstherapien erforderlich, bevor deren Einbezug in die nationale Antimalariabehandlungspolitik avisiert werden kann. Ebenso sind noch Anstrengungen erforderlich um adäquate Präparate zur ‚Heimbehandlung' von Malaria zu identifiziern und sie in den nationalen Richtlinien zu verankern.

Die durch die verschiedenen Studien gewonnen Erfahrungen zeigen eine Palette verschiedener Methoden und Instrumente auf, die verwendet werden können, um die verschiedenen Komponenten nationaler Kontrollprogramme zu evaluieren. So war es beispielsweise schwierig den Einfluss imprägnierter Mückennetze im Rahmen einer ‚Fall-Kontroll Studie' zu ermitteln. Wiederholte ‚Querschnittstudien' erwiesen sich dagegen unter Programmbedingungen als geeigneter, v.a. in bezug auf malariabedingte Anämie in Gebieten mit hohen Übertragungsraten. Zur Evaluation von Interventionsprogrammen werden spezifische Indikatoren benötigt, die sich von denen, die in „randomisiert kontrollierten Studien" verwendet werden unterscheiden. Die Verwendung molekularer Marker für

Monitoring und Evaluation von Antimalariainterventionen zeigt neue Wege in dieser Richtung auf.

Eine verbesserte Malariakontrolle ist durch die Kombination von imprägnierten Bettnetzen und wirkungsvollen Antimalariamedikamenten, v.a. von Kombinationspräparaten, zu erwarten. Die Evaluation, das Monitoring und die Implementierung dieser Kontrollmassnahmen erfordert Partnerschaften zwischen Forschern, Politikern und Gesundheitsmanagern in enger Zusammenarbeit mit anderen Vertretern öffentlicher und privater Bereiche, sowie der Bevölkerung.

List of Tables

CHAPTER 9

CHAPTER 10

List of Figures

PART I : BACKGROUND, OBJECTIVES AND METHODS

CHAPTER 1

Introduction:

Burden of Malaria disease

Malaria is major public health problem in the world. In 1997, more than 40% of the world population lived in areas with a risk of malaria trasmission. Furthermore, in the last few decades there has been a resurgence of malaria transmission in areas where it was previously under control in the Central Europe, Southern Asia and the Pacific (Trigg & Chondrachine 1998). Malaria contributes to a considerable burden in endemic communities with premature deaths, disability from illness and it impedes on social and economic development. Each year about 300 million episodes of clinical malaria disease and about one million malaria deaths occur in the world (WHO 1999).

The majority (90%) of the burden of disease is in Sub-Saharan Africa. It is estimated that malaria contributes to a loss of 39 million disability-adjusted life years (DALYS), of which 34 million are in Africa alone (WHO 1999). The problem of malaria is also increasing in Africa. In parts of Eastern and Southern Africa malaria has extended into previously non-endemic or low transmission areas. The climatic conditions existing in many parts of Sub-Saharan Africa favour high malaria transmission potential (Snow *et al*. 1999). Furthermore, *Plasmodium falciparum* is the predominant parasite species, and it is associated with high virulence, severe morbidity and high mortality.

In Tanzania, malaria accounted for about 33% of all outpatient attendance and hospital admissions in 1996 and it is the leading cause of deaths (34%) in hospital admissions in children under five years (MOH 1998). Health facility reports indicate that there are an increasing number of admitted cases of malaria since 1982 (Kilama & Kihamia 1991, MOH 1998). Reliable data on mortality burden caused by the disease are not available as most deaths occur at home and there is no adequate vital event registration system in place

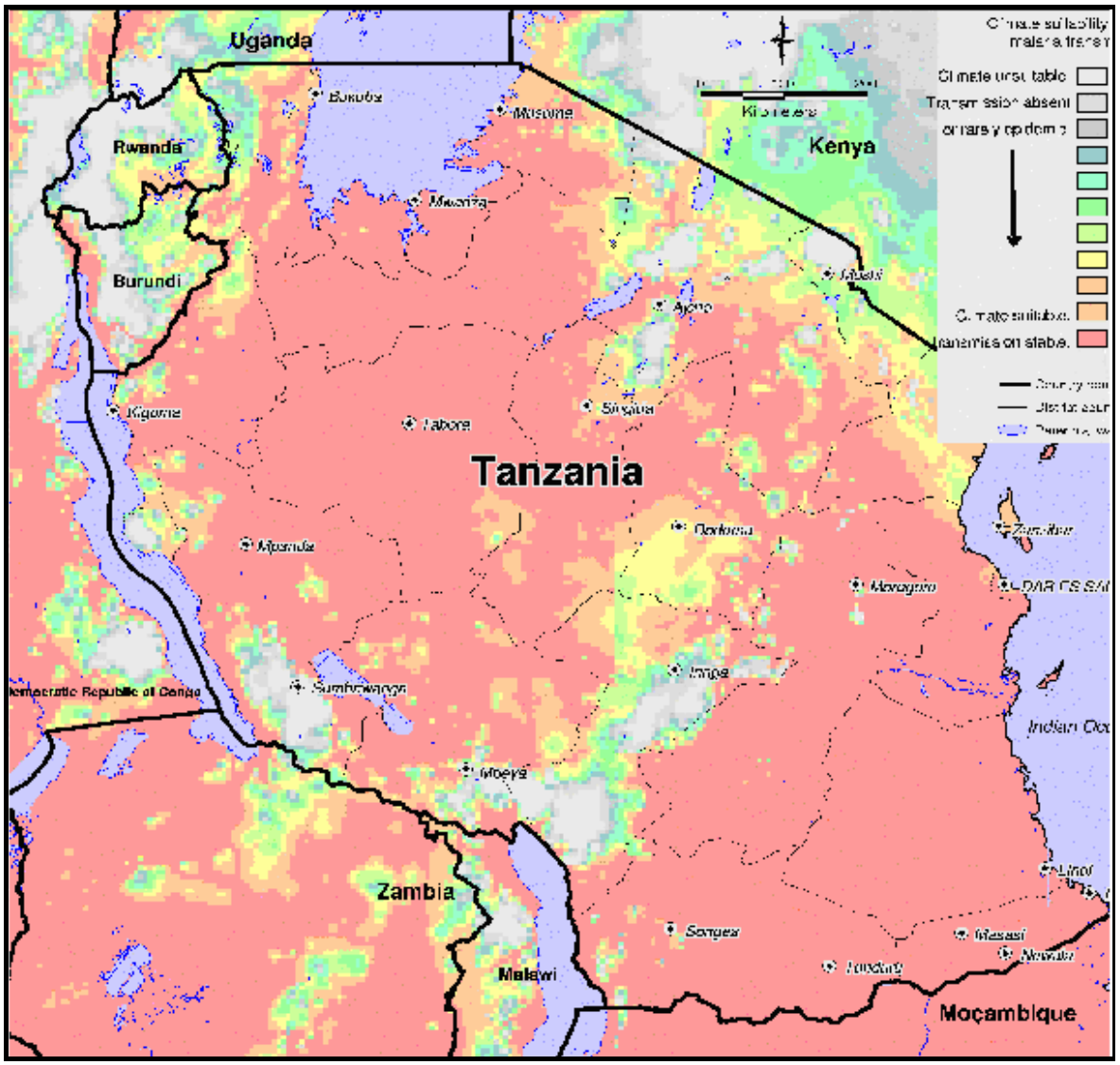
(Kitange *et al*. 1996, Snow *et al*. 1999). Demographic surveillance data from Morogoro rural district indicate that malaria is a major cause of death in children and even among adults (Kitange *et al*. 1996).

Plasmodium falciparum is the main parasite species in Tanzania and it accounts for more than 90% of all infections. Other malaria species found are *P. ovale* and *P. malariae*. These frequently occur as mixed infections with *P. falciparum*. *P. vivax* is very rare in Tanzania (Kilama & Kihamia 1991).

Malaria transmission in Tanzania has been described by Clyde (1967) as a sea of stable and high transmission with islands of low or no transmission, especially at high altitudes (Fig1). Estimates of population at risk in Tanzania indicate that 28 million people live in malaria endemic areas, 1.3 million in epidemic malaria areas and only about 0.6 million in very low risk areas (MARA/ARMA: http:/www.mrc.ac.za/maracrt). The main vectors are *Anopheles gambie* complex and *Anopheles funestus*. The climatic and environmental factors favour the existence of an abundance of these vectors resulting in high vectorial capacity for malaria transmission. This makes malaria control difficult in many areas of Tanzania.

The burden of malaria and the consequence of the disease in the health of the population has been characterised in detail in an area in the Kilombero valley, Southwest Tanzania (Tanner *et al*. 1991). It has been estimated that on average there are about 0.7 and 0.6 episodes per child per year of clinical malaria and severe anaemia in children under five years living in the area (Menendez *et al*. 1997).

Figure 1: Distribution of stable malaria transmission in Tanzania
(source: MARA/ARMA Collaboration)



It is widely accepted that transmission intensity influences the prevalence and incidence of malaria infection and associated complications. Severe anaemia and cerebral malaria are the two major forms of severe disease leading to death. It has been observed that in areas of lower transmission the incidence of clinical disease is much more spread out in early childhood and cerebral malaria predominates as severe disease presentation. In areas of high transmission, the burden of morbidity and mortality is concentrated in the very young children and is much less in older children and adults. This is due mainly to early acquisition of functional immunity to clinical disease. In these areas severe anaemia predominates as the severe disease presentation (Marsh & Snow 1999, Schellenberg *et al*. 1999). These differences in cerebral versus anaemia patterns may therefore be important in monitoring changes of transmission intensity over time and may be valuable indicators for assessing impact of control measures.

Several studies have shown a positive correlation between parasitaemia and anaemia, and further demonstrated that parasitaemia is the primary cause of anaemia in very young children in Africa (Kitua *et al*. 1997, Newton *et al*. 1997). The pathogenesis of malarial anaemia is complex and includes the process of haemolysis, sequestration of red cells, and dyserythropoiesis (Weatherall & Abdalla 1982). Malarial anaemia may develop rapidly following an acute malaria attack or may develop insidiously over a period of time; many patients fall in between these two extremes (Abdalla *et al*. 1980).

The emergence and spread of parasite resistance to commonly used antimalarials has exacerbated the problem of anaemia in Sub-Saharan Africa, since persisting parasites contribute to the occurrence of anaemia (Bloland *et al*. 1993). In the Kilombero, 60% of children treated with chloroquine (the recommended first line antimalarial), fail to respond within 14 days (Hatz *et al*. 1998). Hospital management of the severe forms anaemia involves blood transfusion (Newton *et al*. 1997 , Schellenberg *et al*. 1999) and there is an increasing concern that the transfusions are a potential risk for HIV transmission in children (Greenberg *et al*. 1988 , Holzer *et al*. 1993). In addition, most children at risk of severe anaemia live beyond reach of hospitals able to provide such blood transfusions (Font & Nathan, unpublished data). Furthermore, severe anaemia is a silent disease that is less recognised in the community and therefore not easily treated (Menendez *et al*. 1997). Hence, there is an

urgent need to implement effective malaria control strategies in the Kilombero valley and Tanzania as whole.

Malaria control strategies

The World Health Organisation (WHO) has identified malaria as a priority health issue in the world and initiated the Roll Back Malaria Cabinet Project (RBM) in 1998. In this new initiative the WHO, United Nations Children's Fund (UNICEF), United Nations Development Programme (UNDP), World Bank (WB) and various collaborators join forces to fight malaria. RBM aims at achiving a 50% reduction of the malaria burden by 2010. The initiative has identified six elements to achieve the objective: (1) early detection of malaria illness, (2) rapid treatment of those who are ill, (3) multiple means for prevention of infection, (4) strengthening of health sector and intersectorial activities, (5) a powerful sustained social involvement and movement, and (6) focused research for new tools and better implementation (Nabaro 1999). These main elements are an elaboration of the basic elements of the global malaria control strategy devised in 1993. The main strategy for malaria control is still early diagnosis and treatment of clinical cases (WHO 1993). Since, the increasing incidence of antimalarial drug resistance is undermining the effectiveness of this strategy, alternative cost-effective and sustainable control measures are urgently required.

Malaria prevention strategies in Tanzania

Environmental modification to control the scourge of malaria in Tanzania has a long history. In the 50's several programmes were implemented in the more populated urban areas (mainly Dar-es salaam and Zanzibar). But this is only feasible in urban areas and requires functional administrative and implementation structures (Kilama 1991). People in urban areas use several mosquito repellent measures, including aerosol insecticides and mosquito coils. In rural areas those who can afford use these insecticides and many more use more traditional preventive measures, such as burning of leaves. These mosquito repellent measures have doubtful benefits in preventing malaria. In semi-immune population chemoprophylaxis with effective antimalarials is only recommended for pregnant women (WHO 1984). Chemoprophylaxis in children is not recommended for fears of interference with the development of protective immunity and the acceleration of drug resistance. Furthermore, it

may be impossible to achieve continuous suppression in a significant proportion of the population and it may then be better to use the scarce resources for treatment. Malaria vaccines will go a long way in reducing the burden of malaria in people in endemic areas, especially children. However, there is limited hope for a vaccine in the near future. A recent trial of SPf66 in infants in Tanzania did not show any protection (Acosta *et al*. 1999).

Vector control by insecticides has been implemented in both urban and rural areas in Tanzania. In rural areas, the Pare-Taveta project in Northeast Tanzania was the most elaborated control effort. Spraying of households was conducted from 1955 to 1959 and the impact of these control measures was monitored (Bradley 1991). Both urban and rural spraying programmes were successful in reducing the burden of malaria in short periods. In the Pare-Taveta project, the infant mortality rate was reduced by about 20% and haemoglobin levels increased about 26% during the intervention period, compared to before the intervention (Bradley 1991). Unfortunately, problems in sustaining the spraying in these areas clearly demonstrated the difficulties of such a strategy. The programmes required high financial and human resource inputs, which could not possibly be maintained. These were mainly "vertical" programme with specialised spraying teams and had limited community involvement, hence there was also a growing reluctance of the population to co-operate with the spraying activities. Although transmission was significantly reduced in the programmes, it was not interrupted.

Currently, preventive malaria control is being re-considered using insecticide treated nets (ITNs), including treated bed nets and curtains, which do not require a large national programme infrastructure for implementation. Studies in Muheza indicate that ITNs have similar efficacy to indoor spraying and are cheaper to implement (Curtis *et al.* 1998).

ITNs in Tanzania

The use of protective measure similar to bed nets can be traced to traditional behaviours in some tribes in Tanzania. Examples are the use of 'MTUTI', a sleeping bag made of thatched palm leaves in the Rufiji delta (Mayombana *et al*. unpublished data) or the use of nets made of cloth 'baba kalala wapi' in the Kilombero Valley (Minja H. pers. Comm). Only a small proportion of people in the Kilombero Valley used bed nets in the 1980's and early 1990's

(Fraser-Hurt & Lyimo 1998). The main reason for using bed nets in this setting was protection against mosquito nuisance rather than protection against malaria disease.

The treatment of these bed nets with insecticide is a revival of an old idea that was started in the Second World War with the treatment of soldiers' uniforms to prevent malaria and other vector borne diseases (Lindsay & Gibson 1988). The ITNs act by both being a physical barrier protecting those sleeping under them, and by killing and repelling mosquitoes hence reducing their survival and infection rates (Lines 1996). Hence those using ITNs properly have a reduced exposure to malaria infecting mosquitoes and as a consequence have a reduced malaria disease burden. Different types of insecticide on the net have been shown to have slightly different killing and repellency effects although they mostly belong to the class of synthetic pyrethroids (Curtis *et al*. 1996)

After the initial success in experimental hut trials (Lines *et al.* 1987) and small scale studies, large trials were implemented in Tanzania as in many other parts of Africa (Premji *et al.*. 1995). Large randomised controlled trials were also conducted in many parts of Africa to establish the efficacy of ITNs in reducing morbidity and mortality. A summary of the results of these randomised controlled trials showed an average protective effect on mild malaria episodes of 46% in stable malaria areas when controls did not use nets, and a protective effect of 37% when controls used untreated nets. Moreover, protective effects were shown on the prevalence of high parasitaemia (31%). A modest improvement in packed cell volume (2%) and weight gain was also observed in children sleeping under treated nets (Lengeler, 1998). Most importantly, the regular use of ITNs under trial conditions prevents approximately 6 deaths for every 1000 children protected every year across a large range of transmission intensities. Hence, there was a recent call by African leaders to protect 60% of African children by 2005 and large-scale pilot programmes are underway in several areas in Africa (Anonymous 1999).

ITNs implementation strategy

The translations of promising research results into effective public health action, is a huge task. There are at least 60 million children living in areas at risk for malaria in Africa and their nets, once provided, will need to be treated regularly (every 6-12 months) over many years (although there is currently hope for development of permanently treated nets). Various options for financing and implementation of ITNs have been tried, most of them on a relatively small scale (up to 10 villages). There are three main traditional implementation models (Feilden 1996): (1) the integration of ITNs distribution into a community pharmacy network (eg. the Bamako initiative programme in western Kenya: Hill (1991)), (2) sales through local health units (eg. Fraser-Hurt and Lyimo 1998) or the existing PHC system (D'Alessandro *et al.* 1995), and (3) distribution through community groups (eg. Premji *et al.* 1995). Despite these various programmes which contributed much useful operational experience, we do not yet have sufficient experience to recommend specific large-scale ITNs implementation strategies for all the varied social, cultural and economic conditions in Africa. Hence, launching a number of large programmes (population of over 100,000) using different pragmatic approaches will allow locally-relevant implementation approaches to be found.

Social marketing is a flexible implementation model that has proved successful in resource-poor countries for interventions such as oral rehydration salts (ORS) and condoms. In this approach commercial marketing methods are applied to a product which has a social benefit, with the main motivation being social improvement rather than financial gain to the marketer (Andreasen 1986, BASICS 1998). Much attention is paid to the main target group (i.e. for malaria: children and pregnant women) and much effort goes into understanding the perception, knowledge, attitudes and practices of this group in order to optimise promotion and distribution. Social marketing entails an effective public-private partnership which may be particularly useful for ITNs: unlike drugs and vaccines, ITNs may be seen as a commercial commodity rather than a medical product. Social marketing of ITNs has recently been started in various African countries, for example the Central African Republic (in 1996), Tanzania, Rwanda, Kenya and Zimbabwe.

Lastly, the social marketing programmes are also not large enough to allow coverage of whole countries. Hence, different strategies for up-scaling the implementation to national scale need to be developed involving public-private partnerships.

Impact of ITNs under programme conditions

It is still unclear whether social marketing can be used to distribute ITNs in the community while retaining the benefits of the nets seen in randomised control trials. Usually one can not assume that the results of the controlled trials are directly translated or replicated in programme settings (Lengeler & Snow 1996). Experience with the Gambian national bed net programme that concentrated on treatment of already available bed nets showed that the coverage, compliance and percentage re-treatment of the nets were well below the level achieved in an earlier controlled trial. The estimated impact on overall mortality was only 25% (D'Alessandro *et al*.1995) as compared to 42% in the earlier controlled trial (Alonso *et al*. 1991).

Moreover, it is not known what impact the pattern of distribution will have on the occurrence of disease in the community. Earlier work indicated that there are short range (within the same room) protective effects of ITNs on unprotected people sleeping nearby (Lines *et al*. 1987) but this has not been shown everywhere (Rowland *et al*. 1996). Work conducted in Ghana supports the claims of short distance protective effects on those without bed nets. Among non-users the mortality risk increased by 6.7% with every 100 meters shift away from the nearest compound with treated bed nets (Binka *et al*. 1998). More recent work in Kenya indicated the presence of a 'mass effect' due to ITNs that confers protection to nearby non-users. While this spatial phenomenon is very important from the public health point of view, it also has bearing on the estimated effectiveness of ITNs in programme evaluations. If deflection of mosquitoes to those without ITNs occur, with a resulting increase of disease in this group (Rowland *et al*. 1996), then there will be an overestimation of the protective effectiveness. On the other hand, if the killing effect is predominant with a reduced risk for those near the ITNs (Lines *et al*. 1987) then the measured effect will be biased toward zero, as has been demonstrated in some areas (Binka *et al*. 1998, Howard *et al.* 2000). Further to these distance effects, coverage was also shown to be an important parameter as the efficacy was observed to be highest with high compliance. The distribution pattern and coverage

levels attained in these programmes may determine the level of protection observed in those who use them (Binka *et al*. 1998)

Treatment of uncomplicated malaria in Tanzania

The use of ITNs as a preventive measure is not going to interrupt transmission in many of the areas in Africa and therefore cannot eliminate the need for effective treatment of cases. Indeed after the collapse of the few major preventive programmes in the 1950 and 60's, early diagnosis and prompt treatment with an effective antimalarial was adopted as the main stay of the control effort in most African countries (WHO 1993). However, the implementation of this strategy also faces many challenges. Most people who fall sick with malaria-like symptoms are given antimalarial drugs stored at home and frequently in sub-optimal or incorrect drug dosage (Mwenesi *et al.* 1995, Nyamongo 1999, Nsimba *et al.* 1999). Many factors contribute to the preference for shops and drug stores rather than existing health services. These include lack of drugs in public sector facilities and convenience. There are more shops and drug stores than health facilities, and they may be more easily accessible, in terms of time to reach them, time spent waiting for service, and opening times.

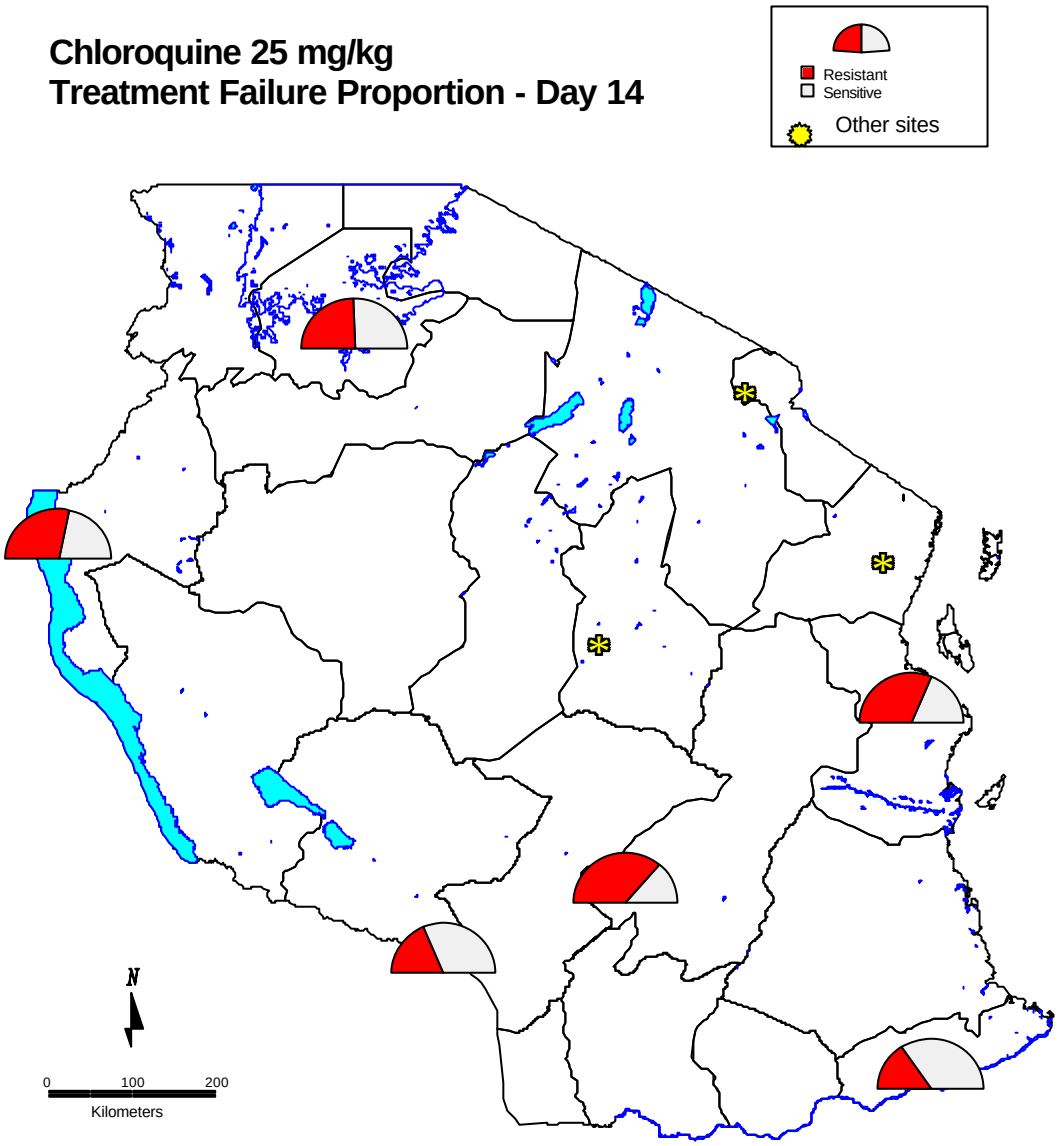
There are concerns that the wide scale use of antimalarial drugs encourages the development and spread of *Plasmodium falciparum* resistance and threatens the effectiveness of the early diagnosis and treatment strategy in many parts of the world. Resistance to chloroquine, the cheap and safe antimalarial, has been reported with increasing frequency in Tanzania (Kilimali & Mkufya 1985a, 1985b, Mshinda *et al.* 1996). Work conducted as part of the National malaria control programme, showed that on average half of the children treated with chloroquine ended up with inadequate clinical response within 14 days (Figure 2). The work also demonstrated the presence of resistance at a lower level of the second line drug Sulphadoxine/pyrimethamine (MOH 1999).

Figure 2:

Antimalarial Drug Resistance - Tanzania

Sentinel Site Results
1997 - 1999

Chloroquine 25 mg/kg
Treatment Failure Proportion - Day 14



Data Sources: MOH, WHO, EANMAT

Mapped by MOH / TEHIP
July, 1999

When treatment is not successful, patients often look for alternatives. For malaria, treatment-seeking behaviour patterns vary a great deal, with constant interchange between formal and traditional providers. Studies in Ifakara and Rufiji found that only a quarter of the mothers and caretakers came back for re-treatment, if there was no improvement after initial treatment at a formal health facility (Bjorkman 1991, Muela-Hausmann *et al*. 1998). Treatment failure increases the risk of development of complicated malaria, with convulsive episodes in children or severe anaemia.

Perceptions of malaria disease severity vary and they reflect the perceptions of effectiveness of different treatments and services (Snow *et al.* 1992, Mwenesi 1995, Nsimba *et al.* 1999). Convulsive illness (*degedege*) is often regarded as a separate disease, for which traditional healers are considered to be a superior source of care (Makemba *et al.* 1996, Mwenesi *et al.* 1995, Minja *et al.* 2000). Perceptions of disease causation are of significance also for uptake of other interventions including ITNs (Minja *et al.* 2000).

Different levels of health care necessitate the consideration of the choice of drugs to be promoted at particular level. The wide availability of chloroquine for home treatment was advantageous in facilitating early treatment but its indiscriminate use has lead to rapid rise of resistance. The reliance on presumptive treatment rather than diagnostic microscopy at dispensary level, and the use of diagnostic strategies such as those of the Integrated Management of the Childhood Illnesses (IMCI) have clear benefits in terms of ease and cost of implementation. But they also increase drug pressure and the risk of resistance developing in the drugs being used. Together all these factors make it necessary to develop new alternative drugs and evaluate the optimal strategies for their introduction in the community.

Evaluation of the Control tools and programmes:

The description of the main malaria prevention and treatment strategies given above, highlights the continued need of developing and testing new tools and strategies to combat the increasing problem of malaria in many parts of Africa. On the preventive side, this will involve the development of new tools like malaria vaccines, which will take some time to accomplish. The curative side will involve the identification of new drug targets, as the current armoury of antimalarial drugs are based on very few targets in the parasite

(Winstanley 2000). Once these tools have been identified, rigorous testing of the identified compounds or tools should be done, to demonstrate their safety and efficacy in humans.

Thereafter, operational research to explore better ways of introducing the intervention in the community should be carried out. With ITNs much effort had gone into try out different delivery channels, as described above. Previously, much emphasis has been laid on the demonstration of efficacy of interventions in randomised controlled trials. Once efficacy was demonstrated the interventions were implemented in large programmes. Recently, more emphasis has also been laid on demonstrating that the expected benefits of the intervention are realised when the interventions are delivered in a programme setting (Lengeler & Snow 1996, Habicht *et al*. 1999). These evaluations aim to encourage the allocation of resources to sustain and expand the programmes to cover whole populations in endemic countries (Bryce *et al*. 1994 , Lengeler & Snow 1996) . The programme evaluations are further complicated by the fact that in most situations it is not possible to have a proper control group. Also there is often limited opportunity for establishing an elaborate evaluation system that is required to accurately assess exposure and outcome events in the target population (Habicht *et al*. 1999, Mohr 2000). Therefore, relatively cheap and easy evaluation tools are required.

Summary

A large part of Tanzania has high malaria transmission and the burden of disease is increasing. The disease is concentrated in young children and frequently presents as malaria anaemia, especially in very high transmission areas. The emergence and spread of drug resistance are undermining the current strategy of early diagnosis and treatment. Therefore there is an urgent need to investigate and evaluate new appropriate tools for the control of malaria in Tanzania. This thesis describes a series of studies conducted in the Kilombero Valley to assess the value of a new preventive tool (insecticide treated nets) and a new curative tool (Co-artem®) to combat malaria. These studies also explored issues on the design and methodologies for the evaluation of malaria control. Lastly, the experience gained from this work is used to highlight the many factors that influence the translation of research results into public health policy.

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CHAPTER 2

Goal and objectives

Goal

To evaluate the value of preventive (insecticide treated nets) and curative (Co-artem®) interventions in reducing malaria morbidity in an area of intense perennial malaria transmission.

Objectives:

- To determine the effect of insecticide treated nets on anaemia (Hb below 8 g/dl) in children under two years of age living in the IC-KINET DSS area by means of annual cross-sectional surveys.

- To determine the effectiveness of insecticide treated nets in reducing mild malaria episodes in children aged under five years in one village in the Kilombero Valley by means of cohort and nested case-control studies.

- To compare the performance of a case-control versus a cross-sectional approach for assessing the impact of insecticide treated nets in reducing the malaria morbidity in children under five years of age in one village in the Kilombero Valley.

- To determine the effect of spatial patterns of distribution of insecticide treated nets on malaria morbidity in children under five years in one village in the Kilombero Valley.

- To determine the efficacy of the new antimalarial Co-artem® compared to chloroquine in the treatment of uncomplicated malaria in children under five years of age.

- To investigate issues and determinants that are important in the development of a national antimalarial treatment policy.

CHAPTER 3

Design And Methods

Study area and population:

The flood plains of the Kilombero river extend 250kms from Southwest to Northeast, and are bordered by the Udzungwa range of mountains in the Northeast and Mahenge Mountains in the Southeast. Alluvial soils that are flooded every year support grassland vegetation. Diverse ethnic groups inhabit the plains and the majority are either subsistence farmers cultivating rain fed rice, maize cassava and/or fish from the Kilombero River and its tributaries. Several studies have been done to describe the disease patterns and assess their impact on health indicators of the communities living in these areas (Tanner *et al*. 1987, Tanner *et al*. 1991). These studies identified malaria and malarial-anaemia as a major public health problem in this area of high malaria transmission (Tanner *et al*. 1987). There is intense year-round malaria transmission (Charlwood *et al.* 1998). On average every person receives above 300 infective bites per year (Smith *et al*. 1993). The main vectors are *Anopheles gambiae ss, Anopheles arabiensis* and *Anopheles funestus*. It has been estimated that on average there are about 0.7 and 0.6 episodes per child per year of clinical malaria and severe anaemia in children under five. The main malaria control measure is prompt diagnosis and treatment of clinical cases. Chloroquine is still the first line antimalarial and its consumption is high. There are reports of rising chloroquine resistance in the area with only 80% of children responding to treatment within 7 days (Mshinda *et al.* 1996). Further detailed studies where conducted in Idete village (08^{o} 5' S; 36^{o} 30' E), which has features representative of the rural villages in the valley. The village is one of 18 in the Kilombero valley under demographic surveillance (DSS) (Schellenberg *et al.* 1999).

Social marketing and distribution of nets

The Kilombero bed net project (KINET) was implemented in the Kilombero valley using a social marketing approach and aimed to promote and distribute insecticide treated nets and insecticide for net treatment on a large scale. "*ZUIA MBU*" branded nets and insecticides were sold and distributed in the community using public and private distribution channels,

and a system of community door-to-door distributors. The implementation was staggered, with the first phase involving 18 villages. The implementation was expanded progressively to cover the whole of the two districts by the end of 1999. Planning and progress meetings involving project staff, district authorities and experts were held regularly during the period of implementation.

Demographic surveillance

The health impact assessment was restricted to the 18 villages located in the phase one area. In order to facilitate the evaluation of morbidity and mortality a demographic surveillance system (IC-DSS) was established. The system was adapted from the Navrongo demographic surveillance system (Binka *et al*. 1999). The IC-DSS covers 18 villages in the Kilombero Valley: 6 in Kilombero District and 12 in Ulanga District. The system involves visiting every household in the 18 villages once every 4 months. During these visits demographic and vital events like births, deaths and migration, are recorded in a household record book (HRB). The information is then entered in a relational data-base at the Ifakara Health Research and Development Centre (IHRDC) data unit. Using this system the study area was assessed to have approximately 55,000 residents and 3533 children under two years of age in 1997.

Passive case detection at Idete dispensary

For detailed morbidity assessment a passive case detection system (PCD) was established at Idete village dispensary. All children in the DSS database who were under the age of five on 1st February 1998 were listed, assigned a study number and provided with a special card bearing their name, date of birth, area of residence and DSS identifiers. This list was updated every 6 months to include new-borns and those children who had migrated into the village and who were therefore classified as new residents in the DSS. Children under five who were sick or had a history of illness were seen at the dispensary by a Rural Medical Aide. A clinical form was filled and information was entered in a database at the IHRDC data unit. The diagnosis, laboratory results and medication given were also written on the patient cards. The drug supply and services at the Idete dispensary were improved as part of the project to reduce the need of children to seek care elsewhere.

Case-control study

Using the PCD at Idete dispensary, a case control study was done between February 1998 and August 1999, to assess the impact of ITNs on mild malaria episodes. Children who were found to have a temperature of more than 37.4 ^{O}C and any parasitaemia were classified as cases. Children who had signs and symptoms of severe disease (e.g. haemoglobin <5.0 g/dl) were excluded from being cases.

For each case, one age-matched dispensary control was randomly chosen among the children who had come for growth monitoring or attended for another cause of disease, within two weeks of the attendance of the case. Separate records were kept for all the children who were not sick and had attended for growth monitoring. An additional community control was randomly chosen from the DSS database matched for age and area of residence (hamlet). If a control could not be found, then a child of an adjacent hamlet was chosen. Age was matched to within one month for infants, within two months for those between 12 - 24 months of age, and within 3 months for those above two years. A special Foxpro program was written and was run every week to identify cases and controls from the PCD, MCH attendance and DSS databases.

Both cases and controls were then visited at home, individual verbal consent was sought from the guardian and a questionnaire applied. The use of ITNs and other risk factors was assessed, including age of the child, tribe, religious affiliation, mother's education, family's social economic status, nutritional status, vaccination status, access to clean water, antimalarial and antipyretic use, condition of the net and its use in the previous month. A blood sample was taken from controls who had not given a blood sample at the dispensary in the two weeks prior to the day of the interview. Cases and controls were not eligible for re-recruitment as either cases or controls for a period of one month.

The sample size was calculated using Epi Info 6 for an unmatched design (matched designs need slightly fewer numbers). The sample was estimated to be able to show a 40% effectiveness against mild malaria episodes (summary estimate is about 46% from controlled trials (Lengeler 1998)), assuming a 30 % use of ITNs in the control group, five percent significance level and 90% power, giving a total of 454 cases. The sample was increased by 10% to allow for incomplete information and refusals, giving a total of approximately 500 cases to be recruited in one year. We used a concurrent sampling design, i.e. a case could be a control latter, and vice versa. The incidence of clinical

episodes of malaria was estimated to be 0.92/child/ year in children aged 12-30 months in Idete (Alonso *et al*. 1996). It was expected that the incidence rate would be slightly higher when taking children below 24 months.

Cross-sectional surveys

The impact of ITNs on the prevalence of parasitaemia and anaemia was assessed using annual cross-sectional surveys. Three annual cross-sectional surveys where conducted in a sample of children under two years of age living in the DSS area (Schellenberg *et al*. 1999). The first survey was done at the time of launching the social marketing campaign in June 1997, and two other surveys were carried out at the same period (June to August) in the subsequent two years. This period also coincided with the end of the rainy season when malaria anaemia is most prevalent (Kitua A. pers. Comm).

A simple random sample was selected from the DSS database for the first survey, and a two-stage random sampling (sampling 6 villages then sampling children from these) was done for the subsequent surveys. Children from Idete village and Kivukoni were not included in the subsequent surveys due to participation in other studies. The demographic surveillance data provided the sampling frame. For each year a different sample of children was selected from the database.

The sample size for the baseline (1st year DSS cross-sectional) was calculated using Epi-6 to get a sample which could estimate the proportion of children with haemoglobin below 8 g/dl to within +/- 2.5% (SE). Estimates from a study in the village of Kiberege (Fraser-Hurt *et al*. 1999) showed that the proportion of children with anaemia (Hb below 8 g/dl) was 30% for those without nets. Assuming a 95% confidence level and 2.5% standard error for the estimate, 296 children were required. Adding 10% more to account for refusals and non-availability a total of 325 children was sampled. For the subsequent DSS cross-sectional surveys, a review of the sample size was done taking into consideration the prevalence of anaemia, as estimated from the baseline survey, and the clustering of sampling. The sample size was calculated to estimate a 30% difference in the proportion of anaemic children between those who use ITNs and those who don't, assuming a 95% confidence level and 80% power. 330 children were sampled for each subsequent survey.

All the sample children were traced at home, consent from the parent or guardian requested, a questionnaire applied, clinical examination and anthropometric measurements performed, and a blood sample was taken for microscopy and haemoglobin estimation, as described below.

One cross-sectional assessment was also done in Idete village in June-August 1998. All children who were under-five years of age on 1st February 1998 were visited at home and a questionnaire applied to assess their use of ITNs and other risk factors for malaria infection and anaemia (similar to the main cross-sectional surveys). A blood sample (for malaria parasites and Hb estimation) was taken for children who had not given a blood sample at the dispensary during the two weeks prior the day of the interview.

Mapping of houses in Idete

The distribution patterns of the ITNs and the effect of high coverage of ITNs was investigated in Idete village. The position of the houses and other important service outlets including the dispensary were later determined using a portable Global Positioning System (Garmin, Thousand oaks, USA). The geo-referenced points were then used to calculate the distance between houses and between the houses of residence and the dispensary. Demographic data was collected from the updated DSS database.

Spatial positioning of events and variables was done by linking the mapped households with data from the PCD and Idete cross-sectional survey. Coverage of ITNs and untreated nets were calculated for each individual child during the cross-sectional survey. The number of nets per 1000 population living in houses other than the index child and within a specific radius were calculated. The radii of 50m (R_{50}), 100m (R_{100}), 200m (R_{200}) and 400m (R_{400}) were chosen considering the indication from studies done elsewhere (Binka *et al*, 1998; Hii *et al.* 2000). Further coverage was categorised as low (0 ITNs/1000 persons), moderate (1-300 ITNs/1000 persons) and high (>300 ITNs per/1000 persons)

Clinical trial of Co-artem®

The comparative efficacy of Co-artem® (Artemether + Benflumetol: CGP 56697) and chloroquine was assessed in a clinical trial at the 'mother-and-child' out-patient clinic at St Francis District Designated Hospital between February 1996 and September 1996 (Hatz *et al*. 2000). Inclusion criteria for selection were: age 1-5 years; body weight >5kg;

microscopically confirmed *P.falciparum* infection, with parasitaemia >5,000/µL blood; fever (axillary temp ≥37.5^{o}C); living within 5 km of trial site; feasibility of participation and informed consent; not participating in any other trial. Exclusion criteria were parasitaemia <5,000/µL; absence of fever; intolerance to oral medication; signs/symptoms of severe/complicated malaria; severe malnutrition or kwashiorkor; history of other antimalarial drugs within 48 hours; known sensitivity to chloroquine; any known chronic underlying disease.

Eligible children were randomised to receive either Co-artem® or chloroquine. The children in the Co-artem® treatment group received 4 doses of paediatric tablets at 0, 8, 24 and 48 hours. Trial medication for each child was contained in an individually numbered blister pack. Children were assigned treatment upon presentation by allocating the blister pack with the lowest available number. The contents (chloroquine or Co-artem®) were allocated randomly in blocks of 6. Each paediatric Co-artem® tablet contained 10mg artemether + 60mg benflumetol (½ the adult tablet level) and 1, 2, 3 or 4 tablets were given at the 4 dosage times according to body weight (5-10kg body weight, 4 doses of 1 tablet; 10-15kg, 4 doses of 2 tablets; 15-20kg, 4 doses of 3 tablets; 20-25kg, 4 doses of 4 tablets). Children in the chloroquine treatment group similarly received 4 doses over 3 days, according to body weight at 25mg per kg body weight as follows: 5-10 kg: ½ tablet, ¼ tablet each dose; 10-15kg: ¾ tablet, ½ tablet each dose; 15-20kg: 1 tablet, ½ tablet each dose; 20-25kg: 1½ tablets, ¾ tablet each dose (each tablet contains 150 mg chloroquine base).

Children were then visited at home for the first 3 days to administer medication and monitor side effects. There were then followed up at the clinic on day 7,14, 21, 28. Clinical examination and screening for malaria parasites was done during follow-up.

Interview and clinical procedures

A medical officer (the author) saw all study children in the main DSS cross-sectional surveys and the Co-artem® trial. A Rural Medical Aide using similar procedures saw children who were sick or had a history of illness when attending Idete dispensary, as well as those included in the cross-sectional survey in the village. All parents/guardians were asked for consent for children to participate using information sheet prepared specifically

for each study. History of illness was recorded using standard forms at the clinic for each study.

A standard questionnaire was applied to all children visited at home and who participated in all the cross-sectional surveys and the case control study in Idete. A questionnaire was used to assess exposure to treated bed nets and other potential risk factors. These factors included antimalarial treatment, anthropometric measurement, socio-economic status, tribe, religion, travel outside study area, illness in the previous month, history of blood transfusion, educational status, fostering and net usage.

All study children had their axillary temperature checked with an electronic thermometer. Weight was measured with a hanging scale and height measured with a special tape with the child lying down for those under two, and with child upright for those over two years. Physical examination was done with the child on the mother's lap. Splenomegaly was palpated on the mother's lap for those children below 2 years of age, and in an upright position for those above 2. Splenomegaly was recorded as palpable or not. Information on any other abnormalities was recorded. Finger prick blood samples were made with sterile lancets and drops of blood were collected on slides, Hemocue® micro-cuvette and a microtainer.

Treatment of sick children was done following the normal good clinical practice procedures of the hospitals in Kilombero and Ulanga Districts. Children with Hb below 8 g/dl were given haematenics, folic acid 5 mg once a day for three weeks, and ferrous sulphate 200 mg once a day for three weeks. For the home visits, the attending clinical officer treated sick children. In the main cross-sectional survey, asymptomatic children with parasitaemia above 2000 per microliter were traced and given a standard dose of chloroquine or sulphadoxine/pyrimethamine (SP).

Assessment of parasitaemia

Thick and thin films were stained with Giemsa stain. All blood films were read twice, independently, with the microscopist not knowing the intervention status (either bed net or drug treatment) of the child, and a third time if the ratio of densities from the first 2 exceeded 1.3 or was less than 0.67, or if one was positive and the other negative. A definitive result was based on a majority verdict for positivity and the geometric mean of

the 2 closest positive density counts (Alonso *et al*.1994). 20 thick film fields were examined before the slide was declared negative. If asexual forms of *P. falciparum* were found, then 200 thick film fields were screened for the presence of malarial parasite species. Identification of *P.falciparum* was followed by a tally counter count of asexual forms and leucocytes. Present gametocytes were counted similarly. A peer review of 282 slides was done. There was a 87% agreement in terms of negative/positive results between the 2 counts.

Measurement of haemoglobin

Haemoglobin was measured using the HemoCue® system (HemoCue AB, Ängelholm, Sweden). A drop of blood was placed in a special microcuvette which contained a hemolyzing agent (sodium desoxycholate, sodium nitrite, and sodium-azide). The erythrocyte membranes are disintegrated by sodium desoxycholate, releasing the haemoglobin. Sodium nitrite converts the haemoglobin iron from the ferrous to the ferric state to form methaemoglobin, which then combines with azide to form azidemethaemoglobin. The meters measured the amount of light absorbed by the sample within the microcuvette in the 540nm range, to estimate the haemoglobin level. The method has been found to be easy and accurate for measuring haemoglobin (von Schenck *et al*. 1986).

DNA processing and PCR

Five µl of blood were lysed in 50 µl GTC solution (4 M guanidine-isothiocyanate, 25 mM Na citrate pH 7.0, 0.5% Na sarcosylsulphate), 5 µl β-mercaptoethanol, and mixed with 50 µl TE saturated phenol and 50 µl chloroform. The aqueous phase was separated, precipitated with isopropanol and DNA redissolved in 30 µl H_20.

A nested PCR was performed for MSP2. *5* µl of DNA were used for the primary reaction and 2 µl of PCR product for the nested reaction in a 100 µl reaction composed as follows: 10 mM Tris pH 8.8, 50 mM KCl, 1.5 mM $MgCl_2$, 0.25% Tween 20, 0.2 mM each NTP, 0.5 pM each primer, 1.25 U taq polymerase. Primer pairs used were S2 and S3 for the primary reaction and S1 and S4 for the nested reaction as published by Foley *et al.* (1992). Both PCR reactions were performed in a Perkin Elmer Thermocycler 480 with the following

profile: 5 min at 94 ^{o}C and 30 cycles: 1 min at 94 ^{o}C, 2 min at 55^{o}C, 2 min at 70 ^{o}C. Negative controls were included with each set of PCR reactions.

The different MSP2 alleles were genotyped as previously described (Felger *et al.* 1993). 20 µl of nested PCR product were subjected to restriction digests with the restriction enzymes Ddel, Rsal, Hinfl, ScrF1, respectively, and run on a 10% polyacrylamide gel. All digests of one restriction enzyme were loaded side by side for all samples of an individual patient and sizes were calculated using a standard commercial size marker. RFLP patterns were visualized by ethidium bromide staining and documented electronically. All gels were analysed by two independent researchers.

Data processing

All data collected in the study was double entered into a database (Foxpro®) at the IHRDC data center. Consistency and logical checks were done using programs written in Foxpro® (Microsoft Corporation, Redmond USA).

Analysis

In the case-control assessment, cases of mild malaria were compared with controls primarily with regard to their exposure to ITNs. Matched pairs were analysed by univariate analysis, then by multivariate analysis. Matched pairs multivariate analysis using conditional logistic regression was done using STATA® (Stata Corporation, Texas USA). Comparison was made of the attendance and incidence of episodes of anaemia and parasitaemia at the dispensary among users and non-users of ITNs. The relative rates were calculated in STATA®.

Analysis was done for all the three cross-sectional surveys combined. The impact of the nets on haemoglobin level, anaemia, parasitaemia and splenomegaly was estimated using multiple linear and logistic regression models taking into account the village cluster sampling for year 2 and 3, using robust regression approaches in STATA® (Stata Corp. 1999). The effect of different time points of observation (surveys) was included as one of the explanatory variables.

Anaemia was classified as haemoglobin level below 8.0 g/dl since this is the level that has been associated with increased mortality (Stoltzfus 1997) and this is consistent with earlier studies in the area (Menendez *et al*. 1997). Parasitaemia and splenomegaly were classified as either present or absent. Use of treated nets was categorised based on the respondent's answers on ownership, and if they were "ever treated" or "not treated". There are currently no simple ways to assess insecticide content on the nets in the field.

Other factors considered in the multivariate models included use of the net, condition of the net, age, sex, ethnicity, religion, nutritional status, access to the dispensary, shops and covered wells. Treatment history and attitudes toward health seeking were also included, as were factors related to the family size and income. The cross-sectional surveys in Idete was analysed similarly.

The statistical modelling part for neighbourhood or short-distance effects was done using generalised linear mixed models (Breslow & Clayton, 1993) to measure the impact of categorical explanatory variables on binary outcomes of having anaemia, harbouring parasites and owning an ITN, under consideration of spatial correlation. Continuous fixed effect variables are discretisized into several categories to check their linear influence. Because this analysis showed non-linearity in all cases, they were categorised in the final models.

We assume that near observations in space are likely to have the same outcome. To adjust for such a spatial dependence structure, the correlation function takes the value of one for observations close together and it decreases with increasing distance.

If p_i is the probability outcome for observation i, then using a logit link function leads to the model:

$$\text{logit}(p_i) = b^t C_i + e_i$$

where b is the vector of coefficients and C_i the vector of fixed effects for observation I with 1 in the first place to include an intercept term. The error term e_i has the general form $\text{Cov}(e_i, e_j) = s^2 f(d_{ij})$, where d_{ij} measures the euklidian distance between location s_i and s_j. For $f(d_{ij})$ we choose the exponential type $f(d_{ij}) = \exp(-r \bullet d_{ij})$, but compared the fit as well with models incorporating different choices of spatial covariance types. In addition to better estimates for the fixed effects, this setting allowed us to describe the size and decay

of spatial dependency through s^2 and r, respectively. Finally the analysis was done using the SAS GLIMMIX macro, which uses iteratively reweighted likelihoods (Wolfinger & O'Connel, 1993) to fit the models. To compare the spatial with the non-spatial models, we applied likelihood ratio statistics. The macro can only accommodate one observation per location, therefore the youngest child was chosen from houses with multiple children. A repeat of the analysis using a randomly selected child from these households yielded similar results.

Quality control

The medical officer (the author) did a repeat of 5% of interviews and physical examination and observed 5% of all physical examinations and interviews in the Idete surveys. All forms were checked for completeness before being accepted into the data room. Clinical data entered in the computer was checked for logical errors weekly. Standard quality control procedures for IHRDC data center and laboratory were applied. An independent laboratory in the United Kingdom did a review of the parasitological results and good agreement was observed. Daily Hemocue® calibrations were done.

Regulatory approval

This thesis describes a series of studies that were conducted in a period of four years and included both hospital and community based work. Furthermore, the studies on treated bed nets were part of a larger multidiscipline evaluation. All the studies received institutional scientific and ethical approval from the IHRDC, and the National Institute for Medical Research. The KINET programme evaluation and the Co-artem® trial had approval from the Ministry of Health and the Commission of Science and Technology that has the mandate of overseeing all research in Tanzania.

Sensitisation, community and individual consent

For the community-based studies a series of meetings were held first at district then ward and finally at village level to get consent from the authorities to implement evaluation. After the approval of the authorities public village level meetings were held to sensitise and get community consent for the programme. For the hospital-based studies approval was sought from the hospital board and the staff of the St Francis Designated District Hospital. Idete village leadership and dispensary staff were consulted for approval of the dispensary studies.

The Idete dispensary studies were further explained at public meetings at hamlet level. At the time of implementation of all the studies, individual verbal consent was requested from the parent or guardian of the child, and a written or finger printed consent was also asked for the hospital-based trial. All children who were sick in the community studies were treated according to the good clinical practice of the Kilombero district health facilities and treatment guidelines of the Tanzania Ministry of Health.

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PART II : INSECTICIDE TREATED NETS

CHAPTER 4

KINET: a social marketing programme of treated nets and net treatment for malaria control in Tanzania, with evaluation of child health and long-term survival

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Abstract

We present a large-scale social marketing programme of insecticide-treated nets in 2 rural districts in south- western Tanzania (population 350 000) and describe how the long-term child health and survival impact will be assessed. Formative and market research were conducted in order to understand community perceptions, knowledge, attitudes and practice with respect to the products to be socially marketed. We identified *Zuia Mbu* (Kiswahili for 'prevent mosquitoes') as a suitable brand name for both treated nets and single-dose insecticide treatment sachets. A mix of public and private sales outlets is used for distribution. In the first stage of a stepped introduction 31 net agents were appointed and trained in 18 villages: 15 were shop owners, 14 were village leaders, 1 was a parish priest and 1 a health worker. For net treatment 37 young people were appointed in the same villages and trained as agents. Further institutions in both districts such as hospitals, development projects and employers were also involved in distribution. Promotion for both products was intense and used a variety of channels. A total of 22 4 10 nets and 8072 treatments were sold during the first year: 18 months after launching, 46% of 312 families with children aged under 5 years reported that their children were sleeping under treated nets. A strong evaluation component in over 50 000 people allows assessment of the long-term effects of insecticide-treated nets on child health and survival, anaemia in pregnancy, and the costs of the intervention. This evaluation is based on cross-sectional surveys, and case-control and cohort studies.

Introduction

Despite malaria being the largest public health problem in Africa south of the Sahara, with over one million associated deaths each year (WHO, 1997), little progress has taken place in control during the past decades. Prompt treatment with an effective antimalarial remains the basis of malaria control strategies in most African countries (WHO, 1993). Preventive transmission control is being reconsidered using insecticide-treated nets (ITNs, including treated bednets and curtains) which do not require a large national programme infrastructure for implementation. In a meta-analysis of African trials ITNs were found to reduce clinical malaria episodes by 48% and to improve anaemia status by an average 0.5 g/dL (Lengeler, 1998). Most importantly, the regular use of ITNs under trial conditions prevents approximately 6 deaths for every 1000 children protected every year across a large range of transmission intensities. Many international agencies (e.g., UNICEF, WHO, World Bank, Organization of African Unity) have recognized that malaria control is an urgent priority in order to improve child survival and are now making plans for implementation of ITNs (WHO, 1996; UNICEF, 1998; USAID, 1998).

The translation of promising research results into effective public health action is a daunting task. There are at least 60 million children living in areas at risk for malaria in Africa and their nets, once provided, will need to be treated regularly (every 6-12 months) over many years. Feilden (1996) reviewed various options for financing and implementation of ITNs, most of which have been tried on a relatively small scale (up to 10 villages). These fall into 3 main implementation models: (i) the integration of ITNs distribution into a community pharmacy network (e.g., the Bamako Initiative pro- gramme in Western Kenya (Hill, 1991), (ii) sales through local health units (e.g., Fraser-Hurt & Lyimo, 1998) or the existing primary health care system (D'Alessandro *et al.,* 1995), and (iii) distribution through community groups (e.g., Premji *et al.* 1995). Despite much useful operational experience, it seems premature to recommend specific large-scale ITNs implementation strategies for the African continent. The launch of a number of large programmes (population of over 100 000) using different pragmatic approaches will allow these strategies to be optimized.

Social marketing is a very flexible implementation model that has proved successful in resource-poor countries for interventions such as oral rehydration salts (ORS) and condoms (BASICS, 1998). Social marketing is an approach where the experience and

methods of commercial marketing are applied to a product which has a social benefit, with the main motivation being social improvement rather than financial gain to the marketer (Andreasen, 1995). The approach usually uses a branded product that can be marketed and advertised professionally. Much attention is paid to the main target group-sometimes called customers-and much effort goes into understanding the perception, knowledge, attitudes and practices of this group. Social marketing entails an effective public-private partnership which may be particularly useful for ITNs: unlike drugs and vaccines, ITNs may be seen as a commercial commodity rather than a medical product. Social marketing of ITNs has recently been started in various African countries, for example, the Central African Republic (in 1996), Rwanda, Kenya and Zimbabwe (in 1997).

The long-term impact of ITNs on small children in areas with high malaria transmission (an arbitrary cut-off being an annual entomological inoculation rate over 100) remains a controversial issue. The potential con- sequences of delaying acquisition of immunity are worrying in that in such areas it has been suggested that overall survival could be better without ITNs (Snow *et al.*, 1997). However, good data on the issue are scant and the discussion has been based on indirect evidence. Following the discontinuation of malaria control trials in the past no evidence for a delay or a 'rebound' in mortality was found (Molineaux & Gramiccia, 1980; Bradley, 1991; Greenwood, 1997). Further, the indirect evidence presented to support the idea of a delay in child death in areas of high transmission has been questioned (D'alessandro & Coosemans, 1997; Lengeler *et al.,* 1997; Lines, 1997; Moljneaux, 1997). Only long-term randomized controlled trials could answer this question reliably but these would be unlikely to be ethical or acceptable to the communities involved. Not many alternative designs remain. One possibility is to compare users of ITNs to non-users in the frame of a large-scale programme: combining this estimate with information from coverage surveys would allow estimation of community effectiveness (Lengeler & Snow, 1996). Although the current debate does not warrant delaying the implementation of ITNs programmes the issue needs to be addressed and monitored by more than one large-scale ITNs programme.

We present an overview of the KINET (pronounced 'key-net') project in Tanzania. The project, based at the non-governmental Ifakara Health Research and Development Centre, has developed a social marketing system for getting nets and insecticide to a scattered rural population of 350000 people. A strong evaluation component in over 50 000 people

allows monitoring of the long-term effects of ITNs on health and child survival, together with an assessment of the costs of the intervention.

Background

Study area

Kilombero and Ulanga Districts lie in Morogoro Region in south-westem Tanzania, about 320 km from Dar-es-Salaam (Fig. 1). Much of the area lies in the low- lying flood plain of the Kilombero River (average altitude 270 m), which divides the 2 districts. The Udzungwa mountains lie to the northwest and there is also an upland area around Mahenge town (over 1000 m). The area has a rainy season from November to May, although rain may fall in any month of the year. Annual rainfall range is approximately 1200-1800 mm. 'Me population is about 350 000, with an average density of about 10 people /km^2. There are 109 villages in the 2 districts, ranging in size from <1000 people to >6000. Average household size is about 5-5 people.

There is a wide mix of ethnic groups including Wandamba, Wapogoro, Wabena, Wabunga and Wahehe. Many local houses have mud walls and thatched roofs, while up to one-third have brick walls and corrugated iron roofs. Rice, maize and cassava are commonly grown for home consumption. The main agricultural exports from both districts are rice, timber and charcoal. Fishing is also common, both for local consumption and for export as smoked fish to the towns of Morogoro and Dar- es-Salaam. Many families have a second house known as *a shamba* (farm) house in low-lying farmland areas where they stay during the rice-planting and harvesting seasons.

The public health system has a network of village health workers, health posts, dispensaries, health centres and hospitals with varying quality of care. In Ifakara town, the capital of Kilombero District, the main hospital is a large well-equipped mission Designated District Hospital. The hospital in Mahenge, the Ulanga District capital, has more limited facilities. There is a further mission hospital in Malinyi, serving the south-westem part of

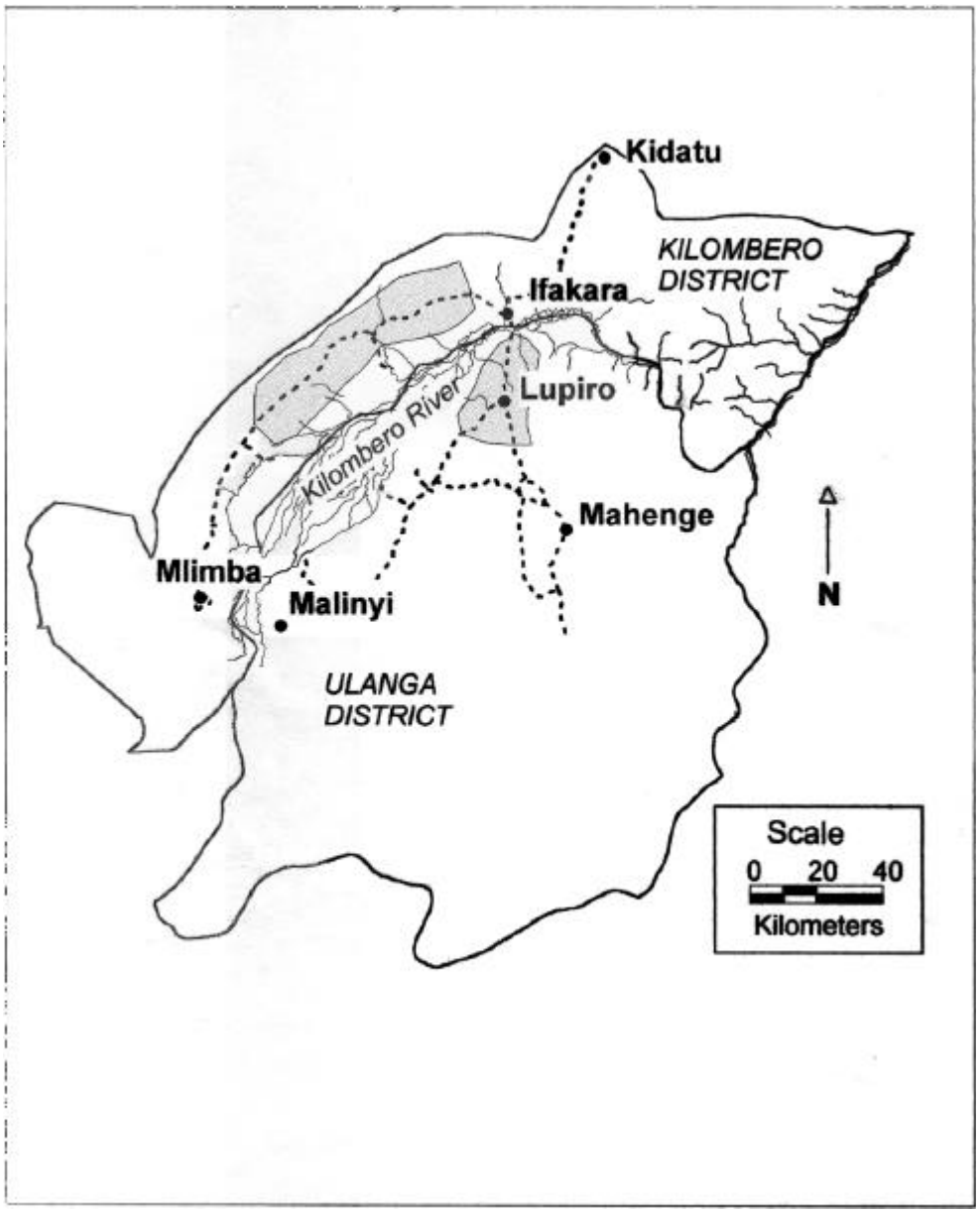

Fig. 1. The KINET programme area in Morogoro Region, south-westem Tanzania. Shading indicates Phase 1 area (under demographic surveillance). The town of Ifakara is approximately 37 ^{o}E and 8 ^{o}S.

Ulanga District. The mother-and-child health (MCH) services are well developed and vaccination coverage is high with 78% children receiving all Expanded Programme on Immunization (EPI) vaccines by age 1 year (F. Font, personal communication). There are no paved roads and some villages are cut off for parts of the year by flooding. Limited seasonal bus services run up to 3 times each day between the towns of Ifakara, Mahenge and Malinyi. The TAZARA railway links the towns of Ifakara and Mlimba.

Malaria and mosquito net use

Malaria is the foremost health problem as reported through the health services and as perceived by local people, both for adults and children (Tanner *et al.,* 1991). Malaria transmission due to *Plasmodium falciparum* is intense and perennial, despite marked seasonality in mosquito densities with a peak in the rains. *Anopheles gambiae and An. funestus* are the main vectors, with an estimated 200-300 infective bites per person per year occurring in rural areas close to Ifakara (Smith *et al.,*1993). Life-threatening malaria in most of the area occurs largely in children, and commonly presents in those aged < 1 year (Snow *et al.,* 1994).

A baseline survey conducted in 1996 found that 37% of households (3817/10 299) had at least 1 net. The main motivation for their use was mosquito nuisance rather than malaria control, with use being widely reported as seasonal. A previous study at the Ifakara Health Research and Development Centre allowed preliminary assessment of various ways to distribute nets and net treatment in the area close to Ifakara town (Fraser-Hurt & Lyimo, 1998).

The social marketing programme

We describe here the background work preparing the social marketing campaign from July 1996 to May 1997, and then cover the issues of product, price, place and promotion.

Sensitization and market research

Sensitization meetings with village leaders were held in all the 18 villages of the Phase 1 distribution area (shaded area in Fig. 1). Each half-day meeting took the form of an open discussion between project and community leaders of the health problems of the community, ways to prevent malaria including ITNs, and the issues of how to get ITNs to the community in a sustainable way. The concepts of sustainability and cost recovery led

to long discussions: most community leaders had no previous experience of projects that aimed for substantial cost recovery and found the concepts hard to understand. There was a common misconception that the Swahili term for 'project' (*mradi*) involved being given things at little or no cost to the consumer.

An initial survey confirmed that virtually all people in the area knew of mosquito nets and that round and rectangular white polyester nets manufactured in Tanzania were generally available in the towns. Qualitative studies on community preferences for different types of net suggested that rectangular, dark green, high-quality polyester nets were likely to be popular. They were needed in 2 sizes (180 X 150 X 100 cm and 180 X 150 X 130 cm) in order to accommodate local sleeping patterns. People said they would prefer coloured nets to white nets since they would not need washing as often. Many people had heard of net treatment, owing to a previous UNICEF project in the area and to the avail- ability of Rotary-funded treated nets in lfakara (Fraser- Hurt & Lyimo, 1998), but very few had tried it.

Further qualitative studies in 2 small villages found that malaria was often not perceived as a life-threatening problem, but as a fever-related illness which attacked all ages. This finding was confirmed by related work carried out at the same time in Ifakara town (Hausmann- Muela *et al.,* 1998). Severe conditions perceived as causing child deaths, such as *bandama* (enlarged spleen), *degedege* (convulsions) and *homa kali* (high fever) were not widely thought to be caused by malaria. Consequently, it was decided to highlight messages related to malaria as a cause of child deaths, including those seen as *bandama, degedege and homa kali,* in promotion campaigns. Nuisance biting by mosquitoes was consistently felt to be a major problem and this was the main reason for people using mosquito nets. Few people were aware that malaria-transmitting mosquitoes were more likely to bite late at night than in the early evening: without this knowledge it is hard for people to understand how nets might prevent malaria.

We identified *Zuia Mbu* (Kiswahili for 'prevent mosquitoes') as a suitable brand name for both treated nets and insecticide treatment. lUs brand name and a logo for *Zuia Mbu* (Fig. 2) were developed together with an advertising agency in Dar-es-Salaam and tested locally. The brand and logo are used on all products and promotional materials.

Fig. 2. The logo used for the *Zuia Mbu* brand used by the KINET programme.

Products: nets and insecticide

Dark green polyester 100-denier 156-mesh nets were obtained from Siamdutch Ltd, Thailand. Each net was pre-treated at the factory with 20 mg/m^2 deltamethrin, and wrapped in a clear plastic bag with an insert containing information about *Zuia Mbu.*

The insecticide for net treatment was 2-5% lambda-cyhalothrin CS (capsule suspension), a water-based micro-encapsulated formulation produced by Zeneca Ltd (UK). The insecticide was re-packaged by a collaborating project in Dar-es-Salaam in individual 6-mL sachets, each containing enough to treat a single net of any locally available size (Miller *et al.,* 1998).

Price

Village sensitization meetings and experience from a previous project (Fraser-Hurt & Lyimo, 1998) suggested that local people would be willing to pay near cost-recovery price for the nets, but rather less than cost- recovery price for the insecticide. Retail prices were set at TSh 3000 (~US$5-0) for either size of net and TSh 250 (~US$O.42) for the insecticide treatment service. For nets, a commission of TSh 500 per net is paid to each retailer and a further commission of TSh 250 is paid to wholesalers. Thus the project recovers TSh 2250 (~US$3.75) for each net sold, or about 66% of the replacement cost including transport to lfakara and packaging. For insecticide, a commission of TSh 125 per sachet is paid to the retailers and a fürther TSh 25 to wholesalers. The project therefore recovers TSh 100 (~US$O.17) for each sachet sold, about 17% of the replacement cost. Price control for nets, initially a particular worry of the community, is achieved by making the selling price clearly visible on the net packaging and by advertising the price widely.

Place: the distribution system

The social marketing of nets and insecticide was phased-in step-wise in 3 increasingly large areas. A flexible distribution system was chosen in conjunction with community leaders and community members in a series of open meetings. In the first phase, in each village 2 sales agents for nets and a further 2 mobile sales agents for insecticide were chosen regardless of the size of the village. The agents were nominated by the villagers themselves, and included health workers, parish priests, community leaders and shopkeepers. Net sales agents and net treatment agents were both given a 1 -day training seminar, where they learnt how to treat nets and how to keep sales records. These records show the purchaser's name, *balozi* (local political leader), sub-village and village, and permit checks that the products have been sold within the study area. Twice-yearly re-

training and review sessions are also held. The net treatment agents were given a distinctly painted *Zuia Mbu* bicycle to assist with door-to-door sales, plastic basins, gloves, and plastic boxes for storage of sachets of insecticide. Nets and insecticide were initially supplied directly by project staff at weekly intervals, but as the project area enlarged a network of wholesalers was developed to keep agents supplied on a regular basis. Each agent has a contract with the lfakara Health Research and Development Centre, and is paid on a commission basis (see 'Price' above). A reward system for reaching certain sales targets is also used. Agents who do not keep the terms of the contract are replaced.

Promotion and the voucher system for pregnant women and infants

A range of materials to support an information, education and communication (IEC) campaign was developed, including 3 posters (Fig. 3) and a leaflet. These materials, each incorporating ideas from the qualitative studies, were drawn by a local artist and pilot-tested extensively before printing and distribution to health clinics, sales outlets, etc. Billboards were posted along the main roads and one local bus had the *Zuia Mbu* logo painted prominently on its side. The project worked together with the District Health Management Teams in both districts in preparing the campaign.

A discount system to reduce further the cost of a net for mothers of young children and pregnant women was developed for use through health clinics. This system is intended to increase use of treated nets in those most at risk of severe effects of malaria. All women attending antenatal clinics and those attending for routine immunizations are entitled to a discount voucher which gives them a TSh 500 (US$ O.84 or 17% retail value) price reduction for a treated mosquito net. Their clinic attendance card is marked to show that they have received the voucher. The voucher is then presented by the women to the net sales agent in their village. The sales agent then receives a credit from the project to the value of TSh 500 plus a TSh 50 handling charge.

Public-Private mix

KINET uses a pragmatic mix of activities involving the public and private sectors. Such mixes have recently been advocated as an effective strategic approach for large- scale ITNs projects (USAID, 1998). KINET social marketing involves a collaboration between public entities such as the District Health Management Teams and the Ministry of Health, the private sector such as international suppliers and local business people, and the project social-marketing team.

Launching and expansion

The treated nets and insecticide treatment service were launched in 2 large villages on 24 and 25 May 1997 with celebrations including community theatre, songs, a raffle and speeches from community leaders. During the following week sales of nets and insecticide started in all the 18 Phase 1 villages. The project expanded to cover a further 8 villages in December 1997, 35 in June 1998, 18 in December 1998 and will cover the remaining 30 villages early in 1999.

In order to facilitate this expansion in an efficient way, KINET is working to maximize inputs from local project partners such as local employers and mission hospitals. Project partners act as local distributors of *Zuia Mbu* nets and insecticide, using the same promotional materials and price structure, and as key players in the IEC campaign.

Project evaluation: the effect of ITNs on child health and survival

Socio-cultural aspects

Quantitative and qualitative work is being done, including periodic knowledge, attitude, beliefs and practices (KABP) studies, detailed community-based anthropological studies, and semi-structured interviews with sales agents and customers. This work allows a review of how IEC messages are received in the community and the chance to see which new messages might be useful. In addition, it allows evaluation of the discount system and the sales agents themselves, with a view to making improvements so that customers are served better by the project.

Fig. 3. One of the 3 posters developed for the treated net promotion campaign. This poster emphasizes the undisturbed sleep with the use of a *Zuia Mbu* net. Translation: (1) Malaria-carrying mosquitoes bite in the middle of the night, (2) *Zuia* Mbu treated nets repel and kill mosquitoes

Demographic surveillance system (DSS)

This system was started in September 1996 and operates in the 18 Phase 1 villages covered by the study (shaded area in Fig. 1). This area has a population of some 55000 people living in 11000 households. A baseline census was carried out from September to December 1996. Name, sex, date of birth, and relationships within the household were recorded. Household locations were noted on sketch-maps. Rough locations of any *shamba* houses were also recorded. Since January 1997 every household has been visited every 4 months by an interviewer who updates the census record by asking about in- and out-migrations, pregnancies, births and deaths. The system developed originally in Navrongo (Ghana) by BINKA *et al.* (1998) was used with few modifications. Special surveys are added from time to time: for example, the first census round in 1997 was used to record socio-economic status in the household, and educational level for each household member. The DSS gives a full sampling frame for the Phase 1 area, within which vital events are monitored and random samples of households or individuals may be chosen for various in-depth studies.

Effect of treated nets on child survival

Two studies are under way within the DSS. First, a case-control study will assess risk factors for child mortality in the area, with a particular focus on use of nets, treated or untreated. Cases are children resident in the study area who died of any cause aged between 1 month and 5 years. Four controls are chosen for each case from the same area of residence and of approximately the same age. The case-control study will give an estimate of efficacy of the treated nets among children who use them. This can be combined with the coverage estimates from periodic surveys to estimate effectiveness in this target group.

The second study to assess the effect of treated nets on child survival is a birth cohort: all children born in 1998 and 1999 will be enrolled. At enrolment a questionnaire is used to elicit information on birth-weight, mother's age and educational level, twinning, family size, birth order and birth interval. At subsequent routine DSS visits, a further brief questionnaire will be used to gather additional information. It is planned to follow these children until their 5th birthdays. Analysis will compare mortality rates in those using treated nets with those using un- treated nets and those using no nets, allowing for any measured potential confounders.

Effect of treated nets on anaemia and malaria in young children

Three annual cross-sectional surveys to assess the effect of social marketing of treated nets on anaemia will be carried out on a random sample of children aged <2 years from the DSS area, one at baseline before the sale of the nets and then after the first and second year of implementation. A questionnaire is applied, a physical examination done and a blood sample obtained. The prevalence of anaemia will be compared between users and non-users of treated nets using logistic regression analysis to control for confounding.

To assess the effect of the interventions on malaria and anaemia episodes, a cohort of children aged <5 years residing in the village of Idete is being followed-up and their disease episodes documented, using a passive case- detection system at the village dispensary. Risk factors including treatment-seeking behaviour, household socio-economic status, use of treated nets and mother's education are being assessed by short questionnaires applied through routine DSS visits. Rate ratios of disease episodes (first/only episode) between those using treated nets and those not using them will be compared using Poisson regression to control for confounding. More detailed assessment of the impact of the interventions on malaria episodes is being done within this cohort using a nested case-control study.

Effect of treated nets on anaemia in pregnancy

A cross-sectional survey of pregnant women with rolling recruitment over a period of 12 months is also being carried out using the DSS. The study is designed to determine the prevalence of severe anaemia (Hb <8 g/dl) and to identify major risk factors for this anaemia, including use of treated nets.

Costing of implementation and willingness and ability to pay.

Cost of the implementation to the provider is being assessed. Measures of effectiveness and costs will be combined in a cost-effectiveness analysis (CEA). The costs involved include the initial investment, recurrent costs, capital costs and opportunity costs. Each type of cost is identified by associated activities such as brand creation, promotion, training, distribution, etc. Willingness and ability to pay were elicited from a sample of respondents within and outside the Phase 1 area, who were asked about household expenditure patterns.

Insecticide resistance: entomological indicators

With increasing use of ITNs at community level, it is possible that the usual night-biting behaviour of the main vector of malaria in the area might change to peak in the early evening and early morning, when few people are in bed. Studies to assess changes in mosquito biting behaviour are therefore carried out every year together with bio-assays to monitor any trend in resistance of wild-caught *An. gambiae* to lambdacyhalothrin or deltamethrin.

First results

Demography

The estimated mid-year (1997) population of the Phase 1 area was 54 061 people living in 10 966 house- holds. Average household size is 4-9 people. Almost half (44%) of the population is aged < 15 years, 16% aged <5 years, and the sex ratio (M:F) is 1:1.02. During 1997 the infant mortality rate was 95/1000 live births (181/1902), and annual mortality in children aged 1-4 years was 14.3/1000 (98/6859 child-years). In children aged 5-9 years the annual mortality rate was 3.5/1000 (28/7944 child-years). Total fertility was estimated at 4.7 births/woman.

Willingness and ability to pay

Of those interviewed, 69% (128/185) claimed to be willing to pay the price of US$5 per net and 88% (163/185) were willing to pay US$O.4 per net for a net treatment service. Ability to pay assessed by median overall household expenditure in the month prior to the first survey was US$74. Excluding expenditure on food, a median of US$7 was spent on capital items and US$ 11 was spent on other small items in the previous month. Many households have a bicycle (34%) or radio (11 %). It should be noted that this survey was carried out in the harvest season, when expenditures are at their annual maximum. Further surveys are ongoing.

Sales

Thirty-one net sales agents and 37 mobile net treatment agents were appointed in May 1997 in the 18 villages of the first phase. Among the net agents there were 15 shop owners, 14 village leaders, 1 health worker, and 1 village priest. After 10 months, the priest and 3 village leaders were replaced: they were inactive, mainly owing to their other

commitments. During the same period 10 (27%) net treatment agents were no longer active and have been replaced.

The percentage of households with at least 1 net rose from 37% at the end of 1996 to 52% (5913/11480) in mid-1 998, by which time 24% (2730/11480) of house- holds had at least 1 treated net and 48% (4323/9040) nets were treated. Of a random sample of families with children aged < 5 years, 46 % reported that their children were sleeping under treated nets by April 1998. A total of 22 410 nets and 8072 treatments were sold by the project during the first year. Sales records in the Phase 1 area suggest over 80% nets were sold to residents. As expected, demand peaked after the rains started, when mosquito populations rose dramatically: almost half of the total annual sales were during the months of December and January. Most net treatments were sold to owners of ordinary untreated nets: 31% of those who owned ordinary nets had treated these by December 1997, whereas only 13% of *Zuia Mbu* net owners who had bought their nets at least 3 months previously had re- treated their nets by December 1997.

There was a good response to the discount vouchers, with 26% (1687/6489) of net sales to Phase 1 area residents making use of the vouchers. Ongoing surveys will reveal whether the target group, i.e., pregnant women and those with young children, are the principal users of the discounted nets.

Discussion

Social marketing is a novel and promising approach to promote and supply effective malaria control tools. Its excellent track record for interventions as diverse as ORS, condoms and oral contraceptives suggests that it could perform well for the large-scale deployment of ITNs (USAID, 1998). So far the KINET project has achieved good coverage in a large highly endemic rural area, reinforcing positive experiences with social marketing of ITNs in the Central African Republic, Zimbabwe and Rwanda (A. Boner and L. Jamu, personal communication).

Large-scale ITNs programmes will always be confronted with the problem of finding agents that are both trusted by the community and effective in selling ITNs. The initial choice of net and treatment agents rested largely with village leaders and this resulted in a great diversity of agents selling KINET products. Our early results suggest that commercial

retailers often provide a better service to their communities than village leaders. Retailers are used to selling goods and usually have a larger working capital to invest in net and insecticide consignments. Further, they are available at most times of day and easy for potential customers to find. Future expansion is likely to increase the involvement of the private sector.

The issue of whether health facilities should also sell ITNs and treatments remains open, and there are no current Ministry of Health guidelines on this matter. With the gradual introduction of cost-sharing in Tanzania the selling of ITNs could find a natural place in the system but the issue of who should keep commission from the sales deserves careful consideration. An interesting contrast is seen in how sales commission is shared between 2 MCH clinics selling ITNs in the KINET area (see also Fraser-Hurt & Lyimo, 1998). In one clinic all the staff participate in the sales and the TSh 500 commission on each sale is shared. In contrast, in the second clinic the rural medical aide in charge alone sells nets and keeps the commission; this has led to resentment among other staff and to less active promotion on their part.

In the interests of sustainability it is important to develop a system of wholesalers that follows the existing commercial system. This allows reduction of the intensive investment needed when all agents are supplied weekly by the project. The apparently lower cost-recovery to the project with wholesalers is more than offset by the lower distribution cost. Once an efficient wholesale network is established monthly supplies to wholesalers should be sufficient and the project can then easily expand to a wider area.

Nets were relatively common in our area before KINET sales started. We therefore started to promote and sell insecticide for net treatment as soon as possible so that existing nets might be treated. Informal feedback from the community suggests that people are often uneasy about bringing their nets out in public, and that they would prefer to treat their nets themselves. We have therefore introduced a home-treatment kit developed in Tanzania (Miller *et al.* 1998), consisting of a single- dose sachet of insecticide packaged with disposable gloves and locally developed instructions. The relatively high cost of this packaging is offset against the problems of deliberate or accidental misuse of larger quantities of insecticide, and the advantage that our target group prefer the freedom and privacy of treating their nets at home.

We chose to sell pre-treated nets rather than untreated nets despite the argument that this denies the opportunity of educating people at the time of purchase about the difference between a treated and an untreated net and how to treat a net. Pilot studies with the home-treatment kit suggest that people do not need special training to treat their nets. Selling pre-treated nets may mean that some people will not realize that they have bought a treated net, but we feel their lack of knowledge is an issue best tackled through ongoing targeted IEC concerning net treatment. For example, our treatment agents can make use of net sales records in order to make follow-up visits to those who have bought a net 3 months previously. They can then offer advice on malaria prevention and a net treatment service.

Two key issues remain on the promotion agenda. First, the sales are very seasonal, clearly peaking during the time of maximum mosquito densities. No detailed compliance measures are yet available but it is very likely that the net usage follows the same seasonal pattern. Since malaria transmission is perennial in the Kilombero Valley the all-year use of ITNs needs to be promoted actively. Secondly, KINET is aiming to reach a large and very dispersed rural population with 2 products: nets, for which existing demand is high, and insecticide, for which existing demand is much lower. Promotion will therefore focus increasingly on re-treatment of existing nets and new distribution channels may have to be developed to facilitate this.

An optimal balance between affordability, equity and full cost-recovery is difficult to achieve. KINET has a current low level of subsidy on the treated nets (66% cost recovered) and a high level of subsidy on the insecticide (17 % cost recovered). These costs do not cover a mini- mum programme infrastructure nor the cost of promotion: the project loses a substantial amount of money on every sale. As inter national demand for insecticide for net treatment increases it seems likely that cheaper formulations will become available and the cost of insecticide will decrease. Once a stable demand for nets and net treatment exists, retail prices may be increased towards full cost-recovery levels, with subsidies targeted exclusively through the public health sector using vouchers or in other ways.

Although full cost-recovery is an important consideration, there is more to sustainability than full cost- recovery alone. Many ITNs projects conducted in the past have not survived the end of their project status (e.g., Hill, 1991; Premji *et al.,* 1995) despite a certain level of

infrastructure and a banked revolving fund. Often procurement and ongoing distribution have been beyond the capacity of the local groups. One of the strengths of a public-private mix such as that used by KINET is the inherent sustainability of the private sector distribution system. The remaining issues of procurement and promotion are likely to need special attention at the end of the 'project status' phase. A low-cost social-marketing support service at district, regional or even national level could provide such inputs. Virtually no other intervention in preventive health is entirely self-supporting: if ITNs programmes are (1) feasible on a large scale and (2) efficient through low delivery cost per net or per treatment, they should be able to attract sufficient donor support in the context of the Roll Back Malaria initiative.

The question of long-term effect of ITNs on survival in highly endemic areas is important. Since randomized controlled trials are neither feasible nor ethically acceptable, we have chosen observational studies to compare users of ITNs with non-users, both through a case- control study and the long-term follow-up of a birth cohort. Problems remaining include the difficulty of determining use of treated nets and the influence of potential confounders, many of which are difficult to measure. Experience from other areas of health, for example the health impact of smoking or the impact of ORS, suggests that observational studies can make a useful contribution. However, our results will need careful interpretation. Ideally, such long-term follow- up should be carried out in a number of sites. Other African projects are attempting to do this in Ghana and in Burkina Faso where the population formerly involved in the scientific trials (Binka *et al.,* 1996; Habluetzel *et al.*, 1997) is being followed-up for a further 3 years in order to detect a possible delayed increase in mortality in the former intervention group compared to the former control group (F. Binka, personal communication; E. Sanogo, personal communication). A similar study is planned in Western Kenya (P. Phillips-Howard, perso- nal communication).

The KINET project represents an attempt to see to what extent social marketing is a useful tool in the fight against malaria in a rural African setting. Data are being collected on the key issues of cost and effectiveness of ITNs on child survival, but the results are some time away. In the mean time, the information available to date suggests that social marketing is a useful approach for ITNs, being innovative, popular and sufficiently adaptable to address the varied challenges of a malaria control programme in a rural African setting.

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CHAPTER 5

Impact of an insecticide treated net programme on malaria morbidity in children under two years of age in Tanzania: community cross-sectional study

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Abstract:

Objective:

To assess the impact of social marketing (an approach using marketing techniques to promote and distribute socially beneficial interventions) of insecticide treated nets on malaria parasitaemia and anaemia in children under two years of age in an area of high malaria transmission.

Design:

Annual cross-sectional data were collected at the beginning of the social marketing campaign and subsequent two years. Net ownership and other risk and confounding factors were assessed using a questionnaire. Blood samples were taken from the children to assess prevalence of parasitaemia and haemoglobin levels.

Study participants:

A sample of children under two years of age living in 18 villages in the Kilombero river plain, Southwestern Tanzania.

Main outcome measures:

The presence of any parasitaemia in the peripheral blood sample, and anaemia classified as haemoglobin of less than 8 g/dl.

Results:

There was a rapid increase in net ownership (from 58 to 83%) and treated net ownership (from 10 to 61%). There was an overall increase in the mean haemoglobin (from 8.0 to 8.9 g/dl) of the study children in the successive surveys. Overall, the prevalence of anaemia in the study population decreased from 49% to 26% in two years of implementation. Treated nets had a protective efficacy of 63% (95% CI: 38, 77) on the prevalence of parasitaemia, and 63% (95% CI: 27, 82) on anaemia.

Conclusions

These results demonstrate that insecticide treated nets have a substantial impact on morbidity parameters when distributed in a public health setting.

Introduction

Several studies have shown a positive correlation between malaria parasitaemia and anaemia, and that parasitaemia is the primary cause of anaemia in very young children in Africa (Kitua *et al.* 1997). As a result, anaemia is very frequent in young children in high transmission areas since malarial infections are the norm. Assessment of the impact of chemoprophylaxis in Tanzanian infants indicated that over 60% of the anaemia could be due to malaria in this age group (Menendez *et al.* 1997). The emergence and spread of parasite resistance to commonly used antimalarials has exacerbated the problem of anaemia in Sub-Saharan Africa (Bloland *et al.* 1993).

Hopes for malaria and malarial anaemia control have recently been revitalised by the demonstration that insecticide treated nets can reduce morbidity and mortality. A summary of randomised controlled trials showed an average protective effect of about 50% on mild malaria episodes in stable malaria areas. Moreover, protective effects were shown on the prevalence of high parasitaemia (31%) and overall mortality (19%). A modest improvement in packed cell volume (2%) and weight gain was also observed in children sleeping under treated nets (Lengeler, 1998). Large scale implementation of ITNs is underway in a number of African countries (Anonymous, 1999).

It is not known whether the impressive impact of treated nets in the frame of well controlled randomised controlled trials can be replicated under programme conditions (Lengeler & Snow, 1996). We report the first impact assessment of a large scale treated net social marketing (an approach using marketing techniques to promote and distribute socially beneficial interventions rather than a commercial product) programme on morbidity indicators in children under two years of age in a highly endemic area of Tanzania.

Methods

Study area and population

Social marketing of treated nets started in the frame of Kilombero Net Project (KINET) (Schellenberg *et al.* 1999a) in 1997, covering the Kilombero and Ulanga Districts (population 350,000) in Southwestern Tanzania. Nets and insecticide (branded "Zuia Mbu") are now being promoted, distributed and sold using public and private outlets, and a system of community door-to-door distributors. The retail price of the treated nets was 5.0 US Dollars. While this amount was a non-negligible part of the average annual income in this community, experience shows that a majority of the residents were both willing and able to pay this amount (Schellenberg *et al.* 1999a). The impact of the programme on morbidity and mortality indicators is being monitored in 18 villages under demographic surveillance (DSS). Population characteristics of this area of very high perennial malaria transmission have been described elsewhere (Tanner *et al.* 1991). Moderate anaemia (PCV< 25%) and severe anaemia occur in 61% and 14% of children under five years admitted at the local St Francis District Hospital (Schellenberg *et al.* 1999b). Chloroquine resistance is common: 65% of malaria infections do not clear within one week of chloroquine treatment (Hatz *et al.* 1998).

Design

Three annual cross-sectional surveys where conducted in a sample of children under two years of age living in the DSS area (Schellenberg *et al.* 1999a). The first survey was done at the time of launching the social marketing campaign in June 1997, and two other surveys were carried out at the same period (June to August) in the subsequent two years. A simple random sample was selected from the DSS database for the first survey, and a two-stage random sampling (sampling 6 villages then sampling children from these) was done for the subsequent surveys. A different sample was selected for each survey.

Procedures

The selected children were visited at home and a verbal consent obtained from the parent or guardian. A questionnaire was applied to assess treated net use and other potential risk factors. A physical examination was performed, and temperature, weight and height measurements were also taken. A finger prick blood sample for haemoglobin estimation and parasitological assessment was then taken. Haemoglobin was measured using the portable HemoCue® (HemoCue AB, Ängelholm, Sweden) kit. Slides were stained in Giemsa and

reading was done (without the microscopists knowing the net status) using standard procedures as described elsewhere (Schellenberg *et al.* 1999b). An inspection of the children's sleeping places to assess net use was only done in 1999 because this was strongly perceived as an intrusion in their privacy.

Anaemia was classified as haemoglobin level below 8.0 g/dl since this is the level that has been associated with increased mortality (Stoltzfus, 1997) and is consistent with earlier studies in the area (Menendez *et al.* 1997). Parasitaemia and splenomegaly were classified as either present or absent. Use of treated nets was categorised based on the respondent's answers on ownership and if they were "ever treated" or "not treated". There are currently no simple ways to assess insecticide content on the nets in the field.

Data analysis

Analysis was done for all the three cross-sectional surveys combined. The impact of the nets on haemoglobin level, anaemia, parasitaemia and splenomegaly was estimated using multiple linear and logistic regression models taking into account the village cluster sampling for year 2 and 3, using robust regression approaches in STATA® (STATA Corp.). The effect of different time points of observation (surveys) was included as one of the explanatory variables.

Other factors considered in the multivariate models included use of the net, condition of the net, age, sex, ethnicity, religion, nutritional status, access to the dispensary, shops and covered wells. Treatment history and attitudes toward health seeking were also included, as were factors related to the family size and income.

Results

We identified 985 eligible children. 16 mothers refused consent and 142 could not be traced at their homes. Therefore, mothers and guardians of 827 children were interviewed during the three cross-sectional surveys. 68 children were over twenty four months old at the time of sampling, and the net status was not known for 11 children, and therefore only 748 (91%) children were included in the analysis. Children analysed and those not analysed had similar proportions of anaemia and reported ownership of nets (data not shown).

We observed an increase in the mean haemoglobin level from 8.0 to 8.9 g/dl and a decline in the proportion of children with anaemia (49% to 26%), any parasitaemia (63% to 38%) and splenomegaly (86% to 49%), during the successive surveys (Table 1). The proportion of children having any net increased from 58% to 83% and those having treated nets increased dramatically during the 3 years (from 10% to 61%) indicating a rapid uptake of the socially marketed treated nets, especially in the first year of the implementation (Table1).

Table 1: Characteristics of children surveyed in the 3 cross-sectional surveys (1997 -1999)

Year	1997	1998	1999	Overall
Selected	325	330	330	985
Interviewed*	269 (82.8)	291 (88.1)	267 (80.9)	827 (84.0)
Analysed*	240 (73.9)	269 (81.5)	239 (72.4)	748 (75.9)
Mean age in months‡	14.2 (3.3 to 26.4)	13.5(3.0 to 24.7)	15.4 (2.4 to 25.5)	14.4 (2.4 to 26.4)
Males	122 (50.8)	137 (50.9)	113 (47.3)	372 (49.7)
Mean haemoglobin§	8.0 (0.12)	8.9 (0.10)	8.9 (0.10)	8.6 (0.07)
Anaemia (< 8 g/dl)¶	118 (49.2)	83 (31.0)	62 (26.1)	263 (35.3)
Parasitaemia**	151(62.9)	126(46.8)	90 (37.8)	367(49.1)
Splenomegaly**	207(86.3)	144 (53.5)	117 (49.0)	468 (62.6)
No net	100 (41.8)	49 (18.2)	40 (16.7)	189 (25.3)
Untreated net	116 (48.3)	64 (23.8)	53 (22.2)	233 (31.1)
Treated net	24 (10.0)	156 (58.0)	146 (61.1)	326 (43.6)

Percentages in brackets except where indicated
* Percentage of the total selected
‡ Range in brackets
§ Standard errors in brackets
¶ Classified as Hb ≤ 8 g/dl
** Classified as present or absent

Table 2: Predictors of bed nets ownership (Logistic regression analysis: The final model also included ethnic origin of the child)

Variable	numbers with nets (%)	Adjusted odd ratio (95% CI)	LRT-χ^{2} [a] (ρ-value)
Income categories (quantiles of total family income)			
1st quantile of income	125 (66.8)	1*	
2nd quantile of income	130 (70.7)	1.25 (0.59 to 2.66)	
3rd quantile of income	143 (73.3)	1.13 (0.74 to 1.72)	
4th quantile of income	164 (89.1)	2.74 (1.58 to 4.75)	8.89 (0.031)
No access to covered wells ‡	191 (78.0)	0.61 (0.41 to 0.90)	3.90 (0.048)
Advice care at health facility§	387 (83.4)	2.27 (1.38 to 3.72)	3.90 (0.048)
Advice care at traditional healer§	1 (33.3)	0.12 (0.01 to 1.07)	2.97 (0.085)
Immunised	376 (84.1)	1.92 (0.86 to 4.29)	3.38 (0.066)
Mother educated	395 (79.0)	1.59 (0.85 to 3.00)	3.15 (0.076)

a Likelihood ratio test χ^{2}

* Comparison group

‡ piped clean water classified under covered wells

§ place where guardian of study child advises neighbour to sent child sick with fever

Net ownership and use

Predictors of net ownership (Table 2) included family income, those with high income (fourth quartile) being about 3 times more likely to have a bed net than those with low income (first quartile). This was expected as the treated nets were being sold. By the end of the 2nd year of implementation only 16% of the children were without a net. Children with no access to piped or covered wells i.e. not at the centre of the villages, were less likely to have nets (Table 2). Mothers that mentioned that they would advise their neighbours to send their sick children to a formal health facility were more likely to have nets for their own children (OR=2.3 Likelihood Ratio Test-χ^2, p value=0.048). This might reflect an association between health seeking patterns or perceptions about the value of the formal health system and the decision to have a net or not.

Observation of sleeping places for 171 children in 1999 revealed that, among those who claimed to be using nets, 92.9% (117/126) had a net hanging at the sleeping place. For all 9 children who had a missing net at the sleeping place, we were shown a net claimed to be used. Among those that claimed not to be using nets, 17% (8/45) had a net hanging at the sleeping place. These observations indicated that reported ownership and use provided a reasonable basis for defining bed net status.

Health impact of treated nets

We observed a protective efficacy (defined as 1-odds ratio × 100) on the prevalence of parasitaemia of 63% (95% CI:38 to 77%) and 51% (95% CI: 0 to 76) for treated and untreated nets respectively, when compared with children without nets (Table 3). Parasite prevalence was also related to ethnic group, religious affiliation, use of the net in the previous month and age of the child, with the prevalence in those more than 1 year of age being four times higher than those below 7 months. This is consistent with earlier studies in the same area, which demonstrated that prevalence of parasitaemia increased with age (Kitua *et al.* 1996; Smith *et al.* 1999).

Table 3: Impact of nets on prevalence of any parasitaemia (Logistic regression analysis: The final model also included stunting, no access to covered wells and sex).

Variable	Numbers with parasitaemia (%)	Geometric mean parasite density	Adjusted odd ratio (95% CI)	LRT-$\chi^{2\,a}$ (ρ-value)
No net	132 (69.8)	4404	1*	
Untreated nets	115 (49.6)	2890	0.49 (0.24 to 1.00)	
Treated nets	120 (36.9)	2745	0.38 (0.23 to 0.62)	8.75 (0.013)
Use of net in the last month	107 (34.0)	3291	0.53 (0.35 to 0.79)	6.69 (0.010)
Ethnic group				
Ndamba	49 (36.0)	3901	1*	
Pogoro	76 (66.7)	3423	3.78 (1.62 to 8.87)	
Hehe	42 (43.3)	4315	1.53 (0.74 to 3.16)	
Others	209 (51.1)	3070	2.48 (1.27 to 4.84)	14.63 (0.002)
Age category				
0 – 6 months	17 (28.3)	2040	1*	
7 – 12 months	106 (43.3)	2710	3.00 (0.95 to 9.44)	
13 – 18 months	114 (55.9)	4111	3.64 (1.31 to 10.14)	
> 18 months	140 (56.5)	3622	4.85 (1.57 to 14.96)	13.4 (0.004)
Religion				
Other religion	52 (40.9)	4434	1*	
Muslim	157 (58.8)	2967	2.40 (1.32 to 4.35)	
Catholic	159 (45.3)	3404	1.54 (1.00 to 2.37)	8.85 (0.012)

a Likelihood ratio test χ^2

* Comparison group

Table 4: Impact of treated bed nets on prevalence of anaemia (Hb ≤ 8 g/dl) (Logistic regression analysis:

The final model also included distance to a shop, use of the net in previous month, immunisation status, age and sex of the child)

Variable	Numbers with anaemia (%)	Adjusted odd ratio (95% CI)	LRT $\chi^{2\,a}$ (ρ-value)
No net	103 (54.5)	1*	
Untreated nets	90 (38.8)	0.63 (0.27 to 1.46)	
Treated nets	70 (21.5)	0.37 (0.19 to 0.73)	9.58 (0.008)
Stunted(Z-score≤ -3)	109 (51.2)	2.53 (1.66 to 3.84)	12.95 (< 0.001)
No access to covered wells ‡	87 (35.5)	1.95 (1.24 to 3.07)	7.64 (0.006)
Religion			
Other religion	40 (31.5)	1*	
Muslim	112 (42.0)	1.80 (0.97 to 3.36)	
Catholic	113 (32.2)	0.96 (0.58 to 1.58)	7.31 (0.026)
Advice care at health facility§	125 (26.9)	0.45 (0.19 to 1.11)	4.12 (0.042)
Mother educated	179 (35.7)	1.53 (0.87 to 2.68)	2.93 (0.087)

a Likelihood ratio test χ^2

* Comparison group

‡ piped clean water classified under covered wells

§ advice neighbour to sent child sick with fever to a formal health facility

The mean haemoglobin level was 7.7 g/dl (95% CI:7.4 to 7.9) for those without nets, 8.6 g/dl (95% CI:8.3 to 8.8) for untreated nets and 9.2 g/dl (95% CI: 9.0 to 9.3) for treated nets. Multiple regression analysis showed that there was an increase of haemoglobin of 1.3 g/dl (95% CI: 0.8 to 1.7) for those with treated nets and 1.1 g/dl (95% CI: 0.5 to 1.7) for those with untreated nets compared to those with no nets. Considering the classification of anaemia, a protective efficacy of 37% (95% CI:-46 to 73%) for untreated nets and 63% (95% CI:27 to 82%) for treated nets was observed. Those classified as stunted or as having no access to covered wells were more likely to be anaemic (Table 4). If the cut-off level for anaemia was set at 11g/dl, untreated nets had a protective efficacy of 78% (95% CI:29 to 93%) and treated nets of 82% (95% CI:42 to 94%). Parasitaemia was associated with anaemia: children with high parasitaemia had lower mean haemoglobin compared to those who had no or few parasites (χ^2-trend, $p<0.001$). Lastly, nets had also a high impact on prevalence of splenomegaly with a protective efficacy of 71% (95% CI:39 to 87%) for untreated nets and 76% (95% CI:52 to 88%) for treated nets.

For children without nets, their prevalence of anaemia remained relatively stable over the study period (between 49% and 58%) and this was also the case for the prevalence of parasitaemia (between 68% and 71%). This suggests that there were no major changes in the malaria situation during the period under evaluation.

Discussion

These results have demonstrated that the social marketing approach of distributing insecticide treated nets was very successful and resulted quickly in more than 80% of children under two years of age having access to a net. Our results suggest an overall impact of social marketing of treated nets on health outcomes in the community, with an improvement of mean haemoglobin levels (from 8.0 to 8.9 g/dl) and a decline in the total proportion of children with anaemia (from 49% to 26%), parasitaemia or splenomegaly. The treated nets had an apparent individual protective efficacy of over 60% on the prevalence of anaemia, parasitaemia and splenomegaly. In this study untreated nets were also found to be protective. Overall, most of the changes occurred in the first year of implementation.

These efficacy estimates are higher than those from most controlled trials (Table 5). It is therefore pertinent to question whether this finding may be the result of residual confounding despite the effort made to control for it. This is especially so because our comparison group

was made up of children who did not own nets (non-adopters) in the same community. The tools used to measure confounding factors like social-economic status and health seeking may not be sensitive enough to allow for proper control of confounding. However, factors related to the dynamics of the malaria infection and the associated disease presentation may also explain this finding. For example, it has been observed that variations in transmission strongly affect the estimates of morbidity and mortality in very young children (Marsh & Snow, 1999). Therefore at a given transmission intensity the age of the study participants may be crucial in determining the level of protection. Our finding of high impact in children under two years is in line with other studies that included very young children (Table 5).

Lower impact estimates than ours were observed in a randomised study near Ifakara in a similar age group (Fraser-Hurt *et al.* 1999). This may be due to fact that our study covered a larger geographical area and included study children with a lower average haemoglobin (average haemoglobin of those without nets 7.7 g/dl vs. 8.7 g/dl , t-test =3.9: p=0.0001). It is probable that more anaemic children are more likely to benefit from the intervention.

We conclude that treated nets distributed through a social marketing programme setting were effective and produced a rapid and high impact on parasitaemia and anaemia prevalence in children under two years of age. This strategy has high potential in the control of malaria in Sub-Saharan Africa.

Table 5: Impact of treated net materials on anaemia in controlled trials in Sub-Saharan Africa

Country : Year of Publication	Entomological inoculation rate[a]	Age (months)	Impact on anaemia	
			Mean difference [b]	Protective efficacy
Control: with untreated nets				
Gambia: (D'Alessandro *et al.* 1995)	1 to 10	12 to 48	0.1	
Gambia: (Snow *et al.* 1988)	1 to 10	12 to 108	0.9	
Gambia: (Snow *et al.* 1987)	1 to 10	12 to 108	0.2	
Gambia: (Alonso *et al.* 1991) *	10	6 to 72	0.5	
Control : Without nets				
Sierra Leone: (Marbiah *et al.* 1998)	35	3 to 72	1.8	
Ghana: (Binka *et al.* 1996)	100 to 1000	6 to 59	0.4	
Kenya: (Sexton *et al.* 1990)	300			
Burkina Faso:(Habluetzel *et al.* 1997)	300 to 500	6 to 59	0.5	
Tanzania: (Premji *et al.* 1995)*(<33 pcv)	300 to 700	6 to 40	0.7	49.1
Tanzania: (Njunwa *et al.* 1996)*‡(<32 pcv)	>300	0 to 108		69.7
Tanzania: (Fraser-Hurt *et al.* 1999)	>300	5 to 24	0.4	
Tanzania : This study (<24 pcv)	300[§]	2 to 26	1.5	73.2

a Estimate applicable to the period before insecticide treated nets were introduced or the control group in the trial
b Mean haemoglobin difference in g/dl
* Non-randomized controlled trials
‡ Impact estimate of the peak transmission season
§ Description of malaria situation provided in reference 7

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CHAPTER 6

Usefulness of a dispensary based case-control study for assessing morbidity impact of a treated bed net programme

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Abstract:

Background:

Case-control studies have been proposed as an appropriate tool for health impact evaluation of insecticide treated nets (ITNs) programmes.

Methods:

A dispensary based case-control study was carried out in one village in Tanzania. Each case of fever and parasitaemia in a child under five years was paired with one community and one dispensary control without fever and parasitaemia. Cases and controls were compared with regard to ITNs ownership and other factors assessed by a questionnaire. A cross-sectional survey of factors associated with parasitaemia, including ITN use, was carried out during the study. Dispensary attendance rates of the study children were calculated using the passive case detection data.

Results:

Cases and dispensary controls had higher dispensary attendance rates compared to community controls and children with nets attended more for most of the illness events. A comparison of cases and community controls showed a strong and statistically significant association between untreated net use and being a case (OR 2.1: 95%CI 1.3, 3.4). For those with ITNs there was a smaller and weaker association between risk of being a case and ITN use (OR 1.4: 95%CI 0.9, 2.2). Comparison of cases and dispensary controls showed no association between untreated or treated nets and the risk of being a case (for treated nets OR 0.9 : 95%CI 0.5, 1.4 and for untreated nets OR 1.2: 95%CI 0.7, 2.0). These results are contrary to those from the cross-sectional assessment, where children with ITNs had a lower prevalence of parasitaemia than those with no nets (OR 0.5: 95%CI 0.3 – 0.9), and also contrary to other assessments of the health impact of ITNs in this population.

Conclusion:

The positive association between mild malaria and net ownership is counter-intuitive and best explained by attendance bias, since children with nets attended more frequently for all curative and preventive services at the dispensary than those without nets. Dispensary-

based case-control studies may not be appropriate for assessing impact of treated nets on clinical malaria.

Introduction:

Intervention programmes for community health problems in developing countries have usually been implemented after their efficacy was demonstrated in randomised controlled field trials. Recently more emphasis has been put in assessing the performance of such interventions under programme conditions before wide-scale use (Habicht *et al.* 1999). These evaluations aim to test whether the benefits of the interventions observed under trial conditions are retained in a programme setting. Positive results will encourage allocation of resources to sustain and expand the programmes to cover whole populations in endemic countries (Lengeler & Snow, 1996).

Experience in the impact evaluation of health intervention programmes is limited (Lengeler & Snow, 1996). These Phase IV assessments are complicated by the absence of appropriate control populations and biased access to interventions and health services. Also, there is usually a limited opportunity for establishing an elaborate evaluation system that may be required to accurately assess exposure and outcome events in the target population (Habicht *et al.* 1999; Mohr, 2000). Therefore, inexpensive, simple and non-intrusive evaluation tools are required.

Case-control studies have been proposed as the most convenient and appropriate tools in the evaluation of insecticide treated nets (ITNs) programmes (Lengeler & Snow, 1996). This was further advocated after the first ITNs programme evaluation in the Gambia (D'Alessandro *et al.* 1997). Case-control studies are attractive because they can be performed relatively cheaply and quickly after the initiation of the intervention (Habicht *et al.* 1999). But they also face well-described problems of bias and confounding, as with all observational studies (Schlesselman, 1982).

The use of “passive case detection” through clinics rather than through active surveillance simplifies a case-control study (Rowland *et al.* 1997) and may improve classification of disease status (Kirkwood *et al.* 1997). However, this increases the difficulty of selecting appropriate controls.

Alternatively, cross-sectional surveys can be done. These assess prevalence and lack the time sequence between exposure and disease events if a single survey is carried out (Kirkwood *et al.* 1997). However, repeated cross-sectional studies have been used to assess impact of ITNs programmes (Barutwanayo *et al.* 1991; D'Alessandro *et al.* 1995; Van Bortel *et al.* 1996; Abdulla *et al.* 2001).

Here we describe a case control study relying on passive case detection in an area of Tanzania where other studies have reported a positive impact of an ITNs social marketing programme on child health and survival (Abdulla *et al.* 2001; Schellenberg *et al.* 2001). The programme utilised marketing techniques to promote, distribute and sell pre-treated bed nets and insecticide kits for re-treatment (Schellenberg *et al.* 1999).

Methods:

Study site and population:

The study was conducted in Idete village (08^{o} 5' S; 36^{o} 30' E), Kilombero District, Southeast Tanzania. The village is one of 18 in the Kilombero Valley within a demographic surveillance system (DSS) (Schellenberg *et al.* 1999). The area has intense year-round malaria transmission (Charlwood *et al.* 1998). Prompt diagnosis and treatment of clinical cases is the main control strategy and resistance to chloroquine, the first line antimalarial at the time of the study, was high (Mshinda *et al.* 1996). Children under five years of age living in all the hamlets (vitongoji) of Idete village were included in the study.

Case-control study:

All children in the DSS database who were under the age of five on 1st February 1998 were assigned a study number and given a special card bearing the name, date of birth, the area of residence and DSS identifiers. This list was updated every 6 months to include new-borns and children who had migrated into the village. A passive case detection system (PCD) operated at the only local dispensary between February 1998 and August 1999 and all children under five years who attended the dispensary for any complaints were eligible. A standard form was filled out and a blood sample was taken on all children who had a history of fever in the previous 48 hours, or a presumptive diagnosis of malaria. Haemoglobin (Hb) was measured using the Hemocue® (HemoCue AB, Ängelholm, Sweden) system and thick and thin films were prepared for microscopy. Records were also kept for all children who were not sick and had attended for preventive reasons, such as

growth monitoring. Children with a temperature of more than 37.4 ^{O}C and any parasitaemia were classified as cases.

For each case, one age matched dispensary control was chosen among the children who had come for growth monitoring or attended for being sick for another cause than malaria, within two weeks of the attendance of the case. An additional community control was chosen from the DSS database matched for age and area of residence (hamlet). If a suitable control could not be found then a child of an adjacent hamlet was chosen. Both cases and controls were then visited at home, individual verbal consent was asked from the guardian and a questionnaire applied. A blood sample was taken from controls who had not given a blood sample at the dispensary in the two weeks prior to the day of the interview. Controls with temperature more than 37.4 and any parasitaemia were excluded in the analysis. Cases and controls were not eligible for recruitment again as either cases or controls for a period of one month.

Cross-sectional survey:

In June-August 1998, all children under five years of age on 1st February 1998 were visited at home and a questionnaire applied to assess their use of ITNs and other risk factors for malaria infection and anaemia (using a similar approach to the case-control study). A blood sample (for malaria parasites and Hb estimation) was taken for children who had not given a blood sample at the dispensary in the two weeks prior the day of the interview. The position of all houses with children under five and the dispensary were also determined using a portable Global Positioning System device (Garmin International, Kansas City, USA). The geo-referenced points were then used to calculate the distance from each child's house to the dispensary.

Dispensary attendance rates:

The PCD data were linked to the DSS data to estimate dispensary attendance rates for different illnesses among study children. Attendance for malaria as well as for growth monitoring and other non-malaria related illnesses (including injuries, burns, fungal infestations, conjunctivitis, abscesses, etc.) was done. Mosquito net ownership was ascribed from the cross-sectional data.

Analysis:

In the case-control assessment, cases of mild malaria were compared with controls primarily with regard to their exposure to ITNs. Both unmatched and matched pairs multivariate analysis using logistic regression was carried out using Stata version 6 (Stata Corporation, Texas USA). The risk or confounding factors considered included the number of people in the room where the child slept , sex of the child, age category, time to the nearest shop, access to clean water source, tribe, if the mother or guardian would advise neighbour to send a child sick with fever to a formal health facility, religious affiliation, nutritional status, vaccination status, antimalarial and antipyretic use, mother/guardian's literacy and the condition of the net in terms of the number of holes and its use in the previous month. Family income (quantiles of total family income), which was assessed by asking on the average monthly income from various activities of the family, was also considered. Significance testing was done using the likelihood ratio test. For the cross-sectional assessment, the parasitaemia and anaemia were compared between users and non-users of ITNs, after controlling for confounding using logistic regression.

Results:

Case-control study:

Idete village had a total of 881 children under five in the DSS database on 1st February 1998. A total of 3389 visits of children under five years of age were recorded at the dispensary between February 1998 and August 1999. A total of 587 mild malaria cases were identified which were individually matched with 424 dispensary and 555 community controls. For some cases we could not identify a suitable control from the database and not all of the identified cases and controls could be traced at their homes because of either travelling or moving to farm houses that could not be located. Those available for interview were 461 cases (78.5%), 333 (78.5%) dispensary controls and 423 (76.2 %) community controls. 7 community controls and 8 dispensary controls had fever and parasitaemia and were excluded in the analysis. 40 cases, 45 community and 17 dispensary controls were excluded due to missing information on actual distance to the dispensary.

Interviewed children had an average age of 26 months (95%CI: 24 , 27) for cases, 26 months (95%CI: 25 , 27) for community and 25 months (95%CI: 23 , 26) for dispensary controls. The mean Hb was 9.2 g/dl (95%CI: 9.0 , 9.5) for cases, 10.2 (95%CI: 10.0 , 10.4) for community controls and 10.1 (95%CI: 9.9 , 10.4) for dispensary controls. The Hb difference between cases and either controls reached statistical significance (Wilcoxon rank-sum tests: p<0.001).

Important risk factors for becoming a case compared to community controls included having a net and living far away from the dispensary. In the unmatched analysis, those with untreated nets were about twice as likely to be cases than those without nets (OR 2.1: 95%CI 1.3, 3.4). Those with ITNs also appeared to be more likely to be cases (OR 1.4: 95%CI 0.9, 2.2) but the relationship was not statistically significant (Table 1a). When comparison was made using dispensary controls, there was no apparent protective effect of either untreated nets nets (OR 1.2: 95%CI 0.7, 2.0) (Table1b) and only a small effect of treated nets, which did not reach statistical significance (OR 0.9: 95%CI 0.5, 1.4). Similar results were observed with matched analysis (data not shown).

Distance to the dispensary was a significant predictor of being a case compared to both types of controls. Those living more than 3 kilometres away were twice more likely to be cases (community controls (OR 1.9: 95%CI 1.1, 3.1) and dispensary controls (OR 2.6: 95%CI 1.5, 4.7). There were no other risk factors associated with being a case.

Dispensary Attendance:

Cases and dispensary controls had dispensary attendance rates of 12.5 per thousand while the rate was only 10.7 per thousand for community controls. Children with nets attended more for most of the illness events (Table 2). Distance from the dispensary was a limiting factor for attendance observed by the decrease in overall attendance with increasing distance to the dispensary (chi-square for trend p<0.001). Ownership of ITNs was an indicator for higher utilisation of the dispensary for those living between 0.5 and 3 kilometres but not for those living very close or very far from the dispensary (Table 2).

Cross-sectional study:

In total 652 children were interviewed in the cross-sectional assessment. The analysis included 629 (96.5%) children for whom we had information on both the net and Hb status. The characteristics of the children included in the analysis of the cross-sectional survey

showed that those without nets had a higher prevalence of parasitaemia, anaemia and splenomegaly (Table 3). Comparison of those with ITNs and with no nets in a multivariate analysis showed that those with ITNs had a lower prevalence of any parasitaemia (OR 0.5: 95%CI 0.3 – 0.9). Age of the child and distance to the dispensary were other important factors (Table 4). Positive effects of treated nets were also shown for prevalence of anaemia.

Discussion:

We found a positive association between risk of clinical malaria and ownership of mosquito nets using a case-control design. This finding is counter-intuitive and contradicts the results of the cross-sectional assessment the same village and a repeated cross-sectional assessment conducted in the surrounding villages, which suggested an impact of the ITNs in reducing the prevalence of anaemia and parasitaemia by 60% (Abdulla *et al.* 2001). An estimated 27% reduction in childhood deaths associated with treated nets has also been shown in the same area (Schellenberg *et al.* 2001). The discrepancy is likely to be a consequence of attendance bias in the Idete case-control study. Children with nets attended more frequently for all the services at the dispensary, which may be explained by the higher awareness of health issues or as a consequence of the dispensary being one of the ITN sales outlets. Hence, the exposure of interest pre-determined to some extent the recruitment, resulting in analysis and estimation of impact to be done on an already selected group of individuals. Those with nets would be included as cases if they became sick. But those without nets were less likely to attend the health facility so although they were eligible to be community controls they were not likely to be seen as cases if they became sick with malaria. Thus, the community controls were not comparable with cases and both cases and dispensary controls were not comparable with the general population in the area. The lack of a statistically significant association between ITN ownership and being a case when considering dispensary controls may be due to a lack of power or to the fact that the exposure of interest also determined the likelihood of being a dispensary control. Attendance bias is neither easily measured nor can it be corrected for in the analysis (Sackett, 1979).

Table 1a: Risk factors for being a case of malaria at the Idete dispensary (unmatched analysis using community controls)

Variable	**Cases**	**Community controls**	**Crude odds ratio (95% CI)***	**Adjusted odds ratio (95% CI)**	**LRT – χ^2 (χ-value)**
Number	421	371			
Net ownership					
No net	52 (12.3)	63 (17.0)	1	1	
Untreated net	125 (29.7)	77 (20.7)	1.97 (1.24, 3.13)	2.10 (1.31 , 3.38)	
Treated net	244 (58.0)	231 (62.3)	1.29 (0.85 , 1.93)	1.42 (0.93 , 2.17)	10.33 (0.006)
Distance to the Dispensary					
Below 500 meters	45 (10.7)	60 (16.2)	1	1	
500 – 1500 meters	197 (46.8)	185 (49.9)	1.42 (0.92 , 2.20)	1.39 (0.90 , 2.15)	
1500 – 3000 meters	86 (20.4)	61 (16.4)	1.88 (1.13 , 3.12)	1.97 (1.18 , 3.30)	
Above 3000 meters	93 (22.1)	65 (17.5)	1.91 (1.16 , 3.15)	1.89 (1.14 , 3.13)	9.19 (0.027)

Table 1b: Risk factors for being a case of malaria at the Idete dispensary (unmatched analysis using dispensary controls)

Variable	**Cases**	**Hospital controls**	**Crude odds ratio (95% CI)***	**Adjusted odds ratio (95% CI)**	**LRT – χ^2 (χ-value)**
Number	421	308			
Net ownership					
No net	52 (12.3)	34 (11.0)	1	1	
Untreated net	125 (29.7)	69 (22.4)	1.19 (0.70 , 2.00)	1.19 (0.70 , 2.03)	
Treated net	244 (58.0)	205 (66.6)	0.79 (0.49 , 1.25)	0.86 (0.53 , 1.39)	3.39 (0.184)
Distance to the Dispensary					
Below 500 meters	45 (10.7)	46 (14.9)	1	1	
500 – 1500 meters	197 (46.8)	172 (55.9)	1.17 (0.74 , 1.85)	1.15 (0.73 , 1.83)	
1500 – 3000 meters	86 (20.4)	56 (18.2)	1.57 (0.92 , 2.67)	1.54 (0.91 , 2.63)	
Above 3000 meters	93 (22.1)	34 (11.0)	2.80 (1.58 , 4.94)	2.62 (1.48 , 4.65)	16.39 (<0.001)

Note: The multivariate models were built from variables that included number of people in the room where the child is sleeping, sex of the child, age category, time to the nearest shop, access to clean water source, tribe, stunting (height for age Z-scores ≤-3), family income category (quantiles of total family income), if the mother or guardian would advise neighbour to send a child sick with fever to a formal health facility, mother/guardian's literacy and the condition of the net in terms of the number of holes. All these variables were dropped as their log-likelihood ratio test p value was more than 0.05.

Table 2: Attendance rates for different reasons at Idete dispensary for children with and without treated nets

Attribute	No nets		Untreated nets			Treated nets		
	Number	Rate§	Number	Rate§	**RR‡**	Number	Rate§	**RR‡**
Total number of children in the cohort	134		140			304		
Total days of follow up	52310		59769			132442		
Attendance for growth monitoring	90	1.7	178	3.0	**1.7 (1.3,2.3)**	401	3.0	**1.8 (1.4,2.2)**
Total attendance for any illness	295	5.6	392	6.6	**1.2 (1.0,1.4)**	1221	9.2	**1.6 (1.4,1.9)**
Attendance rate sick with anaemia	28	0.5	38	0.6	**1.2 (0.7,2.0)**	112	0.9	**1.6 (1.0,2.5)**
Attendance rate sick and malaria slide positive	120	2.3	147	2.5	**1.1 (0.8,1.4)**	423	3.2	**1.4 (1.1,1.7)**
Attendance rate sick with diarrhoea	67	1.3	91	1.5	**1.2 (0.9,1.7)**	316	2.4	**1.9 (1.4,2.5)**
Attendance rate sick with non malaria-related illness	56	1.1	77	1.3	**1.2 (0.8,1.7)**	210	1.6	**1.5 (1.1,2.0)**
Attendance rate for *:								
Those living within 0.5 kilometers	42	11.9	59	8.0	**0.7 (0.5,1.0)**	179	11.2	**1.0 (0.7,1.4)**
Those living between 0.5 - 1.5 kilometers	137	5.8	147	6.6	**1.1 (0.9,1.5)**	647	11.9	**2.0 (1.7,2.5)**
Those living between 1.5 - 3 kilometers	37	4.2	90	8.0	**1.9 (1.3,2.9)**	147	7.9	**1.9 (1.3,2.8)**
Those living more than 3 kilometers	67	4.6	78	4.7	**1.0 (0.7,1.4)**	147	4.4	**1.0 (0.7,1.3)**

§: Rate per 1000 person days

‡: Relative rate comparing with those with no nets and 95% confidence intervals in brackets

*: Calculated based on specific total person days of follow up for each distance category

Table 3: Characteristics of the children in Idete village from the cross-sectional assessment

Attribute	**No nets (%)**	**Untreated nets (%)**	**Treated nets (%)**	**Overall**
Children analysed	140 (22.2)	159 (25.3)	330 (52.5)	629
Mean age in months *	36.4 (33.4 , 39.3)	32.2 (30.4 , 36.1)	28.6 (26.6 , 30.8)	31.5 (30.0 , 33.0)
Males	74 (52.9)	76 (47.8)	162 (49.1)	312 (49.6)
Mean Haemoglobin *	9.5 (9.2 , 9.8)	10.0 (9.7 , 10.3)	9.9 (9.7 , 10.1)	9.8 (9.7 , 10.0)
Moderate severe anaemia	17 (12.1)	14 (8.8)	31 (9.4)	62 (9.9)
Mild anaemia	98 (70.0)	101 (63.5)	199 (60.3)	398 (63.3)
Parasitaemia (*P. falciparum*)[#]	98 (70.0)	92 (58.2)	155 (47.3)	345 (55.1)
Splenomegaly	59 (42.1)	41 (25.8)	68 (20.7)	168 (26.8)
Distance to the dispensary less than 1500 meters [§]	62 (49.2)	75 (52.8)	180 (60.8)	317 (56.2)

* : 95% confidence interval in brackets

: Children assessed for parasitaemia were 626

§ : Children assessed for distance to the dispensary were 564

Table 4: Risk factors for parasitaemia in the cross-sectional survey

Variable	**Numbers with parasitaemia (%)**	**Crude odd ratio (95% CI)**	**Adjusted odd ratio (95% CI)**	**LRT –c^2 (r-value)**
Net ownership				
No net	89 (28.3)	1	1	
Untreated net	82 (26.1)	0.57 (0.34 , 0.94)	0.67 (0.39 , 1.15)	
Treated net	143 (45.6)	0.39 (0.24 , 0.60)	0.53 (0.33 , 0.85)	7.09 (0.029)
Age category				
Below 1 year	25 (8.0)	1	1	
1 - 2 years	50 (15.9)	2.95 (1.64 , 5.30)	2.87 (1.58 , 5.25)	
2 - 3 years	77 (24.5)	6.81 (3.77 , 12.31)	6.47 (3.53 , 11.84)	
3 – 4 years	60 (19.1)	6.11 (3.30 , 11.31)	5.33 (2.83 , 10.04)	
Above 4 years	102 (32.5)	8.79 (4.92 , 15.68)	8.58 (4.72 , 15.59)	68.88 (<0.001)
Distance to the Dispensary				
Below 500 meters	26 (8.3)	1	1	
500 – 1500 meters	140 (44.6)	2.29 (1.33 , 3.94)	2.39 (1.33 , 4.30)	
1500 – 3000 meters	60 (19.1)	3.46 (1.80 , 6.64)	3.65 (1.80 , 7.42)	
Above 3000 meters	88 (28.0)	2.18 (1.22 , 3.87)	2.14 (1.15 , 3.98)	14.01 (0.003)

Note: The multivariate model was built from variables that included sex of the child, time to the nearest shop, access to clean water source, religious affiliation, antimalarial use in the last illness, family income category (quantiles of total family income), if the mother or guardian would advise a neighbour to send a child sick with fever to a formal health facility, mother/guardian's literacy, the history of use of the net in the previous month and the condition of the net in terms of the number of holes. All these variables were dropped as their log-likelihood ratio test p value was more than 0.05.

Case-control studies for the evaluation of an intervention, usually compares the risk of being diagnosed with the disease among the adopters and non-adopters of the intervention, which will be similar to assessments using either longitudinal or cross-sectional studies (Kirkwood *et al.* 1997). For all these approaches, the adopters of the intervention are likely to differ from non-adopters in subtle but important ways that cannot be assessed or controlled for in the analysis. The comparison of adopters vs. non-adopters answers a different type of question from intervention vs. control, with the former measuring the health benefit of those who adopt rather than health impact *per se* (Kirkwood *et al.* 1997). Therefore the results of these two comparisons cannot be directly compared. In an ITNs programme, a randomly allocated contemporaneous control group (Lengeler & Snow, 1996) would no longer be ethically acceptable or feasible, as this involves withholding nets from some groups given their proven impact on mortality.

The comparisons of adopters vs. non-adopters in our studies illustrate an particular difficulty of assessing ITNs programme impact where ITNs use is very high. It may then be impossible to make this comparison because of the small numbers of non-adopters, who will represent a highly selected group. Furthermore, the likelihood that there is a "mass effect" of the ITNs (Howard *et al.* 2000) may give some protection to non-adopters and this reduces differences in the malaria disease burden between adopters and non-adopters.

The logistical difficulty of obtaining enough cases and controls adds to the complexity of such studies. In our study the recruitment extended over 18 months and had a high rate of non-interviewed cases and controls. In the previous study in the Gambia a difference in the timing and recruitment pattern of the community and health facility controls was thought to be the source of discrepancy in the study results (D'Alessandro *et al.* 1997). Together, these observations call into question the usefulness of health facility based case-control studies for evaluating the morbidity impact of ITNs programmes. An alternative study design would have been to use active case detection in the community. All children in the village could be visited at home every week, temperature taken from all and blood slides from those with fever. The cases would then those with fever and parasitaemia and the controls would be a random sample of those without. However, this is logistically more complex and expensive, and hence usually unrealistic in the frame of a programme evaluation.

The lack of a simple test to check for insecticide content of the nets (Drakeley C.J. *et al.* 1999) meant that exposure to ITNs could not be accurately ascertained as suggested by work in The Gambia (Muller *et al.* 1994; D'Alessandro *et al.* 1997). Reported ownership of ITNs may have led to some misclassification of exposure in our studies and reduced the power.

The finding that distance to the dispensary is an important predictor of attendance is in line with findings elsewhere (Stock *et al.* 1983). However, it is unclear if the observation of more cases from those living far from the dispensary indicates a true occurrence of more disease in the periphery of the village, or if it is just a reflection of patterns of dispensary attendance and self-medication for malaria episodes in the village. Furthermore, the odds ratios need to be interpreted with caution as cases and controls were matched on area of residence.

Every health programme implementing interventions shown to be effective in randomised controlled trials aims to demonstrate that the desired health impact is also achieved under large-scale implementation – and if not, then why. However, given that (1) programme staff are unlikely to be familiar with epidemiological studies and (2) most programmes wish to invest more of their resources in implementation rather than monitoring, a compromise with regard to the optimal study design will have to be made. The use of simple cross-sectional surveys seems to be an attractive option, if suitable health outcomes can be identified and relevant exposure measures are feasible.

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CHAPTER 7

Spatial effects of the social marketing of insecticide treated nets on malaria morbidity

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Abstract:

Randomised controlled trials have shown that Insecticide Treated Nets (ITNs) have an impact on both malaria morbidity and mortality. Uniform high coverage of ITNs characterised these trials and this resulted in some protection of nearby non-users of ITNs. We have now assessed the coverage, distribution pattern and resultant spatial effects in one village in Tanzania where ITNs were distributed in a social marketing programme. The prevalence of parasitaemia, mild anaemia (Hb < 11 g/dl) and moderate/severe anaemia (Hb < 8 g/dl) in children under five was assessed cross-sectionally. Data on ownership of ITNs were collected and inhabitants' houses were mapped.

One year after the start of the social marketing programme, 52% of the children were using a net which had been treated at least once. The ITNs were rather homogeneously distributed throughout the village at an average density of about 118 ITNs per thousand population. There was no evidence of a pattern in the distribution of parasitaemia and anaemia cases, but children living in areas of moderately high ITNs coverage were about half less likely to have moderate/severe anaemia (OR 0.5, 95%CI: 0.2 , 0.9) and had lower prevalence of splenomegaly, irrespective of their net use. No protective effects of coverage were found for prevalence of mild anaemia nor for parasitaemia. The use of untreated nets had neither coverage nor short distance effects. More efforts should be made to ensure high coverage in ITNs programmes to achieve maximum benefit.

Introduction:

There is growing interest on insecticide treated bed nets (ITNs) as a tool for malaria control, after randomised controlled trials showed that they reduce morbidity and mortality from malaria (Lengeler, 1998). Large scale implementation programmes are underway focusing mainly on operational issues of delivery and distribution of ITNs in a sustainable manner (Anonymous, 1999).

The ITNs act by both being a physical barrier protecting those sleeping under them and by killing and repelling mosquitoes hence reducing the survival and infection rates (Lines, 1996). Hence those with the ITNs and who use them properly have a reduced exposure to malaria infecting mosquitoes and consequently reduced malaria disease burden. The distribution pattern and coverage levels attained in implementation programmes may determine the level of protection observed in those who use them (D'Alessandro *et al.* 1995; Binka *et al.* 1998; Howard *et al.* 2000). Protection is highest among persons with ITNs living in areas with high ITN coverage and use. There are indications that people without nets sleeping nearby ITNs are also protected. Earlier work showed some short range (within the same room) protective effects of ITNs (Lines *et al.* 1987) while other studies did not show such protection (Rowland *et al.* 1996). Work conducted in Ghana supports the claims of short distance protective effects (those near ITNs are also protected) on those without bed nets. Among non-users the mortality risk increased by 6.7% with every 100 meters shift away from the nearest compound with treated bed nets (Binka *et al.* 1998). In the Kenyan coast those living up to 0.5 kilometers away had also lower hospital attendance rates for severe disease (Howard *et al*. 2000).

In the randomised studies ITNs were distributed free to all the intervention groups and uniformly high coverage was ensured (Binka *et al.* 1998;Habluetzel *et al.* 1997;Nevill *et al.* 1996), while in the programme setting the pattern of distribution is dependent on the many factors that determine the uptake of the ITNs intervention. These include social economic factors, distribution channels and local perceptions about ITNs (Fraser-Hurt & Lyimo 1998; Snow *et al.* 1999; Minja *et al.* 2001). This has lead to speculation on what might happen when ITNs are distributed in a programme setting.

It is not clear what patterns of spatial distribution of ITNs will occur in social marketing schemes. Conceivably, market mechanisms may lead to ITNs being widely but thinly distributed, with thus a relatively low coverage. This may be a more efficient way of conferring protection for those without ITNs (Binka *et al.* 1998). Alternatively, ITNs might end up being concentrated where the wealthiest people are whilemalaria transmission and disease is more likely to be concentrated on the poorest segment of the population, who tend live on the edges of the villages and may be less likely to have nets (Bonilla & Rodriguez. 1993; Smith *et al.* 1995; Charlwood *et al.* 1998; Abdulla *et al* 2001). Therefore, spatial effects of ITNs may be important in the understanding and interpretation of the results of impact assessments of ITNs programmes for malaria control.

We report the investigation of the spatial pattern of ITNs in one village covered by a large scale ITNs social marketing programme and the consequent effects on malaria morbidity indicators in children under five years of age.

Methods:

Study population and design.

The study was conducted in Idete village, South Western Tanzania (08^{o} 5' S; 36^{o} 30' E). The residents are mainly subsistence farmers and the main crop is rain fed rice. This is an area of intense year-round malaria transmission. The main vectors are *Anopheles gambiae ss, Anopheles arabiensis* and *Anopheles funestus* (Smith *et al.* 1993; Charlwood *et al.* 1998). A social marketing programme for ITNs has been implemented in this area since May 1997 (Schellenberg *et al.* 1999).

A cross-sectional assessment of all children under five living in all the hamlets ('vitongoji') of Idete was done at the end of the main rainy season June – August 1998. Details of the survey are described elsewhere (Abdulla *et al.* 2002). In summary, children were visited at home and a questionnaire was applied to assess use of ITNs and other risk factors for malaria infection and anaemia. A physical examination was carried out and a blood

sample was taken. The sample was screened for malaria parasites and haemoglobin level (Hb) was assessed using Hemocue® (Angelholm, Sweden).

Age and sex data for the community were available from a Demographic Surveillance System (DSS) established to allow the evaluation of impact of the social marketing programme (Schellenberg *et al.* 1999). ITNs ownership was also assessed in the 4 monthly cycles within the framework of the DSS.

Mapping:

The position of the houses and other important service outlets including the dispensary, were determined using a portable Global Positioning System (Garmin, Thousand oaks, USA). The geo-referenced points were then used to calculate distance between houses and between the houses and the dispensary. Coverage of ITNs and untreated nets were calculated for each individual child in the cross-sectional survey. The number of nets per 1000 population living in houses other than the index child and within specific radii were calculated. Radii of 50m (R_{50}), 100m (R_{100}), 200m (R_{200}) and 400m (R_{400}) were chosen, on the basis of the findings of other studies (Binka *et al.* 1998;Hii *et al.* 2001). Coverage was categorised as low (0 ITNs/1000 persons), moderate (1-300 ITNs/1000 persons) and high (>300 ITNs /1000 persons).

Analysis:

The outcomes of mild anaemia (Hb <11 g/dl), moderate/severe anaemia (Hb<8g/dl) and any parasitaemia in the cross-sectional assessment were compared between users and non-users of ITNs, after controlling for confounding using logistic regression analysis. The explanatory variables also included ITNs coverage and distance to the dispensary (Abdulla et al. 2002). Logistic models were also used to assess the effects of different risk factors on mild and moderate/severe anaemia. Random effects were added on the logit scale of these models to take into account the spatial structure of the data, that is,

$$\log(p_i / 1- p_i) = b^t X_i + e_i$$

where p_i is the outcome probability, b the vector of coefficients and X_i the vector of covariates for individual i. Spatial correlation was incorporated in the random effects e_i, by parameterising their covariance matrix , such that:

$$\text{Cov}(e_i, e_j) = s^2 f(d_{ij})$$

where d_{ij} measures the Euclidean distance between location s_i and s_j. We modeled an exponential decrease of spatial correlation with distance by adopting:

$$f(d_{ij}) = \exp(-r\ d_{ij})$$

but also compared the fit of this model with others, considering different choices of spatial covariance types using the Akaike's information criterion (AIC). Explanatory variables, such as age, distance to dispensary etc., were discretizised into several categories. The analysis was done using the SAS GLIMMIX macro, which uses iteratively reweighted likelihoods (Wolfinger & O'Connell 1993) to fit the models. The likelihood ratio test was used to assess the significance of the explanatory variables on the outcomes.

Results:

652 children were examined in the cross-sectional survey. Details of their characteristics and the assessment of the impact of ITNs on occurrence of anaemia and parasitaemia have been described elsewhere (Abdulla *et al.* 2002). In short, those children using ITNs had lower risk of anaemia (OR 0.47 ,95%CI: 0.30 – 0.75) and moderate/severe anaemia (OR 0.66,95%CI: 0.32, 1.37) compared to those without nets at all. The relationship did not reach statistical significance for moderate/severe anaemia. A statistically significant difference was also observed on the prevalence of any parasitaemia (OR 0.53,95%CI: 0.33 – 0.85). Other risk factors identified included distance to the dispensary, which was positively correlated to the prevalence of moderate/severe anaemia, and any parasitaemia.

Coverage effects:

The DSS database had 941 households in Idete at the time of the cross-sectional assessment. 708 (75.2 %) were present in the village and their houses mapped at the time of mapping exercise. The mapped houses had significantly more members on average, a higher proportion with children under five and fewer single member households than those not mapped (Table 1).

Table 1: Characteristics of the mapped and un-mapped households in Idete village

Attribute	**Mapped (%)**	**Not Mapped (%)**	χ^2 **(P-value)** ‡
DSS – Households	708 (75.2)	233 (24.8)	
Average number of persons *	5.2 (5.0 , 5.3)	3.6 (3.3 , 3.9)	8.160 (<0.001)
Households with children under five years	495 (69.9)	89 (38.2)	74.904 (<0.001)
Households with a single adult member only	68 (9.6)	63 (27.0)	44.465 (<0.001)
Households with known net status	620 (87.6)	146 (62.7)	71.854 (<0.001)
Households with no net	176 (28.4)	44 (30.1)	
Households with at least one untreated net	227 (36.6)	57 (39.1)	
Households with at least one treated net	217 (35.0)	45 (30.8)	0.917 (0.632)
Average treated net per 100 persons	13.3 (11.6 , 15.1)	17.4 (12.1 , 22.6)	0.03 (0.978)
Average untreated net per 100 persons	13.3 (11.5 , 15.1)	20.9 (15.8 , 26.1)	1.827 (0.068)

* : 95% confidence interval in brackets and Wilcoxon rank sum test statistic

‡ : Pearsons χ^2 with Yates continuity correction

There were 626 children under five years of age included in the cross-sectional survey. Analysis presented here was restricted to 564 (90.1%) children classified as DSS members and who had information available on geo-location, bed net and anaemia status. The mean ITN coverage in the study area was 118.8 per 1000 inhabitants (range 0 – 1000). As defined by coverage at 100 meters (C_{100}), 259 (45.1%) children lived in low, 256 (44.5%) moderate and 60 (10.4%) in high ITNs coverage areas (Table 2). Children living in the different 3 coverage levels had similar average age, average haemoglobin level, proportions with mild anaemia and parasitaemia (Table 2). But those living in moderate and high coverage had significantly lower proportions of moderate/severe anaemia and splenomegaly than those living in low coverage areas (9% vs 16.2 and 22.8% vs. 33.6% respectively). Significantly higher proportions of children in the moderate and high coverage groups were living within one and a half kilometers of the dispensary (Table 2). Similar proportions of children with ITNs were observed in the three areas, indicating that coverage did not predict children's net ownership. However, those living further from the centre of the village had a lower proportion of ITNs (173 versus 93 per thousand population for those living within 500 meters and those living over 3 kilometers respectively: extended Kruskal-Wallis test for trend, $p < 0.01$)

The model used to explore the effects of different risk factors on having moderate/severe anaemia (Abdulla *et al.* 2002) was adjusted to investigate the effect of coverage. The results indicate that coverage was an important factor for predicting the risk of having anaemia even after controlling for the other already identified factors (Table 3). There was less moderate/severe anaemia among those living in moderate (OR 0.46, 95%CI: 0.23, 0.91) and high (OR 0.33, 95%CI: 0.09, 1.16) ITNs coverage area compared to those living in low coverage areas. This indicates that coverage is independently associated with the occurrence of moderate/severe anaemia in the study area.

Analysis using other radii did not show significant results for moderate/severe anaemia nor other outcome variables assessed. Furthermore no coverage effects were observed for untreated nets for any radii or morbidity indicators.

Table 2: Characteristics of children living within the different coverage areas (C_{100}) in Idete village

Attribute	**No other ITNs per 1000 persons (%)**	**1 – 300 other ITNs per 1000 persons (%)**	**301 – 1000 other ITNs per 1000 persons (%)**	c^2 **(P-value)** ‡
Children analysed *	255 (45.2)	249 (44.2)	60 (10.6)	
Mean age in months **	32.3 (30.0 , 34.6)	31.7 (29.4 , 34.1)	32.3 (27.7 , 36.9)	0.17 (0.921)
Mean Haemoglobin **	9.6 (9.4 , 9.9)	10.0 (9.8 , 10.2)	9.8 (9.4 , 10.2)	4.85 (0.089)
Moderate severe anaemia	38 (14.9)	16 (6.4)	3 (5.0)	11.89 (0.003)
Mild anaemia	163 (63.9)	151 (60.6)	42 (70.0)	1.95 (0.378)
Parasitaemia (p. falciparum)#	152 (59.8)	126 (50.8)	35 (59.3)	4.49 (0.106)
Splenomegaly §	86 (33.7)	56 (22.6)	12 (20.0)	9.69 (0.008)
Living within 1500m of the Dispensary	100 (39.2)	182 (73.1)	35 (58.3)	58.86 (<0.001)
Owning an ITN	139 (54.7)	112 (45.0)	30 (50.0)	4.78 (0.092)

* Percentage of total children in brackets

** : 95% confidence interval in brackets and Kruskal-Wallis Statistic

: The total of children assessed for parasitaemia was 561

§ : The total of children assessed for splenomegaly was 563

‡ : Pearsons χ^2 with Yates continuity correction

Table 3: Risk factors for anaemia (Hb< 8 g/dl) in children in Idete village

Variable	**Numbers with anaemia (%)**	**Crude odd ratio (95% CI)**	**Adjusted odd ratio (95% CI)**	**LRT –χ^2 (P-value)**
Net ownership				
No net	15 (28.3)	1	1	
Untreated net	12 (22.6)	0.72 (0.32 , 1.61)	0.67 (0.28 , 1.59)	
Treated net	26 (49.1)	0.72 (0.36 , 1.42)	0.64 (0.31 , 1.31)	1.51 (0.470)
Mother literate	20 (37.7)	0.39 (0.21 , 0.69)	0.38 (0.20 , 0.70)	9.84 (0.002)
Given an antipyretic in the last illness	44 (83.0)	3.42 (1.63 , 7.19)	5.13 (2.31 , 11.35)	20.36 (<0.001)
Distance to the Disp.				
Less than 500 M	2 (3.8)	1	1	
500 - 1500 meters	23 (43.4)	3.37 (0.77 , 14.74)	3.26 (0.71 , 14.93)	
1500 – 3000 meters	7 (13.2)	3.02 (0.60 , 15.11)	1.83 (0.34 , 10.02)	
More than 3000 m	21 (39.6)	4.98 (1.13 , 22.00)	5.47 (1.15 , 26.00)	9.28 (0.026)
Coverage of other ITNs within 100m distance				
Low (No ITNs)	34 (64.2)	1	1	
Moderate (1 – 300)	16 (30.2)	0.43 (0.23 , 0.80)	0.46 (0.23 , 0.91)	
High (301 – 1000)	3 (5.6)	0.34 (0.10 , 1.16)	0.33 (0.09 , 1.16)	7.09 (0.029)

LRT: Likelihood ratio test

Neighbourhood or short-distance effects:

Neither the ownership of ITNs, nor having malaria parasites, or mild or moderate/severe anaemia seemed to have any particular spatial distribution (Fig 1a-c). Logistic regression without covariates and including or excluding a spatial adjustment, also did not show any difference in the residuals. The conclusion was confirmed by testing the effects of different spatial correlations structures and by variogram analysis of the residuals from the non spatial model. Multivariate logistic models incorporating spatial (exponential) effects estimated slightly larger standard errors for the fixed effects parameter estimates but this did not reduced the number of significant covariates (data not shown).

Discussion:

Relatively good coverage of ITNs in the target group (children and expectant mothers) was achieved in the social marketing programme. About 61% of children under two years (Abdulla *et al.* 2001) and 52% of children under five years (Abdulla *et al.* 2002) slept under a net treated at least once. This is similar to findings of an earlier exploratory study in the same area using a similar delivery mechanism (Fraser-Hurt & Lyimo 1998) and in Burundi (Van Bortel *et al.* 1996). Assessment of coverage effects show that children who lived in areas with high ITNs coverage had significantly lower anaemia levels when coverage within 100 meters was considered, indicating that the prevalence of anaemia is better explained by nearby ITN coverage than by personal protection alone.

This was similar to effects of ITN coverage on malaria exposure (Lines *et al.* 1987), on severe disease (Howard *et al.* 2000) and on mortality (Binka *et al.* 1998). However, unlike the studies in Papua New Guniea (PNG) (Hii *et al.* 2001) and in Burundi (Van Bortel *et al.* 1996), we did not find any effect of bed net coverage on prevalence of parasitaemia. This may be because the prevalence of parasitaemia is not very closely linked to transmission intensity in areas of high endemicity (Thomas & Lindsay 2000).

Figure 1A: Spatial distribution of houses in Idete village

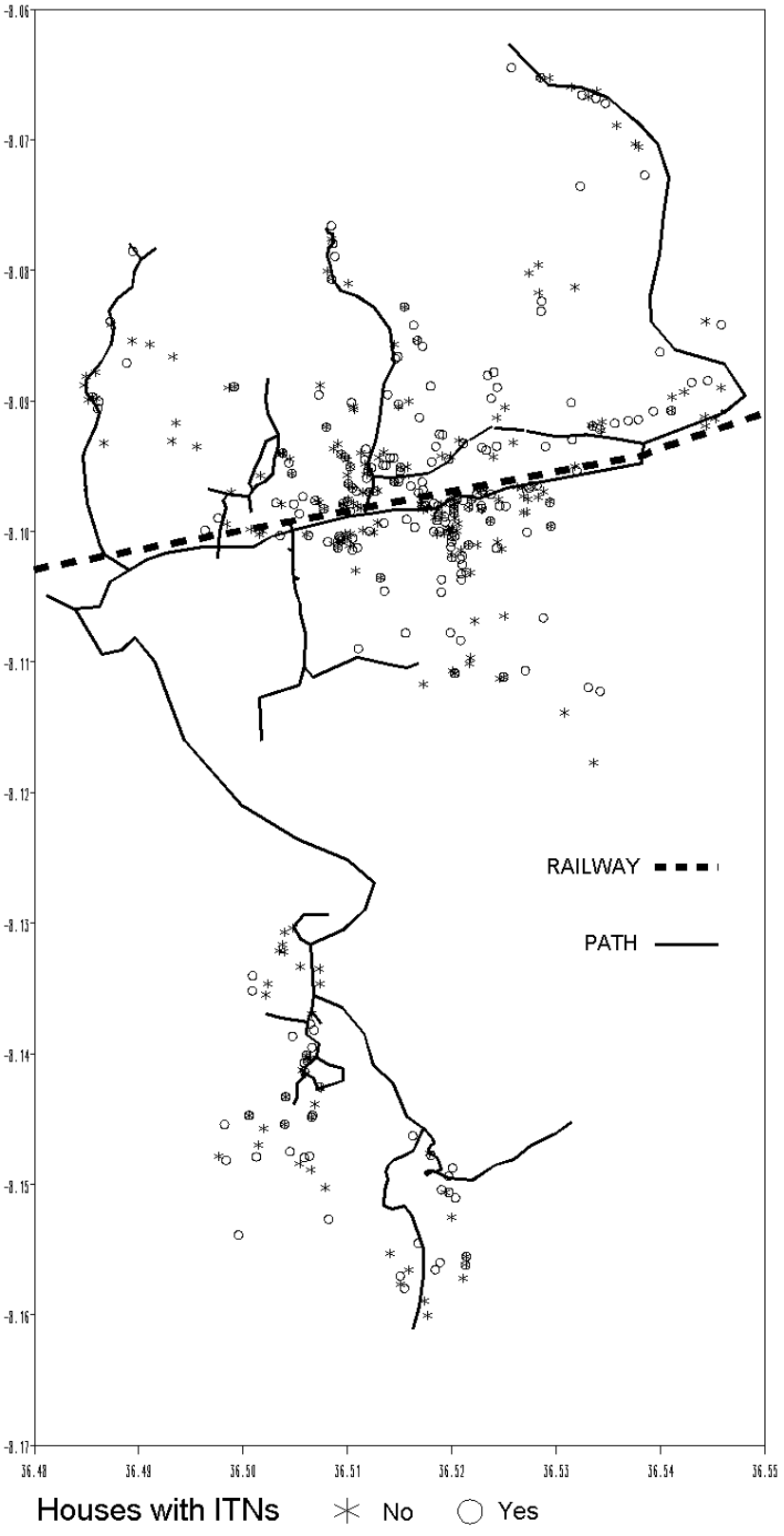


Figure 1B: Spatial distribution of ITNs in Idete village

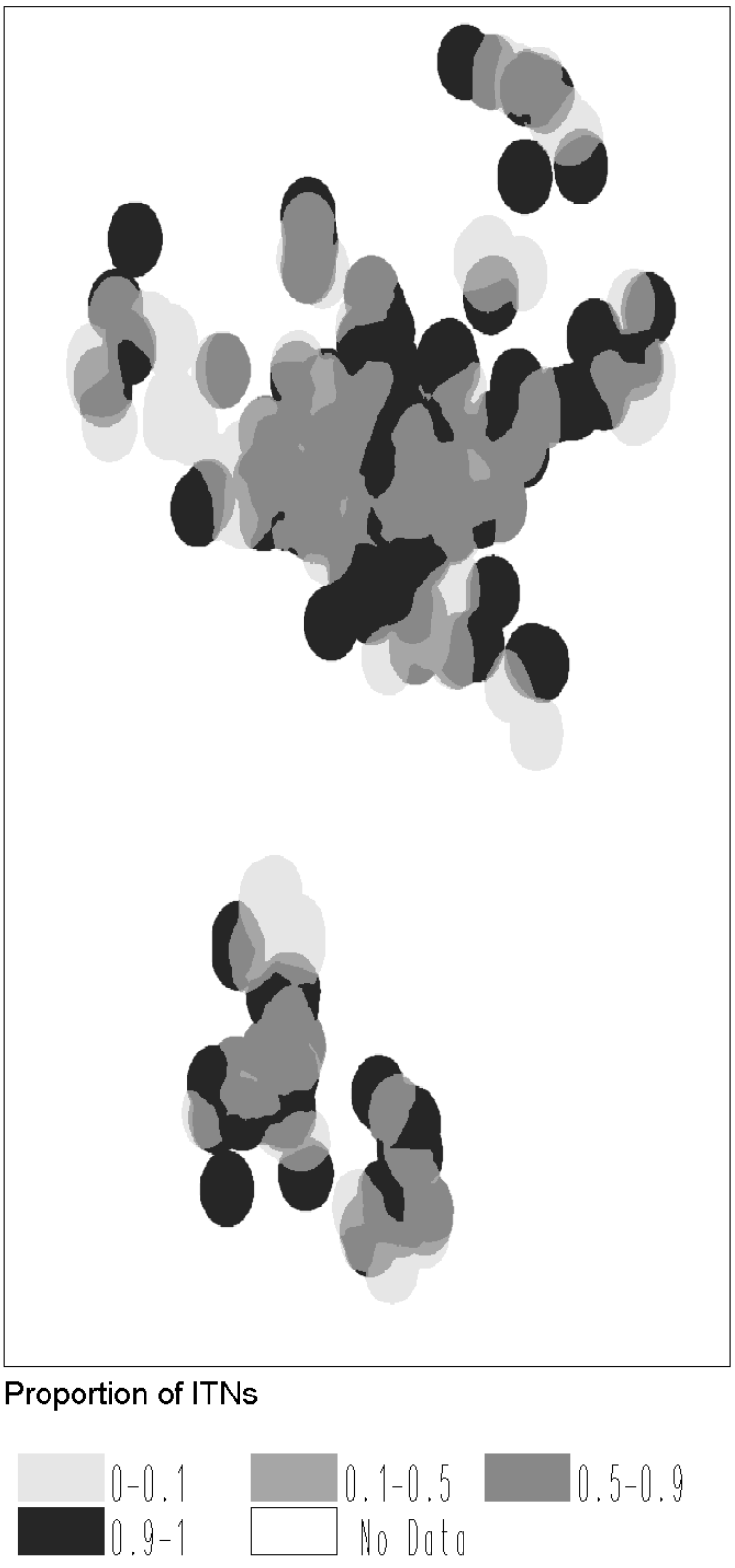


Figure 1C: Spatial distribution of parasitaemia in Idete village

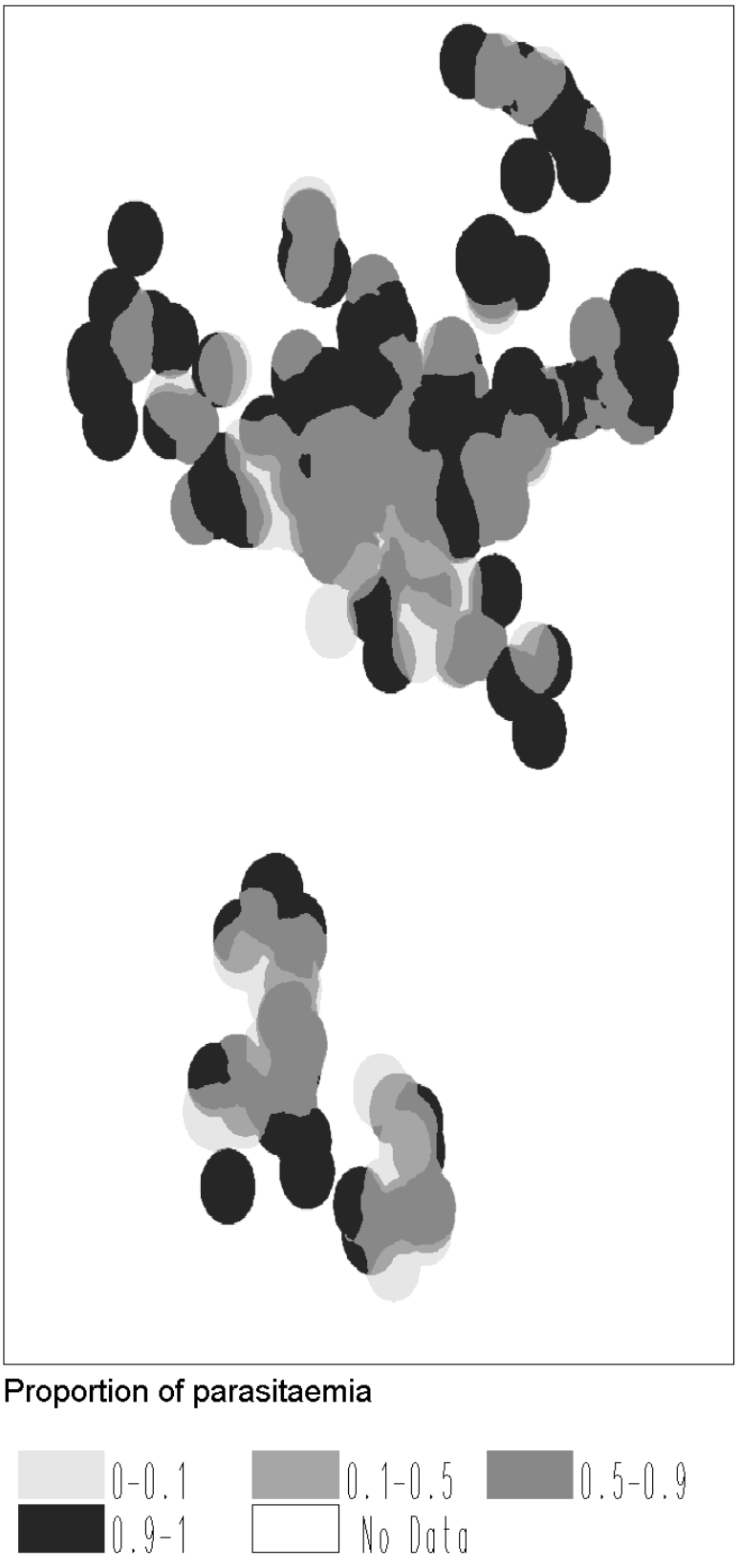
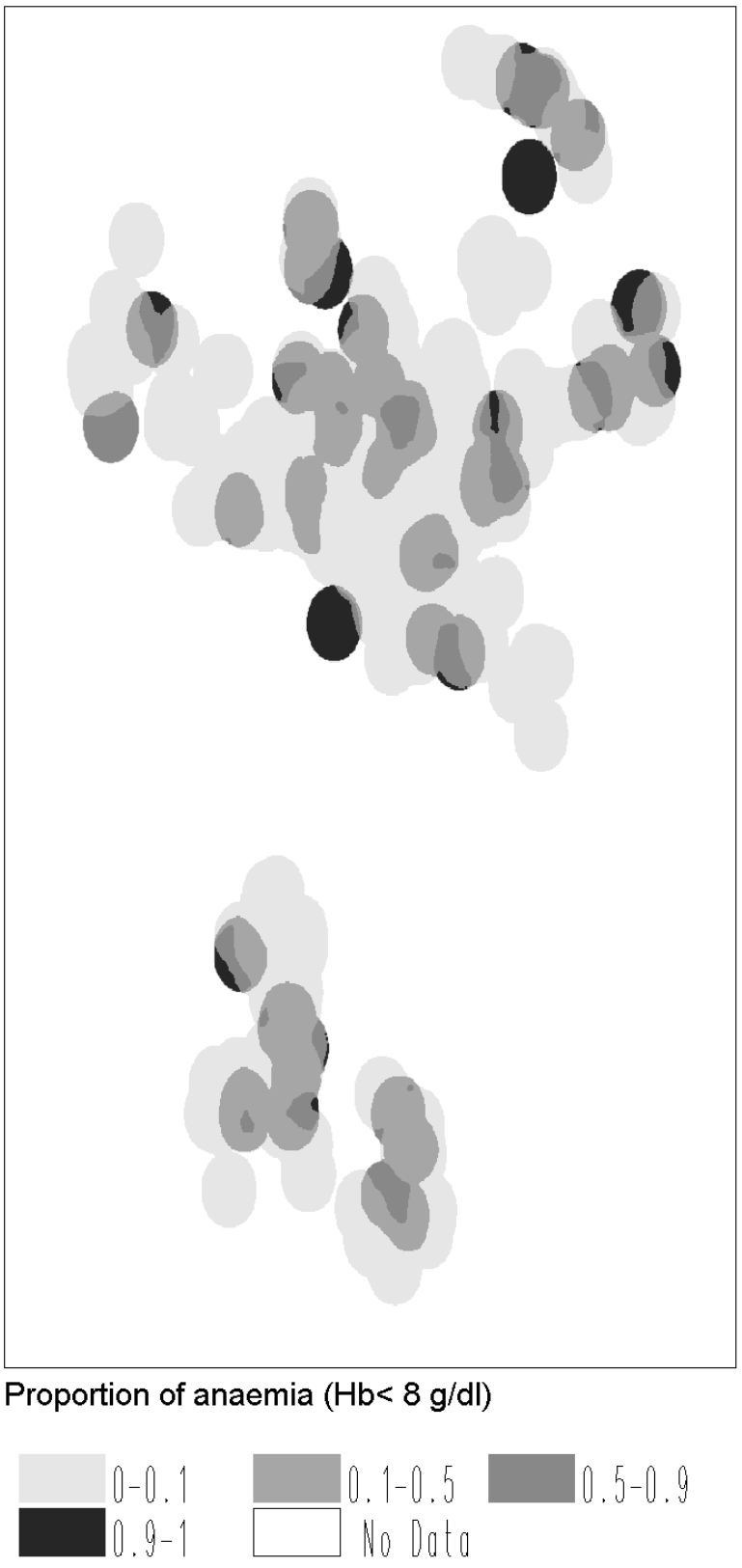


Figure 1D: Spatial distribution of anaemia in Idete village



Unlike the work in PNG (Hii *et al.* 2001), the coverage effects in our study were significant only when considering C_{100}. It may be that at lower radii the coverage effects are higher but we had wider confidence intervals. While at higher radii, the coverage effects are close to zero. It may also be that the effects of the other ITNs around out-weigh the effects of ITNs of the index child at this range, beyond which the coverage effects gets smaller. Or it may be that only at this distance the existing distribution structure of the ITNs makes a difference. Lastly, although some attempt has been made to control for differences in confounding factors like soc-economic status (Abdulla *et al.* 2002), it is still possible that some of the coverage effects that we have observed are mainly a reflection of residual confounding effects. All these issues allow us to make only crude statements about the relationship between coverage effects and morbidity indicators in children.

Allowance for spatial structure with the generalised linear mixed model did not substantially alter the point estimates from the fixed effects logistic regression and there was no residual spatial pattern detectable in the models including distance to the dispensary. Hence the fixed effects models adequately described the relationship of the effects of ITNs on anaemia. The finding that the malaria indicators are related to measured distance from the household to the dispensary (Abdulla *et al.* 2002) presumably reflects the importance of the health seeking behaviour and treatment of malaria on these indicators. Demonstration of diversion or no diversion of mosquitoes (through entomological assessment) might have given some insights to the effects of ITNs that are not easily detectable using morbidity parameters.

The lack of spatial patterns in the distribution of ITNs and morbidity parameters may be a result of imprecision in our tools and methods. Errors in ascertainment of geo-positions with non-differential GPS (Hightower *et al.* 1998) and net treatment with reliance on histories provide by relatives contribute to the limitations of the study. The area studied may have been too small to detect any spatial patterns. Work conducted in a wider geographical area indicated that children living on the fringes of the populated area had more disease (Abdulla *et al.* 2001). A further investigation of the spatial effects in a larger geographical area is therefore required.

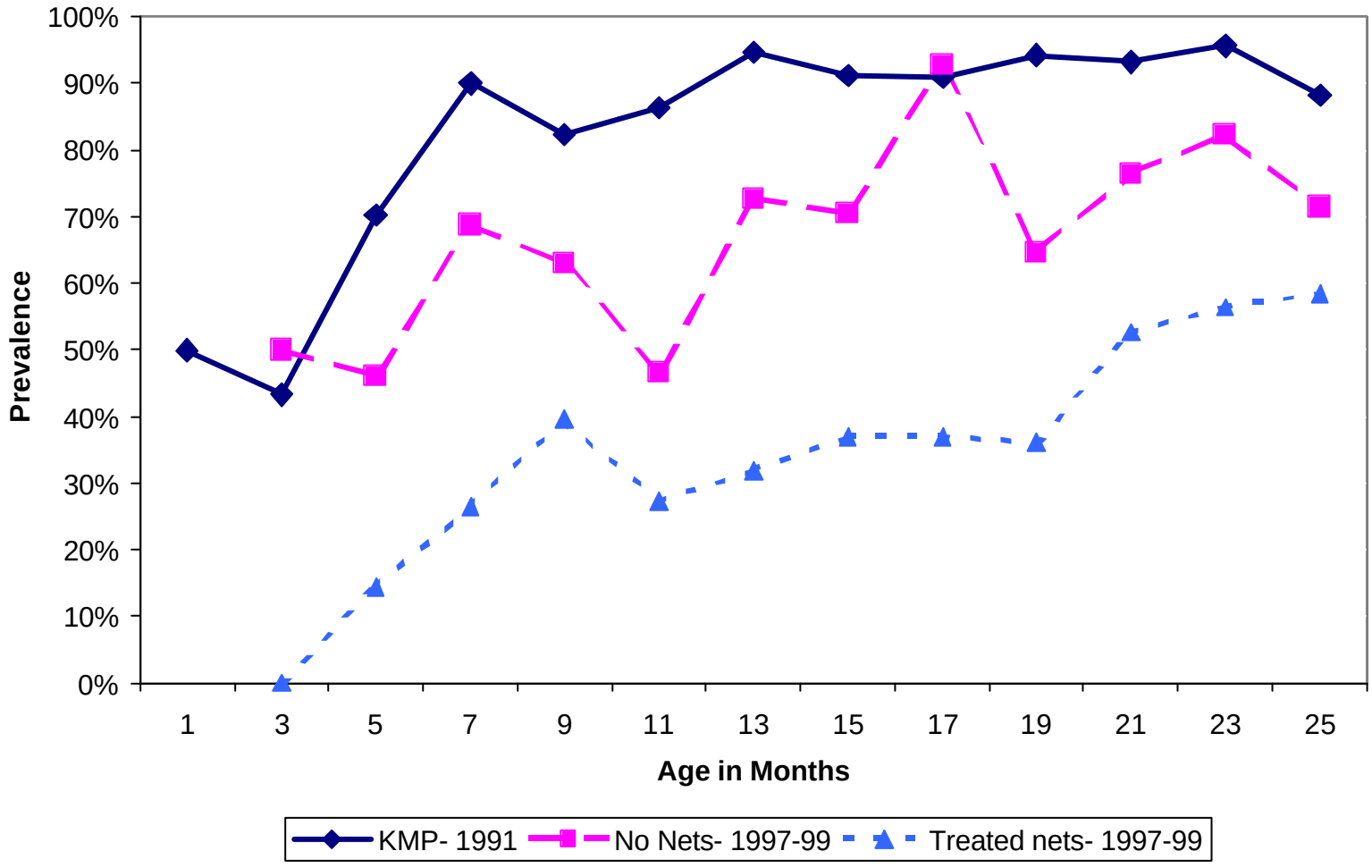
The results indicate that the social marketing campaign has managed to make the ITNs widely available even to those who live on the edge of the inhabited areas, where the risk

of malaria disease is likely to be concentrated (Binka *et al.* 1998). This may have led to some protection being conferred to those without nets and those with untreated nets. In Kenya, a lower risk of admission to hospital for malaria has been observed in children not using ITNs but living in areas with high ITNs coverage compared to those in areas without ITNs (Howard *et al.* 2000). This phenomenon has bearing on the estimated effectiveness of the ITNs observed in programme evaluations. The reduced risk for those near the ITNs will bias the measured effect toward zero if a simple comparison is made of users and non-users. Hence, estimates of effectiveness made by our program (Abdulla *et al.* 2001, Schellenberg *et al.* 2001) are likely to be conservative. Data was too sparse in our study to observe any increase or decrease of disease in those without nets, or examine the effects of those without nets living within different coverage levels or non users living in houses with treated or untreated nets. The cross-sectional survey conducted in a larger geographical area did not show any change in the prevalence of anaemia nor parasitaemia in those without nets in the three years of observation (Abdulla *et al.* 2001).

However, a comparison of the age specific parasitaemia prevalence rates with historical values show that the children both those with and those without ITNs had much less malaria in current studies than a decade ago (Fig 2). This trend indicates that a substantial reduction in malaria endemicity has occurred in the last decade. This may well represent a further beneficial effect of the social marketing program which has not been accounted for in evaluations to date.

We conclude that the social marketing of ITNs resulted in a relatively homogenous distribution of ITNs in the village. There are indications that coverage of ITNs was important in determining the prevalence of anaemia in children and high coverage produces higher impact of ITNs. Hence, efforts should be made to achieve high coverage in ITN programmes. In order to explore this important aspect further, analyses should be done in a larger geographical area together with entomological assessment.

Figure 2 : Age specific malaria parasite prevalence in the Kilombero valley 1991 and 1997-99



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PART III: TREATMENT OF UNCOMPLICATED MALARIA

CHAPTER 8

Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat acute falciparum malaria in Tanzanian children aged 1 -5 years

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Abstract

A randomized, open trial involving 260 Tanzanian children, aged 1-5 years, with acute *Plasmodium falciparum* malaria was conducted to evaluate the efficacy of the combination antimalarial CGP 56697 (artemether and benflumetol), and to compare it with chloroquine, the standard drug used for malaria treatment in the Kilombero area. Children who had received rescue medication within the first 48 h or had a negative slide at the same time were excluded. Seven-day parasitological cure rates were 94% (95% Cl 88-97.5) for CGP 56697 and 35.4% (95% Cl 25.9-45.8) for chloroquine. Using the same definition, the 14-day parasitological cure rates were 86.4% (95% Cl 78.5-92.2) for CGP 56697 and 10.3% (95% Cl 5.1-18.1) for chloroquine. Gametocytes were more effectively suppressed by CGP 56697 than by chloroquine. There were no major adverse events with either drug. CGP 56697 is highly efficacious against *P. falciparum* in this area of Tanzania. The study contributes to the discussion on treatment strategies, particularly whether chloroquine may still fulfil its role as first-line drug in an area of high malaria transmission and very high levels of chloroquine resistance.

Introduction

The development of *Plasmodium falciparum* parasites resistant to currently available antimalarial drugs is a main concern and problem confronting governments and health authorities. Whereas resistance of this parasite against quinine, mefloquine, halofantrine and other antimalarials exists in South-east Asia, the situation in Africa is also alarming despite susceptibility to the newer antimalarials. The efficacy of chloroquine, the most affordable drug on the continent with the highest morbidity and mortality due to malaria, is decreasing. The 7-day cure rate of a standard dose of 25 mg/kg of chloroquine given over 3 days was recently reported to be at 80% in the Kilombero area (Mshinda *et al.* 1996). Quinine resistance is also reported from some African countries (Adagu *et al.* 1996). It is estimated that the annual worldwide death rate from malaria will rise to 7 million if quinine-resistance reaches the same levels in Africa as it does in South-east Asia (Day 1996). Thus, a situation is approaching in many African countries where chloroquine can no longer be the recommended treatment for uncomplicated malaria, and where clinicians may encounter problems in treating small children with acute *P. falciparum* malaria with 3-days regimens of quinine (Kremsner *et al.* 1994). Alternative drugs must be evaluated for the potential challenges of treating this life-threatening disease in the most vulnerable groups of the African population.

CGP 56697 (artemether and benflumetol) is an oral, fixed dose combination of artemether, a semisynthetic derivative of arternisinin, and benflumetol, a synthetic racemic fluorene derivative developed by the Academy of Military Medical Sciences in Beijing. This combination was developed in China for the treatment of *P. falciparum* malaria (Olliaro & Trigg 1995). Artemether is of proven benefit in the treatment of Malaria, but recrudescence is common when it is used as a single agent (Bunnag *et al.* 1995). Benflumetol is also an effective antimalarial with a high cure rate, but is slower in action. The rationale for the combination of the two drugs is to combine the benefits of the fast onset of action provided by artemether with the advantage of the high cure rate associated with benflumetol, given as a short course of four doses over 48 h to foster compliance (unpublished observation). Studies with CGP 56697 on 196 Chinese adults achieved 4-week cure rates of 97.4% (unpublished observation). A similar trial in Thailand on 252 patients which compared CGP 56697 with mefloquine gave 4-weck cure rates of 69% and 82%, respectively (unpublished observation). CPG 56697, however, had a statistically significantly better parasite clearance time (43 h *vs.* 66 h), a faster fever clearance time (32 h *vs.* 54 h), and was more

than twice as rapid in gametocyte clearance (152 h *vs.* 331 h), the latter considered to be of importance in relation to containing malaria transmissibility. Limited data on the efficacy of CGP 56697 among 100 children aged 5-14 years are available from China. A 4-week cure rate of 93% was obtained with a reduced adult dose according to the children's age and weight. Oral CGP 56697 was well tolerated and no serious adverse events were reported. A pilot study of CGP 56697 in West African children aged 1-6 years with uncomplicated *falciparum* malaria showed a good tolerance of the drug (von Seidlein *et al.* 1997).

This communication reports on the first experience on CGIP 56697 in East Africa. Its potential as a reliable addition to the future armoury of antimalarial drugs was tested against chloroquine, the current first-Iine drug according to Tanzanian policy.

Study population and methods

Population

The trial population comprised boys and girls aged 1-5 years (body weight > 5 kg) with acute *falciparum* malaria. They were recruited from the 'mother-and-child' out-patient clinic at St Francis District Designated Hospital, Ifakara, Tanzania. A species prevalence of 93% for *P. falciparum* infections and a malaria related fever prevalence of 5% are reported in this area of permanent transmission among this age group (Smith *et al.* 1993*).* Inclusion criteria for selection were: age 1-5 years; body weight > 5 kg; microscopically confirmed *P.falciparum* infection, parasitaemia > 5,OOO/ml blood; fever (axillary temp 37.5 ^{o}C); living within 5 km of trial site; feasibility of participation and informed consent; not participating in any other trial. Ethical clearance was obtained from ethical committees of the Tanzania Commission for Science and Technology and from Basel University.

Exclusion criteria were parasitaemia < 5,000/ml; absence of fever; intolerance of oral medication; signs or symptoms of severe or complicated malaria; severe malnutrition or kwashiorkor; history of other antimalarial drugs within 48 h; known sensitivity to chloroquine; any known chronic underlying disease.

Each child eligible for the trial had a general medical examination and a medical history taken. The purpose and details of the trial were fully explained to the parent or guardian

and consent forms signed or fingerprinted. 260 children were randomized equally to the CGP 56697 or chloroquine treatment groups (130 to each).

Medication

The children in the CGP 56697 treatment group received 4 doses of paediatric tablets at 0, 8, 24 and 48 h, respectively. Each paediatric CGP 56697 tablet contained 10 mg artemether + 60 mg benflumetol (½ the adult tablet level)

and 1, 2, 3 or 4 tablets were given at the 4 dosage times according to body weight (5-10 kg body weight, 4 doses of 1 tablet; 10-15 kg, 4 doses of 2 tablets; 15-20 kg, 4 doses of 3 tablets; 20-25 kg, 4 doses of 4 tablets).

Children in the chloroquine treatment group similarly received 4 doses over 3 days, relating to body weight at 25 mg total per kg body weight (10, 5, 5 *&* 5 mg/kg) as follows: 5-10 kg, ½ tablet, followed by ¼ tablet at each of the next 3 doses; 10-15 kg, ¾ tablet, ½ tablet each dose; 15-20 kg, 1 tablet, ½ tablet each dose; 20-25 kg, 1½ tablets: ¾ tablet each dose (each tablet contains 150 mg chloroquine base).

The trial medication for each child was contained in an individually numbered blister pack. The contents (chloroquine or CGP 56697) were allocated randomly in blocks of 6. Medication was given whenever possible between meals. Mothers still breast feeding were encouraged to continue. Children who had rescue medication or had negative slides within 48 h after admission were excluded from evaluation. However, they were included in the ITT evaluation (Table 2).

Trial procedure

The trial was a randomized, open, parallel group, comparative, single centre investigation. Children were assigned treatment upon presentation by allocating the blister pack with the lowest available number. On entry (day 0), each child at the out-patient department (OPD) was screened for eligibility criteria and, following parental/guardian informed consent, the first dose was administered, with the child observed in the hospital over 2 h to check for vomiting. Eight hours after treatment started, a field worker (FW) visited the child at home and supervised the administration of the second dose, checked the axillary temperature (T) and completed an adverse events (AE) questionnaire. On Days 1 and 2 (24 and 48 h) the FW visited the patient at home, administered the third and fourth doses, checked T, took finger prick blood for microscopy and completed the AE questionnaire. On Day 3 (72

h), the FW went to see the patient, checked T, took fingerprick blood for microscopy, haematology and PCR and documented any AEs. On Day 7, the child attended OPD for neurological examination, T was checked and fingerprick blood for microscopy, haematology and PCR was taken; AEs were also recorded. On Day 14 a further follow-up was done at OPD, and investigations were done as on Day 7. A similar examination was conducted at OPD on Day 28.

Techniques

Giernsa-stained thick films were used to examine and assess levels of parasitaemia (thin films were only used to confirm presence of other *Plasmodium species).* Prior to patients' inclusion in the trial 20 thick film fields were examined; absence of *P. falciparum* excluded them from the trial. If asexual forms of *P. falciparum* were found, then 200 thick film fields were screened for the presence of malarial parasite species. Identification of *P. falciparum* was followed by a tally counter count of asexual forms and leucocytes. Present gametocytes were counted similarly.

All blood films were read twice, independently, and a third time if the ratio of densities from the first 2 exceeded 1.3 or was less than 0.67, or if one was positive and the other negative. A definitive result was based on a majority verdict for positivity and the geometric mean of the 2 closest positive density counts. A peer review of 282 slides was done. There was a 87% agreement in terms of negative/positive results between the 2 counts.

Urine samples were tested for chloroquine at baseline. Blood samples were taken for haemoglobin, haematocrit, WBC (total and differential) platelets and PCR confirmation of parasitaemia.

Casagrande's method was used for calculation of the sample size (George 1984). Assuming a 7-day parasitological cure rate of 95% for CGP 56697 and 80% for chloroquine, this gave a minimum requirement of 113 for each treatment group (α = 5%, β = 10%). The primary endpoint for the 7-day cure rate (evaluable patients) was defined as the proportion cleared of asexual parasitaemia within 7 days of drug initiation, without reappearance on Day 7. Failures were defined as those patients in whom (a) parasites were present on Day 7, or (b) rescue therapy was given after day 1, but within the first week, when parasites were still present. The primary end point for the 14- day cure rate was the proportion of patients cleared of asexual parasitaemia by Day 7 and without any

reappearance by Day 14. Secondary end points were defined as parasite reductions on Days 1, 2 and 3 and the proportion of children with a negative slide result.

The 95% confidence intervals (C1) for cure rates were calculated by using Pearson-Clopper limits. The 95% Cl for the difference in rates ($p_1 – p_2$) between CGP 56697 and chloroquine was calculated as:

$(p_1 – p_2) \pm u_{1-\alpha/2}\sqrt{[p_1(1 - p_1)/n_1] + [p_2(1 – p_2)/n_2]}$

together with the χ^2 test. For the parasite reductions on Days 1, 2 and 3, the median, 25th and 75th percentiles were calculated and treatment effects tested using the nonparametric Wilcoxon rank-sum test (Woolson 1987).

Results

Demographic and baseline data

During the recruitment phase, 1132 mothers were approached for screening the blood of their febrile children. Two mothers refused to participate in the trial. 454 children had negative slides and 81 children had already been given chloroquine within 48 h. 335 children had either a parasitaemia lower than stated in the inclusion criteria or were living more than 5 kilometers from the MCH clinic. Table 1 summarizes the baseline data of the 260 patients enrolled. None of the children died during the trial period. 21 patients were admitted during the period of the trial (CGP 56697: 7; chloroquine: 14). Premature discontinuations: 118 children were discontinued prematurely during the trial. Unsatisfactory therapeutic effect (96) was the main reason, followed by adverse reactions (8), lost to 'follow-up' (6) and withdrawal of consent (3). 5 had P. *falciparum* counts < 5,000/ml at enrolment and were excluded from analysis. In the CGP 56697 group 18.5% (24) discontinued compared with 72.3% (94) in the chloroquine group.

8 children did not receive the complete CGP 56697 course and only 108/130 completed the chloroquine course. 118 children (CGP, 25; chloroquine, 93) were treated with other antimalarials over the 28 day observation period. 7 in each group were treated for adverse events. All children received an antipyretic (paracetamol), 250 mg, twice daily, over the first 3-4 days. In addition, 183/260 (70.4%) received other medications as follows: ampicillin for bronchopneumonia; iron and folate for anaemia; erythromycin for ulcers or rashes. Co-trimoxazole was given to 2 children on chloroquine.

Efficacy of treatments

Seven-day parasitological cure rates are shown in Table 2. Forty-eight of the total ITT (Intention To Treat) patients had been discontinued from the trial by Day 7, most of them due to unsatisfactory treatment response, leaving 116 evaluable patients in the CGP 56697 group and 96 in the chloroquine group. Of the former, 109 (94%, 95 % CI 88-97.5]) were regarded as cured in terms of the primary end point of parasite clearance, as 6 patients had a positive slide on day 7 and 1 patient received rescue medication 3 days after treatment was started. 6 of the 7 children had parasites only on day 7 and were subsequently found to be negative, thus not becoming new illnesses. In the chloroquine group only 34/96 (35.4%, 95% CI 26-46) were free of parasites by Day 7. The 95% CI for the difference was [48.0, 69.1] ($P < 0.001$).

The related parasite reduction percentages and number of patients with negative blood film slides over Days 1, 2 and 3 are shown in Table 3 and Figure 1. These data relate to the secondary end points. Thus, by day 1, 121 of the CGP 56697 group had achieved 97.8% parasite reduction, rising to 100% by Day 3 (117 patients), compared to a 59% reduction in the chloroquine group on Day 1 (118 patients) to 95.9% (96 patients) on Day 3. The related negative/positive slide relationship is shown in Figure 1. 14-day parasitological cure rates are shown in Table 2. 95/110 (86.4%) of the evaluable CGP 56697 patients had no detectable parasites, compared with 10/97 (10.3%) of the evaluable chloroquine patients.

Table 1: Demographic and baseline data

	CGP 56697 (n=130)	Chloroquine (n=130)
Female/male ratio	1.03	0.61
Age (years) Median (range)	2 (1-5)	2 (1-4)
Weight		
Median	10.6	11.1
Range	6 – 20	7.5 – 18.3
Haematocrit (%)		
Median	31	29.4
Range	17 - 42	14 – 41
Previous malaria infection within 3 months (%)	48	41
Temperature		
Median	38.9	38.3
Range	37.3 – 40.9	36.8 – 40.9
Parasite density (/µl)		
Geometric mean	55017	53575
Range*	5644 - 674933	5124 – 373547

*excluding the 5 children with less than 5000/µl parasites

Table 2: 7 Day and 14 day cure rates

	CGP 56697	Chloroquine
ITT patients		
7 day cure rate (%)	83.8% (109/130)	26.2% (34/130)
Evaluable patients		
7 day cure rate	94% (109/116)	35.4% (34/96)
95% CI*	88 – 97.5	25.9 – 45.8
14 day cure rate	86.4% (95/110)	10.3% (10/97)
95% CI*	78.5 – 92.2	5.1 – 18.1

*using Perasons Clopper limits

Table 3 : Percentage parasite reduction on days 1,2 and 3 (ITT,using all available slides)

	CGP 56697	Chloroquine	Wilcoxon rank test
Day 1 (n = *)	121	118	
Median	97.8%	59%	*P* < 0.001
25 – 75th percentiles	88.7 – 99.8%	-1.9 – 79.8%	
Day 2 (n = *)	120	106	
Median	100%	81.8%	*P* < 0.001
25 – 75th percentiles	100%	45.3 – 96.8%	
Day 3 (n = *)	117	96	
Median	100%	95.9%	*P* < 0.001
25 – 75th percentiles	100%	81.6 – 99.9%	

(n = *) slides available for analysis

Table 4: Gametocytes on days 0,1,2,3,7

		CGP 56697		Chloroquine	
Day (Hours)	Gametocytes	n	%	n	%
0	Not detected	128	98.5	121	93.1
(6 h)	Detected	2	1.5	6	4.6
	Missing data			3	2.3
1	Not detected	114	87.7	112	86.2
(24 h)	Detected	7	5.4	6	4.6
	Missing data	9	6.9	12	9.2
2	Not detected	113	86.9	98	75.4
(48 h)	Detected	7	5.4	8	6.2
	Missing data	10	7.7	24	18.5
3	Not detected	111	85.4	89	68.5
(72 h)	Detected	6	4.6	7	5.4
	Missing data	13	10.0	34	26.2
7	Not detected	115	88.5	80	61.5
	Detected	2	1.5	8	6.2
	Missing data	13	10.0	42	32.3

Table 5: Haemoglobin levels

	% patients (n)			
	CGP 56697		**Chloroquine**	
	<8.0 g/dl	<6.5 g/dl	<8.0 g/dl	<6.5 g/dl
Day 0	16.3 (21/129)	6.2 (8/129)	23.4 (30/128)	10.2 (13/128)
Day 3	23.7 (28/118)	14.4 (17/118)	33.3 (32/96)	16.7 (16/96)
Day 7	19.8 (23/116)	3.4 (4/116)	31.5 (28/89)	6.7 (6/89)
Day 14	8.3 (9/108)	0.9 (1/108)	16.9 (12/71)	4.2 (3/71)

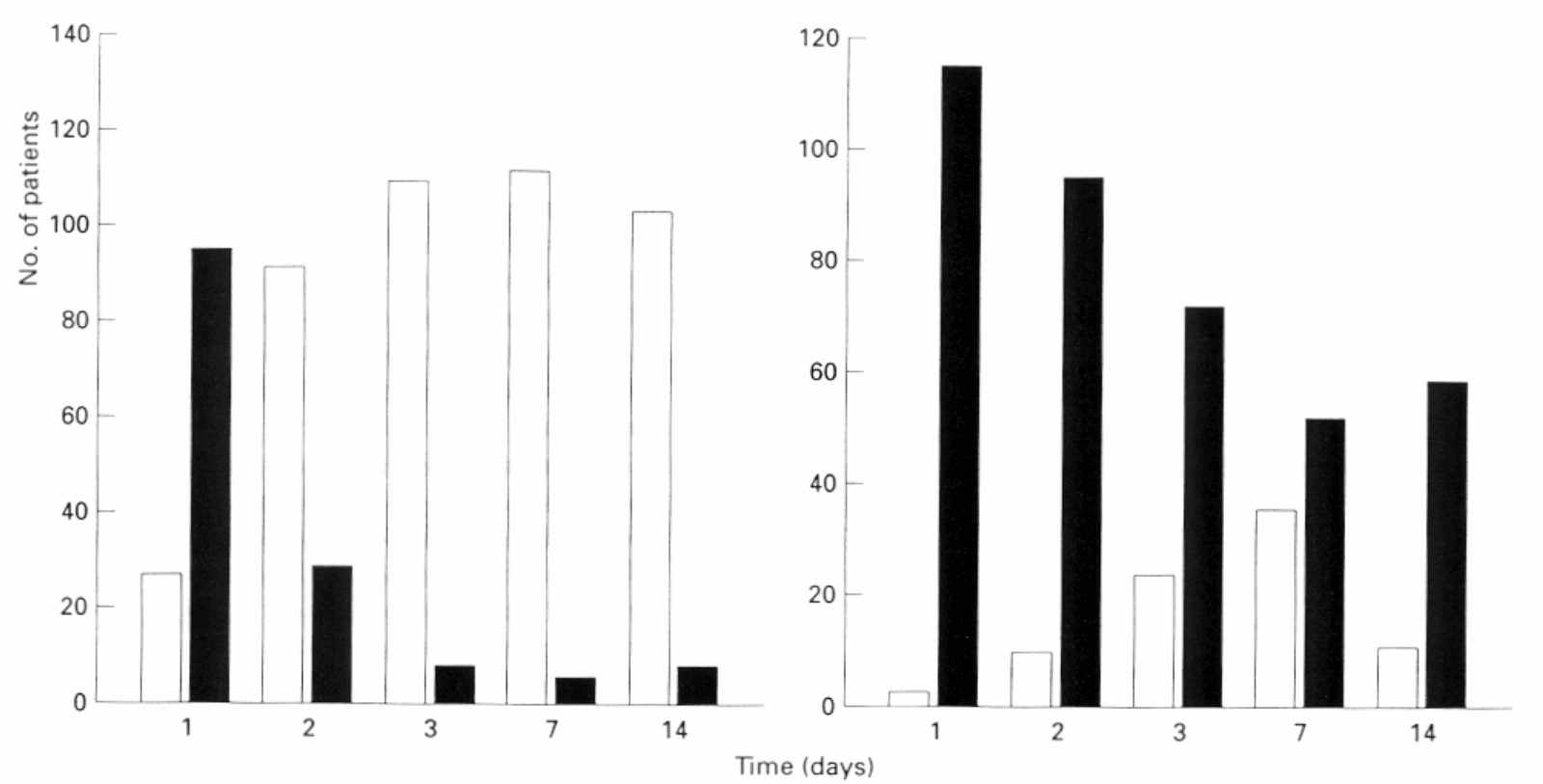

Figure 1 Number of patients with positive (■) or negative (□) blood film slides in (a) the CPG 56697 group and (b) the chloroquine group. All patients and all slides available before rescue medication was given were included, regardless of the evaluability criteria.

20 of the CGP 56697 patients were not evaluable for the 14- day cure rate. Those additional to the non-evaluables for Day 7 were patients who did not have a slide taken at the two week follow-up. Of the evaluable 110 patients of the CGP 56697 patients, 7 were recorded as failures from the first week, with another 8 failures by day 14. Of these 8 new cases, 3 had only one positive slide on this visit, but were subsequently negative without rescue medication. Thus only 5 children on CGP 56697, i.e. less than 5%, had early recrudescence. Four of the 8 children tested by PCR had confirmed new infections (Irion *et al.* 1998). For the chloroquine group the 62 failures from the first week had increased by a further 25 by Day 14.

Gametocyte counts are summarized in Table 4. Twelve patients (9.2%) on CGP 56697 and *15 (11.5%)* on chloroquine had gametocytes detected within the first 72 h (Days 0-2). By Day 7 the figures were 2 (1.7%) and 8 (9.1 %), respectively. The high drop-out rate for those on chloroquine made comparisons unreliable beyond Day 7.

Clinical features and adverse events: 48 h after treatment started, the temperature was still above 39 ^{o}C in 4 children from the chloroquine group, whereas all children treated with CGP 56697 had a temperature below 38 ^{o}C. The most frequent signs and symptoms reported at any time during the trial were unspecific signs and symptoms (abdominal pain, headache, rigors). 37% presented with coughing and 18% with diarrhoea. Sleep disorders occurred in 39% (CGP 56697) and 37% (chloroquine).

These signs and symptoms tended to disappear with treatment in both groups and resolved faster in the CGP 56697 group. No serious drug-related adverse events were recorded in either group of patients. There were no significant differences in the incidence of abdominal pain, fatigue, headache, vomiting, anorexia, diarrhoea or sleeping disorders between the 2 regimens, neither at the beginning nor with onset during the observation period. The overlap of malaria symptoms with drug-related adverse events was apparent as were confounding symptoms due to concomitant diseases. Minor drug-related adverse events included rashes in 3.8% (CGP 56697) and 3.9% (chloroquine), and pruritus in 0.8% (CGP 56697) and 6.2% (chloroquine).

Several laboratory parameters were affected by the patients' disease status at presentation. Table 5 lists the evolution of haemoglobin levels in the two groups. The anaemia worsened with the disease resolution, on Days 3-7, but improved thereafter in the

CGP 56697 group. Only about 50% of the children on chloroquine were still on study, as the other needed rescue medication and had dropped out. 40% of all patients had below normal platelet counts at baseline (<150 $\times$ 10^9/L), but by day 7, 95% had normal values. The laboratory parameters were consistent with the disease status at baseline, improving with disease resolution due to a successful response to drug therapy.

Of 157 children tested for chloroquine in urine at baseline, 97 (62%; CGP 56697: 59%; chloroquine: 67%; difference between the 2 regimens not significant) were positive, indicating recent medication. The presence of chloroquine in the urine at baseline was not related to the cure rates at 7 and 14 days in either group. However, it seemed to positively affect the 28 days cure rate by as much as 23% in the CGP 56697 group (14/30 children without *vs.* 29 of 42 with detectable chloroquine). The full evaluation of the parasite genotype dynamics using PCR technology is presented elsewhere (Irion *et al.* 1998*).*

Discussion

The efficacy of artemether-benflumetol (CGP 56697) in the treatment of acute falciparum malaria in young children (age 1-5 years) was compared with that of chloroquine, the presently used standard drug in this area. The parasite reduction rate found was 97.8% at 24 h rising to 100% on Days 2 and 3 (compared to 59% at 24 h rising to 81.8% and 95.9% for chloroquine). These results were paralleled by rapid reductions of fever in the CGP 56697 group, which was slower with chloroquine, with temperature still elevated in some patients 24-48 h after treatment started. The 7-day cure rate of 94% and the 14-day cure rate of 86.4% (compared to 35.4% and 10.3% % for chloroquine) showed a similar efficacy in young Tanzanian children to that in 100 Chinese children, aged 5-14, where a 28-day cure rate of 93% was recorded (unpublished data). Taking into account all parasitological and PCR findings of the children treated with CGP 56697, the recrudescence rate by day 14 was found to be below 5%.

Irrespective of the type of drug, the children in this trial suffered a series of mostly mild adverse events. One common adverse event not drug-related and noted in 37% of all patients was a dry, unproductive cough at baseline, which appears to be a symptom associated with the disease. Interestingly, a further 40% of all patients developed this symptom after treatment onset: some of them had another episode, some newly reported this symptom after baseline. This phenomenon has been reported previously in India

(Kulkarni 1996). Its pathogenesis may be related to cytoadherence ligands (Smith *et al.* 1996) but the mechanisms are unclear.

The haematological figures were similarin both groups, as was the anaemia at presentation. Both are features of the disease which improved with response to successful therapy.

Gametocyte reduction levels can be considered a very important feature of antimalarial drug therapy. The ability to rapidly suppress gametocyte formation is important in some endemic areas in reducing transmissibility. Arternisinin and its derivatives reduced gametocytes 8-fold in primary infection and up to 18-fold in reinfection, compared with mefloquine (Price *et al. 1996).* The authors suggested that the 50% drop in malaria on the Thai/Burmese border in 1994, coinciding with use of artesunate, reflected its antigametocyte activity rather than the benefits of its treatment efficacy on clinical malaria. In our study 12 children (9.2%) on CGP 56697 and *15 (11.5%)* on chloroquine had gametocytes detected over the first 72 h (Days 0-2, Table 4). By Day 7,1.7% of the CGP 56697 group were positive for gametocytes as against 9.1 % of the chloroquine group, emphasizing the beneficial effect of the former in suppressing gametocyte formation. This confirms the trend observed in other studies. The epidemiological impact of this gametocidal activity remains to be established. It may merit carefully designed intervention studies in holoendemic settings in Africa.

The results of this study, in relation to previous investigations (Koella *et al.* 1990; Mshinda *et al.* 1996), confirm that chloroquine resistance is of growing concern in this area of Tanzania. These papers suggested that resistance may be a reflection of the immunological status. This is also supported in this study by the fact that recrudescent infections appeared in chloroquine-treated patients who initially showed higher parasite densities than patients who cleared parasitaemia (data not shown). In addition, a higher drug pressure in the periurban study site, and the higher parasite densities may have contributed to the surprisingly higher failure rate than the one found in a rural community of the Kilombero area by Mshinda *et al.* (1996). Hence, chloroquine may not be an efficacious first-line drug for uncomplicated *falciparum* malaria in this area of Tanzania.
In conclusion, the combination therapy of artemether- benflumetoi (CGP 56697) was shown to be a highly efficacious antimalarial therapy for young Tanzanian children aged 1-5. It achieved a 94% cure rate, accompanied by rapid parasite reduction and clearance

rates. 6 of the 7 cases with parasites detected on day 7 were positive only on that day and had subsequently no parasites. This is an important point when considering the likely span of useful therapeutic life of this drug.

CGP 56697 also showed some antigametocyte activity, which may be of some importance in limiting malaria transmission. It is recommended as an efficacious
antimalarial which may be particularly important to prevent the development of severe *falciparum* malaria.

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CHAPTER 9

Distinction of recrudescences from new infections by PCR-RFLP analysis in a comparative trial of CGP 56697 and chloroquine in Tanzanian children.

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Abstract

Objective

To test the efficacy of a new compound drug (CGP 56 697) against acute, uncomplicated falciparum malaria.

Method

Reappearing parasites were analysed by PCR-RFLP within a randomized controlled trial. 130 patients received chloroquine and 130 patients were treated with CGP 56 697. Samples from 96 patients with parasitological failure were tested by PCR-RFLP for MSP2 of *Plasmodium falciparum.* Seven days after treatment 32 patients of the chloroquine control group with reappearing parasites were tested by PCR and one infection was unequivocally determined as a new infection. After 7 days, in the CGP 56 697 group, 6 samples were tested in which one new infection was identified. Similar observations were made one and three weeks later in both groups.

Results

Although a high multiplicity of infections on admission was observed, there was no significant correlation between multiplicity and either recrudescence or new infection. Patients in both treatment groups with subsequent recrudescent parasites had higher initial mean parasite densities than patients who cleared. Those of the patients with recrudescent parasites who were treated with CGP 56 697 had higher initial parasite densities than those treated with chloroquine. The rate of re-infection increased with time as expected in holoendemic areas and appeared to be higher in chloroquine patients. Generally, CGP 56 697 showed a superior clearance rate, successfully cleared higher parasite densities and suppressed new infections over a longer period of time.

Conclusion

The PCR analysis confirmed that reinfections beyond day 7 are significant in areas highly endemic for malaria and showed the necessity of excluding these when estimaring 14 day clearance rates. Provided new infections are excluded, the 28-day clearance rate can also be used to determine the efficacy of antimalarial drugs in highly endemic areas, and adds to our knowledge of drug resistance and dynamics of infections in people living in such areas.

Introduction

For the last 50 years chloroquine has been an efficient drug with low toxicity for treatment of malaria in most tropical countries. Since the first report of chloroquine resistance from eastern Africa in 1978, it spread rapidly all over the continent (Henry *et al.* 1994). Today about 50% of African *Plasmodium falciparum* strains are resistant to chloroquine, but the pattern of resistance varies with geographical location (Creasey *et al.* 1990). In Ifakara, Tanzania, where this trial took place, 20% of *P. falciparum* strains were reported to be resistant to chloroquine in 1988 (Koella *et al.* 1990). In the present trial, the 7-day cure rate of chloroquine was found to be only 30% (Hatz *et al.* 1998).

Currently there is general agreement that combination treatment with two differently acting drugs should be considered (Peters 1987). One drug should be fast-acting with a short half tife to reduce parasite numbers quickly, the other should be slow-acting and possess a long half life (White & Olliaro 1996). The use of both drugs in conjunction both provides effective treatment and reduces the chance of recrudescence. The data presented here derive from an efficacy trial of such a combination drug made of artemether and benflumetol (CGP 56 697) (Hatz *et al.* 1998).

Artemether is a semisynthetic chiral compound derived from the Chinese medical herb qing hao *(Artemisia annua L.)* which had been used as malaria treatment for centuries (Qinghaosu Antimalarial Coordinating Research Group 1979). Since the rediscovery of artemisinin in 1972 (Klayman 1985), severat studies have been conducted with different derivatives in tropical countries (Arnold *et al.* 1990; White *et al.* 1992). The common results of these studies are shorter parasite clearance times and shorter fever clearance time than with any of the other antimalarial drugs.

In addition, artemisinin and its derivatives are effective against chloroquine-resistant strains (Qinghaosu Antimalarial Coordinating Research Group 1979; Bunnag *et al.* 1991) and antigametocydal (Price *et al.* 1996). Since artemisinin and its derivatives have a high recrudescence rate (Qinghaosu Antimalarial Coordinating Research Group 1979), it can only effectively be used when combined with another long-acting drug, in this case benflumetol. There is little published data available on benflumetol. It was developed by Chinese scientists at the Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences (AMMS), Beijing and registered in 1991 (Acaderny of Military

Sciences 1993). Antimalarial, blood schizontocidal activity was reported (Wernsdorfer *et al.* 1996). A study in China with CGP 56 697 on 100 children aged 5-14 years reported a 28-day cure rate of 93% (Liu *et al.* 1995). A study of 5 to12 year-olds is in progress in Thailand, where CGP 56 697 is being tested in cornparison to oral quinine treatment.

The appearance of parasites in peripheral blood after treatment may be taken as proof of failure in areas with low transmission, where reinfections are likely. However, in areas of high endemicity, appearing parasites may originate from a new infection and presence of parasites cannot be taken solely as proof of recrudescence. Microscopy can readily determine parasite species and densities, but is not able to distinguish between recrudescent or new infections. Hence, for drug trials in highly endemic areas, methods to identify individual parasite infections must be developed in order to distinguish between true relapses or new infections. Techniques applying PCR restriction fragment length polymorphism (RFLP) to a polymorphic locus will allow such identification (Felger *et al.* 1993). In this study we applied PCR-RFLP for the MSP2 (Merozoite Surface Protein 2) locus, coding for a polymorphic plasmodial membrane protein, to unequivocally identify recrudescent or new infections after drug treatment. MSP2 amplification and distinct restriction patterns in conjunction with extensive sequence information allow the discrimination of almost all different genotypes found (Thomas *et al.* 1990; Smythe *et al.* 1991; Felger *et al.* 1993, 1997).

Patients and methods

Study design

This was a randomized, open, comparative, single centre trial to compare the efficacy and safety of a new oral combination, CGP 56 697, with chloroquine, the current treatment in Tanzania for uncomplicated acute *falciparum* malaria. The study was conducted in lfakara, Tanzania, a holoendemic area with perennial transmission (Hatz *et al.* 1998). Patients were children aged 1-5 years living within 5 km of the out-patient clinic of St. Francis Hospital, lfakara. They were treated either with chloroquine or CGP 56 697. A total of 260 children were enrolled in the efficacy study (130 in each group). Finger prick blood samples for PCR were taken on day 0 (day of treatment), day 3, day 7, day 14, and when possible on day 28.

At each of the three time points (days 7, 14 and 28) blood samples from a subset of parasitological failures were used for PCR analysis. Samples could not be analysed from all failures because many had already received rescue medication. Conversely, multiple samples were included from patients who were defined as parasitological failures at repeated surveys but who remained asymptomatic and hence were not treated.

DNA preparation and PCR

Five µl of blood were lysed in 50 µl GTC solution (4 M guanidine-isothiocyanate, 25 mM Na citrate pH 7.0, 0.5% Na sarcosylsulphate), 5 µl β-mercaptoethanol, and mixed with 50 µl TE saturated phenol and 50 µl chloroform. The aqueous phase was separated, precipitated with isopropanol and DNA redissolved in 30 µl H_20.

A nested PCR was performed as described elsewhere (Saiki *et al.* 1988). Briefly, *5* µl of DNA were used for the primary reaction and 2 µl of PCR product for the nested reaction in a 100 µl reaction composed as follows: 10 mM Tris pH 8.8, 50 mM KCI, 1.5 mM $MgCl_2$, 0.25% Tween 20, 0.2 mM each dNTP, 0.5 pM each primer, 1.25 U taq polyrnerase. Primer pairs used were S2 and S3 for the primary reaction and S1 and S4 for the nested reaction as published by Foley *et al.* (1992). Both PCR reactions were performed in a Perkin Elmer Thermocycler 480 with the following profile: 5 min at 94 ^oC and 30 cycles: 1 min at 94 ^oC, 2 min at 55 ^oC, 2 min at 70 ^oC. Negative controls were included with each set of PCR reactions.

The different MSP2 alleles were genotyped as previously described (Felger *et al.* 1993). 20 µl of nested PCR product were subjected to restriction digests with the restriction enzymes Ddel, Rsal, Hinfl, ScrF1, respectively, and tun on a 10% polyacrylamide gel. All digests of one restriction enzyme were loaded side by side for all samples of an individual patient and sizes were calculated using a standard commercial size marker. RFLP patterns were visualized by ethidium bromide staining and documented electronically. All gels were analysed by two independent researchers.

Data analysis

Patients were included in the efficacy analysis as parasitological failures if they were parasite-positive by microscopy or if rescue medication (quinine) had been required at or before the respective time point. They were included as treatment successes if an

aparasitaemic sample (by microscopy) was available for the time point and no other parasites had been recorded between completion of treatment and collection of that sample. Genotypes found by PCR either in samples from day 0 or day 3 were considered to be present initially and considered as baseline. Recrudescence was deemed to have occurred if the RFLP pattern of an allele seen at baseline (day 0 and/or day 3) was detected by PCR on any consecutive follow-up day. New infections were defined as having completely different RFLP patterns in follow-up samples from those seen at baseline. Hence, new infections with the same MSP2 genotype would have been considered as recrudescences. Estimates of recrudescence and new infection rates were made separately for days 7, 14, and 28 (Figure 1). For each day, the recrudescence rate was estimated as the proportion of tested samples found by PCR to contain recrudescent parasites, multiplied by the failure rate (failures/total patients included) for that day. A similar calculation was carried out for patients defined by PCR as being newly infected.

Results

In the population enrolled for the study in Ifakara, the 7-day and 14-day parasitological cure rates for chloroquine were 35.4% and 10.3%, respectively, and for CGP 56 697 94% and 86.4% (Hatz *et al.* 1998). Our analyses consider a rather more inclusive group of patients (Table 1) than those of Hatz *et al.* (1998) did: we also included patients whose parasitaemia never cleared. The numbers of patients who were thus included in the analyses, and the numbers for whom samples were analysed by PCR-RFLP for each time point are shown in Table 1. The relative efficacy of chloroquine was even poorer when these early failures were included (Table 1), and by day 28 the cure rate was only 5% with chloroquine compared to 64% with CGP 56 697.

In 82.5% n = 83) of the samples tested by PCR, multiple infections were detected throughout the observation time.

Table 1: Patients with microscopically detectable parasites on follow-up days, PCR results, and estimated cumulative recrudescence- and new infection-rates

Drug	CGP 56 697			Chloroquine		
Day	7	14	28	7	14	28
number of patients included	118	113	118	115	116	119
n failures (%)	9 (7.6)	18 (15.9)	43 (36.4)	81 (70.4)	106 (91.4)	113 (95.0)
n failures tested by PCR	6	7	23	32	52	44
n with recrudescences only	2	2	3	21	20	17
n with recrudescences and new infections	0	1	7	10	27	20
n with new infections only	1	4	12	1	5	6
n PCR negative	3	0	1	0	0	1
% of tested patients with recrudescences	33.3	42.9	43.5	96.9	90.4	84.1
estimated % all patients with recrudescences	2.5	6.8	15.8	68.2	82.6	79.9
% of tested patients with new infections	16.7	71.4	82.6	34.4	61.5	59.1
estimated % of all patients with new infections	1.3	11.4	30.1	24.2	56.2	56.1

* Patients were counted as failures for the 7- (14-, 28-) day cure rate if parasites were present at any time point after day 3, or if rescue medication was given before the respective observation period. For further details see patients and methods part.

Table 2: Mean multiplicity[1)] of initial infections in patients with recrudescent or new parasites by treatment group.

	CGP 56 697			Chloroquine			
	n	mean multiplicity	std err	n	mean multiplicity	std err	p=[2)]
new infections	17	2.5	0.3	2	1.5	1	0.27
recrudescent	13	3.3	0.3	56	3.0	0	0.28
Wilcoxon p=[3)]		0.11			0.14		

[1)] multiplicity refers to the number of different genotype pattern identified in one sample.
[2)] Wilcoxon's test compares between treatment groups within patients with new infections or with recrudescent infections.
[3)] Wilcoxon's test compares between new infections and recrudescences within treatment group.

Table 3: Representative examples of infection dynamics with recrudescent and new infections after Chloroquine or CGP 56 697 treatment

Patient #	day 0	day 3	Day 7	day 14	day 28	Infection (R/N)	patient (R/N)	drug (CGP/CQ)
85	**Wos6** Wos34 Wos12 Ifa34 3D7(330)	Wos6 **K1**	**Wos34** Wos12	Wos34 Wos3 **K1**	**Wos6** Wos34 Wos12 Wos3 **K1** 3D7(250) 3D7(320)	R R R N R C N N C	R	CQ
68	**K1** **Wos12** 3D7(340)	K1 Wos12 3D7(410)		K1 Wos12 3D7(340)	**K1** **Wos12** 3D7(390) 3D7(410) 3D7(500)	R R R N R N	R	CGP
230	**3D7(380)**	**3D7(380)**		D10 3D7(330) 3D7(480)	**D10** Wos12 3D7(330) 3D7(370)	N N N N C N N	N	CQ
181	Ifa30 3D7(430)	3D7(430)		K1	K1	N C C	N	CGP

3D7 infections (except sequenced genotypes) were defined by their fragment size after Hinf I digest. Genotypes printed in bold face appeared as comparatively dominant PCR products and underlined genotypes with strong PCR products, the remaining genotypes were comparatively weak. (R=recrudescence, N=new infection, C=cleared infection, CQ=Chloroquine, CGP=CGP 56 697) shaded=microcopy negative=clearance of parasites

Table 4: Initial geometric mean density in patients with recrudescent or new parasites by treatment group.

	CGP 56 697			Chloroquine			
	geom. mean density (parasites/µl blood)	95 % confidence limits		geom. mean density (parasites/µl blood)	95 % confidence limits		
		lower	upper		lower	upper	p=[1)]
Cleared or new infections	49000	39000	61000	22000	10000	47000	0.08
Recrudescent	73000	49000	108000	50000	39000	66000	0.31
Wilcoxon p=[2)]	0.06			0.05			

[1)] Wilcoxon's test compares between treatment groups within patients with new infections or with recrudescent infections.
[2)] Wilcoxon's test compares between new infections and recrudescences within treatment group.

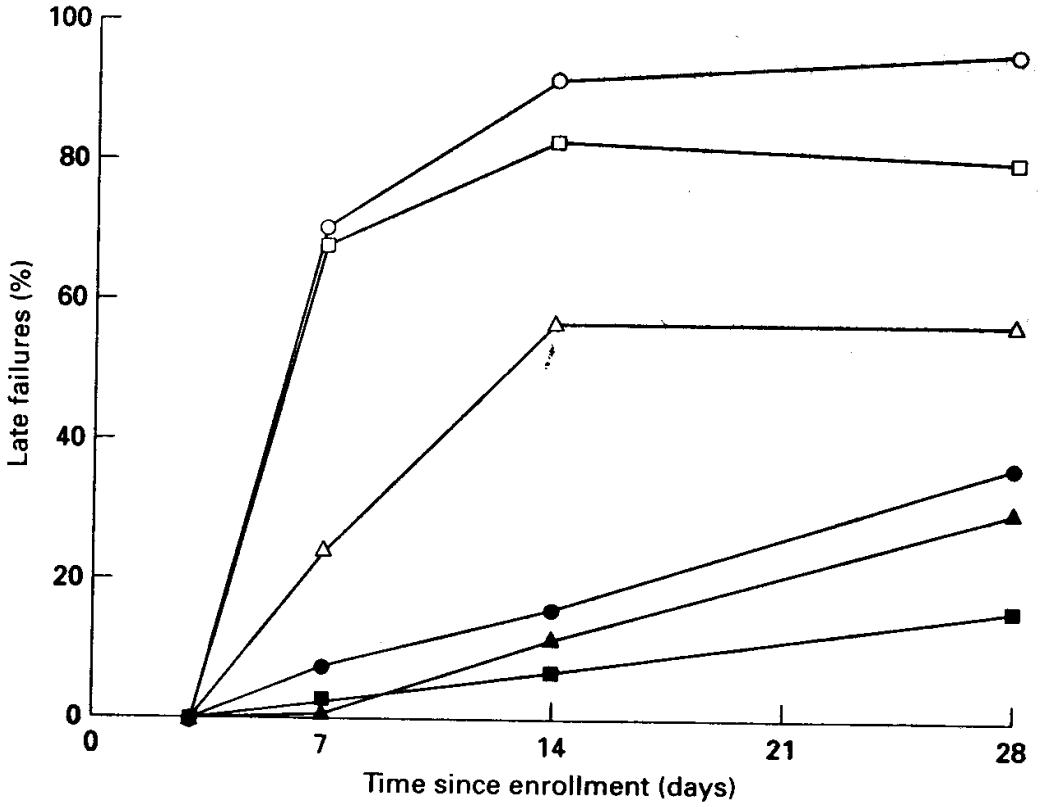

Figure 1 Calculated recrudescence rates and new infection rates for the population of the efficacy trial in Ifakara. Percentages were calculated from data of PCR analysed samples. The results from these samples have been used for the estimation of recrudescence and new infection rates of all included patients (for details see methods part). Open symbols represent individuals treated with Chloroquine, closed symbols represent individuals treated with CGP 56 697.
○, ● total defined failure rate;
□, ■ recrudescence rate as calculated from PCR results; △, ▲ new infection rate as calculated from PCR results.

Mean multiplicity of infection (number of allele types detected) at baseline and on follow-up days in the two comparison groups is shown in Table 2. In agreement with other studies (Feiger *et al.* 1994; Contamin *et al. 1995,* 1996; Ntoumi *et al.* 1995; Robert *et al. 1996;* Beck *et al. 1997)* there was extensive MSP2 allelic diversity. 54 different genotypes of MSP2 could be identified by PCR-RFLP at baseline. The most frequent of these were Wos 12 (14%), Wos 6 (6.6%), $3D7_{(340)}$ (5.8%), $3D7_{(330)}$ (5.6%), and KI (5.3%). Five additional genotypes were found only in follow-up samples.

In two patients, a genotype which was subsequently found recrudescent, was found on day 3 but not on day 0. In all other cases, recrudescent parasites were already found on day 0. Four representative examples of the dynamics of infection are shown in Table 3. The genotype pattern specific for the recrudescent parasite persisted in 66% of patients with recrudescent parasites until day 28 (often as the most dominant PCR band). In 4% and 9%, RFLP patterns persisted until day 25 or 20, respectively. In only 7% and 13% of the patients the RFLP pattern disappeared without rescue treatment after day 7 or 14, respectively. However, besides recrudescent parasites, new genotypes appeared additionally during the follow-up period (new infections). The sample of these patients had to be defined as recrudescent due to the persistence of one genotype found at enrolment. Table 1 lists the number of samples with microscopically detectable parasites, recrudescences and new infections, for both groups on each day. From these results, the estimated recrudescence and new infection rates are given in Figure 1. Initial mean parasite densities in both treatment groups were higher in patients with subsequently recrudescent parasites (Table 4). Mean parasite density at admission in patients with subsequent recrudescences was higher in patients treated with CGP 56 697 than in patients treated with chloroquine(Table 4).

Discussion

An analysis of the infection dynamics after drug treatment was performed using parasite genotype date in a comparison trial of chloroquine and CGP 56 697 treatment for nonsevere malaria. In areas with high endemicity for *Plasmodium falciparum,* such as in the Kilombero valley, Tanzania, where individuals receive > 300 infective bites per year (Smith *et al.* 1993), re-appearance of parasites alone after treatment cannot be taken as indicator of recrudescence. Both drugs used in the trial are known to be inactive against hepatocytic parasite stages, therefore they would not affect the development of new blood

stage infections immediately after drug concentration decreases. Thus techniques to unequivocally identify individual parasite infections are needed. We used MSP2-RFLP genotyping which has been proven to have sufficient discrimination power to identify most individual infections (Beck *et al.* 1997). In areas, where multiple infections are frequent, this technique proved to be equal to multiloci analyses (Snounou & Beck 1998). We are aware that PCR analysis could miss some genotypes, if single samples were used to characterize each episode. This could happen either because of suppression of concurrent low density infections by a superimposed high density infection, or because of sequestration of infected erythrocytes at the time of sampling. We decided to use as baseline both day 0 and day 3. Although in many samples genotypes appeared at day 3 which were not seen at day 0, these genotypes recurred in only two patients and were defined as recrudescence. In all other cases, the genotypes of recrudescent parasites were already contained in the day 0 RFLP pattern. The extent of resistance against a given drug can only be estimated if re- infections can be excluded. In this trial, after chloroquine treatment only 3.3% of all parasites appearing up to 28 days were new infections, indicating the inability of chloroquine to clear parasites completely. But recrudescent parasites, especially those with high allele frequencies, could also be reinfections with the same parasite genotype. In contrast to chloroquine treatment, 45.5% of parasites appearing after CGP 56 697 treatment were new infections.
The usefulness of analysing 28-day cure rates has often been disputed, in particular in areas of high endemicity, where new infections are very likely to occur within 28 days. But in this study, only 22% of the observed parasites were shown to be new. The remainder still comprised recrudescent parasites and must be considered as late failures, hence making the 28-day cure rates a useful outcome measurement.

The dynamics of individual infections, with persisting genotypes, disappearing genotypes, and new genotypes all appearing within one sample, raises the question whether the persistent or the new infection is clinically significant. Since in multiple infections, quantification of PCR products may not be correct, we can only speculate that the dominant infection would result in a dominant PCR product. In all but 8 cases, the dominant PCR product at recrudescence was already contained within the baseline samples. With caution, this may imply that in most cases the recrudescent infection might be responsible for the major parasitaemia and perhaps for the clinical presentation.

Initial parasite genotypes able to persist after treatment might be explained by the fact that any drug, in particular artemisinin derivates, only reduce the parasite load (White & Olliaro 1996) and remaining parasites might undergo a quiescent stage (Kyle & Webster 1996). In case of recrudescence, it has to be assumed that benflumetol, the slow-acting component of CGP 56 697, was not able to eliminate those quiescent stages completely It has been debated whether true resistant parasites against a given drug must exist (Nakazawa *et al.* 1995), but the above hypothesis would allow recrudescences without genetically manifested resistance against the drug. The mode of action of benflumetol is not yet understood, as it is not known for how long quiescent parasites can survive in the host. Nevertheless, the high cure rate and comparatively low recrudescence rate of CGP 56 697 give strong support to the notion of using compound drugs in the treatment of falciparum malaria. This is supported by the fact that the mean density of initial infections was much higher in recrudescences seen in the CGP *56 697* group than in the chloroquine group. Also, the higher initial parasite density between those who experienced recrudescences and those who cleared the infection in the CGP 56 697 group adds to the argument that CGP 56 697 can eliminate larger numbers of parasites, but apparently fails to clear very high densities, resulting in recrudescence of the remaining parasites. It may be speculated that the slow-acting compound of CGP 56 697 (benflumetol) suppresses new infections for much longer than chloroquine, as can be seen in Figure 1, where the rate of new infections is much higher in the chloroquine group.

The fact that multiplicity of initial infections has no influence on whether a patient experienced a recrudescence, clearance or new infection, would also support the above hypothesis. The failure to observe any association might be due to the small size of the comparison group, since few patients had new infections only. No samples were tested from patients who were parasite-negative over the full observation period. High initial parasite densities do predict recrudescence. This is quite compatible with the absence of a correlation between multiplicity and recrudescence because densities were not correlated with multiplicity. Sometimes many parasite genotypes simultaneously persisted, so persistence cannot merely be a consequence of high load of a single parasite genotype. These recrudescences might be due to insufficient resorption of the drug or drug consumption by parasites, and not to true genetic resistance. In conclusion, identification of recrudescent parasites after drug treatment may not only help to estimate drug efficacies more precisely, it also adds to our knowledge of drug resistance and dynamics of infections in people living in highly endemic areas.

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CHAPTER 10

Challenges and Recommendations: The Development Of Antimalarial Policy in Tanzania

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Introduction

Early and effective treatment is one of the main pillars of malaria control, and is the most widely implemented strategy to control the disease in tropical Africa. However, the worsening problems of drug resistance in many parts of the world have led to increasing difficulty in making decisions on the choice of antimalarial drugs to be used in implementing the early treatment strategy. In Tanzania, the Ministry of Health is currently in the process of reviewing the national malaria treatment policy. This paper discusses some of the challenges of developing such a treatment policy. It focuses on chloroquine (CQ) and sulphadoxine/pyrimethamine (SP) which are the main antimalarials currently being discussed in Tanzania. However, the issues raised are also relevant to other types of antimalarials.

Conceptual framework

Few publications are available on the issue of policy-making for malaria control. A few countries in Africa have already reviewed their policies (Schapira 1989, Fevre & Barnish 1999). The World Health Organisation Regional Office for Africa, (WHO-AFRO) is in the process of developing a framework for changing malaria treatment policy, highlighting the issues to be considered for the policy review process in a country. The issues identified include the objective of malaria treatment, efficacy of antimalarials assessed at the national sentinel sites, treatment-seeking behaviour for malaria, and cost-effectiveness analysis (WHO-AFRO 1999).

To simplify the understanding and the description of the reasoning behind the decisions in the process of changing a malaria treatment policy, we propose a triangular interactive framework (Fig 1)**,** which has clinical, epidemiological, and economic and health system dimensions. The clinical dimension incorporates all the factors that influence the occurrence of the disease and its complications. It also encompasses the choice of antimalarials used to treat cases of disease, and issues concerning their efficacy and safety in different populations. The epidemiological dimension refers to the question of the prevalence of different *Plasmodium* strains, and the status, development and spread of resistance to antimalarials. It also includes consideration of the geographical distribution of

malaria transmission and the resultant burden of disease in a population. The economic and health system dimension comprises intrinsically intertwined factors, which include health-seeking behaviour patterns, costs and cost-effectiveness, levels of health care, the infrastructure of the health system, structures for decision-making, and the decision making processes. The following paper reviews information on all three dimensions that could assist the policy review process in Tanzania.

Clinical dimension

Objective of malaria treatment

The goal of most of the national malaria control programmes in Africa is to reduce morbidity and mortality associated with malaria. But most programmes have not yet defined the objective of malaria treatment precisely. This poses some problems during the review of treatment policy (Bloland & Ettling,1999). Defining the objectives of treatment will assist in determining whether the recommended drugs reach the goal of therapy, and will also help to establish criteria for deciding what levels of resistance or failure can be tolerated.

It has been suggested that the objective of malaria treatment may vary according to the level of malaria endemicity. In this view, parasitological clearance is considered to be essential only in areas of low transmission, whereas in areas of intense transmission the aim should be clinical cure; that is, clearance of signs and symptoms and prevention of clinical recrudescence 14 days after treatment (WHO 1994). The underlying assumption is that in areas of intense transmission, clearance of acute symptoms can prevent the bulk of severe disease and mortality even without parasitological cure (Hoffman et al 1984, Brandling-Bennet et al 1988).

The problem with this view is that it underestimates the contribution of persisting parasitaemia to morbidity (for example anaemia) and mortality. Studies in the Kilombero district, Tanzania, an area of intense malaria transmission, have shown that the clearance of peripheral parasitaemia during treatment of children under five years is beneficial, as it reduces the risk of developing a further clinical episode (Kitua et al 1996). Kitua et al. also demonstrated the importance of low level parasitaemia for the occurrence of anaemia in children (Kitua et al 1997). In Bagamoyo, an area where the clinical treatment failure rate

is 50%, not only was there a severe fall in haemoglobin concentration in children who had early treatment failure (Ekvall et al 1998), but even in children successfully treated with CQ there was no improvement in haemoglobin concentration. Similar observations on the failure of CQ to produce haematological recovery were recorded in Kenya and Malawi (Bloland et al.,1993, Verhoeff et al., 1997, Brabin & Ganley 1997).

Severe anaemia contributes directly to mortality in women and children (Stoltzfus et al 1997), though it is hard to assess the magnitude of the problem, since anaemia is not widely recognised in the community as a life-threatening disease (Mwenesi et al 1995) and most childhood deaths occur at home, so the causes are not easy to clarify (Tanner et al 1991, Slutsker et al., 1996). The hospital case fatality rate for severe anaemia for children under five years of age was estimated to be 6% (Schellenberg D et al., 1999). Community case fatality figures are not available, but are expected to be higher, as the majority of children with severe anaemia in Tanzania live beyond the reach of facilities which can manage the condition, for example by providing blood transfusion.

Therefore, even in areas of intense transmission, it is important that the treatment offered should also prevent the occurrence of complications of the disease such as severe anaemia. Hence, we suggest that in Tanzania the objective of treatment should be clearance of symptoms and prevention of recrudescence of symptoms within 14 days, and also the clearance of peripheral parasitaemia.

Choice of an alternative drug

The useful life of the current first line drug in Tanzania (CQ) is coming to an end because of high parasite resistance. About 52% of children treated with a standard dose of CQ (25mg/kg) are not cured within 14 days (MOH 1999). In several countries in Southern Africa (White 1999), SP was considered to be the most appropriate drug to replace CQ. Studies have shown that SP is efficacious in Tanzania, with an average clinical failure rate of 10-15% (MOH 1999). Amodiaquine (AQ) is another possible candidate. It seems currently to be more efficacious than SP, but its acceptability has been a problem among health workers due to fears of side effects (Nevill et al 1994, MOH 1999) - although a review of studies on safety and efficacy of AQ concluded that the drug is safe provided its use is monitored (Olliaro et al 1996). There is also concern that the effectiveness of AQ may be reduced by cross-resistance between it and CQ (Olliaro et al 1996). In Tanzania,

it has already been observed that in an area of very high CQ resistance there is also a relatively high AQ resistance (Abdulla S. et al, personal communication) (Table 1).

Malaria diagnosis

Malaria diagnosis in areas of high endemicity poses a significant challenge during assesment of efficacy of antimalarial drugs and in routine practice. Presence of parasite in blood with or without sign and symptoms are not definitive indication of malaria disease.

Epidemiological dimension

Antimalarial treatment policy is formulated at the national level. A sentinel monitoring system has been established, with 8 sentinel sites, in order to generate data that is representative of the whole country. The efficacy of CQ, SP and AQ has been evaluated using a modified WHO 14-day test (EANMAT 1999). CQ failure rates were high in all the 8 sentinel sites, with an average of 52%, indicating that resistance is widespread in Tanzania. For SP, in contrast, failure rates below 10% were observed except at one focus (Muheza District in north-eastern Tanzania) where there was a high failure rate of 30% (MOH 1999).

There are several factors that contribute to the development and spread of resistance to antimalarials. These range from host population factors such as appropriate use of the drugs, amount of use, duration of use, and time for clearance of the drug, to parasite population factors like the biomass of parasite exposed to the drug, the duration of exposure, and the mechanism of resistance. This mechanism may affect the speed with which resistance can develop. For example, resistance to SP is apparently due to the stepwise accumulation of point mutations in the genes controlling the drug-target enzymes dihydrofolate reductase and dihydropterate synthetase. This may explain why resistance can develop rapidly. Resistance to CQ, on the other hand, involves changes in the process of drug uptake and transport through the cell, which may require a more complex series of mutations. This may explain why CQ resistance only appeared after the drug had been in use for a long time.

Table 1: Comparison of advantages and disadvantages of three commonly-used antimalarials

	CHLOROQUINE	SULPHADOXINE /PYRIMETHAMINE	AMODIAQUINE
Efficacy	47% (28% - 72%)	90.5% (66%-93.6%)	95.4% (94%-96.5%)
Cost of treatment one episode (with tablets in children)	US $ 0.01	US $ 0.01	US $ 0.03
Availability	+++	++	+
Side effect	+	++	++
Cross resistance with Chlorquine	Not Applicable	No	Yes
Selection for resistance	Not applicable	Rapidly	Slowly

There is, however, a lack of concrete information on the rate of growth of resistance to SP (or any other drug) in various epidemiological settings. This makes it difficult to predict the useful life of any antimalarial. In Thailand, SP became useless after about 10 years of widespread use (WHO 1994). So far, the experience in Africa is not so bleak. Clinical treatment failures in Malawi are still less than 10%, though the change was introduced 7 years ago. (Macheso A. personal communication).

Resistance to the drug most commonly used can be expected to increase mortality rates. Assessments from West Africa show that this is indeed the case for CQ resistance (Trape et al., 1998). In Tanzania, the magnitude of the effect of chloroquine resistance on mortality is not known, but it is expected to be substantial in view of the widespread high levels of CQ resistance, and the high number of people who develop malaria. Anecdotal reports indicate that most deaths associated with febrile illness occurred at home, after attending a formal health facility (AMMP/TEHIP, unpublished data).

Interestingly, most of the information collected so far is on children under five years old. Little is known about the contribution of older children and adults either in terms of the dynamics of resistance or of the burden of disease. Information from an Adult Morbidity and Mortality Project (AMMP) suggests that malaria is also among the important causes of mortality in those above 15 years of age (Kitange et al 1996). Work at sites with continuous demographic surveillance will provide more information in the future.

Economic and health systems dimension

Malaria treatment-seeking behaviour

Even the best drug policy will be ineffective unless consumers and providers comply with it. Their behaviour must be considered if a rational policy is to be implemented and have a substantial impact on the reduction of morbidity and mortality. In East Africa, shops and drug stores rather than health facilities are the main source of antimalarials. Most people who fall sick with malaria-like symptoms are given antimalarial drugs stored at home. The course of treatment given is usually incorrect and the drugs often sub-optimal. (Mwenesi et

al 1995, Nyamongo 1999, Nsimba et al 1999). Many factors contribute to the preference for shops and drug stores. These include lack of drugs in public sector facilities, and convenience. There are more shops and drug stores than health facilities, and they may be more easily accessible, in terms of time to reach them, time spent waiting for service, and opening times. Public facilities are often closed at weekends or at night. The financial cost of an illness episode can also appear to be less when drugs are bought from a shop, since shops will even sell 1/3 of a dose (Table 2).

Table 2: Sources of antimalarials among 1263 interviewed people from different parts of Tanzania

Drug Sources	Chamwino Central-TZ	Kyela Southwest-TZ	Mlimba Southeast-TZ	Total
	N=446	N=411	N=406	N=1263
Government health facility	96.7%	22.9%	13.1%	51.0%
Private health facility	1.6%	4.2%	13.1%	5.4%
Drug store/shops	1.7%	79.9%	68.4%	42.2%
Other	0%	0%	5.3%	1.46%

TZ: Tanzania

When treatment is not successful, patients often look for alternatives. For malaria, treatment-seeking behaviour patterns vary a great deal, with constant interchange between formal and traditional providers. Studies in Ifakara and Rufiji, found that if there was no improvement after treatment from a formal health facility, only a quarter of the mothers and caretakers came back for re-treatment (Muela- Hausmann *et al.* 1998, Bjorkman 1991). Alternative sources of care included private health care or visits to traditional healers. If the response to treatment is poor, complicated malaria may develop, leading to convulsive episodes in children. These are often regarded as a separate disease, *degedege*, for which traditional healers are considered more competent than hospitals (Makemba A.M *et al.* 1996, Mwenesi *et al.* 1995).

Thus, in cases where the first-line drug is not effective, a significant proportion of patients do not return to health facilities where they might obtain treatment with second-line drugs. Even for those who do return to the health facilities for further treatment, clinicians tend to

repeat the same treatment unless the patient has severe malaria. Therefore, the drug used as first line therapy in Tanzania needs to be very efficacious.

Up to now, national Malaria Control Programmes have not paid enough attention to the way that malaria and its complications are managed at household level, the importance of self-treatment and the role of shops and drug stores in the provision of malaria treatment. The challenge for a national programme is to ensure that effective antimalarial drugs are available easily to all (Brugha R *et al.* 1999**,** Tanner and Vlassoff 1995). Encouraging home treatment may even facilitate early treatment (Deming *et al.* 1989). Hence, a policy need to be developed that addresses this level of care.

Costs and cost-effectiveness assessments

Drug-resistant malaria and the related deaths and treatment failure will carry a cost in terms of disability and loss of life. A model was developed that balanced the cost caused by drug resistant malaria and related deaths under different drug regimens in a fixed time period (Schapira *et al.* 1993). It was then used to find the optimum time to change the drug regimen, and the point where CQ treatment failure reaches between 15% and 25% was proposed. Other workers used decision analysis models to compare the cost and effectiveness of CQ, AQ and SP treatments (Sudre *et al.* 1992). SP was the most cost-effective treatment when the prevalence of chloroquine resistance in *Plasmodium falciparum* at the RIII level was greater than 14-31%, depending on compliance. A similar decision tree analysis model was developed that takes into account changes over time (Goodman *et al.* 1999). This was later applied to Tanzania- specific data, and clearly demonstrates that at current levels of resistance to CQ, a policy of using SP as the first line drug is more cost effective. This was the case over a 10-year projection. Considering changes in outpatient drug costs only, using the SP regimen rather than the CQ regimen over the 10 year period would cost US$ 0.46 per operational failure averted, or US$33 per death averted (Abdulla S. *et al.*. 2000). This seems to be less cost-effective.

The actual choice of what strategy to implement is determined more by the ability of individuals and communities to pay the absolute costs than by assessments of cost-effectiveness. The use of a more expensive drug than chloroquine may be assessed to be more cost-effective, but the absolute cost of implementing the treatment strategy may be beyond what the community can afford.

In Tanzania, calculations of economic benefits must also take into account the fact that the government health services do not pay for all the uncomplicated malaria cases that occur in the community, since many people buy drugs privately and treat patients at home. The little money there is must be allocated to competing priorities in health care, of which malaria is only one. Hence what is important is to have a policy which will use the small amount of money that can be invested in reducing the problem of malaria as effectively as possible. An optimal policy will be harmonised with what individuals in the community can do to help themselves.

Acceptable levels of resistance: when should the drug be changed?

Various attempts have been made to establish resistance levels for changing malaria treatment policy. Some were based on parasitological resistance levels and others on treatment failure rates. Estimation parameters that included the cost of drugs, compliance and levels of parasitological resistance had the greatest effect on generating cost-effectiveness ratios. For CQ, parasitological resistance (RIII) levels of 14- 31% have been suggested. (Sudre *et al.* 1992), while for treatment failures a cut-off of between 15% and 25% was proposed for the switch from CQ to SP (Schapira *et al.* 1993). Others have proposed that a change should be made when the median duration of clinical response is no longer below 14 days and /or when haematological recovery is not optimal even with clearance of parasitaemia (Bloland *et al.* 1993). The WHO, while leaving the national programmes to establish an "acceptable level" based on the available options and financial position of the country, has proposed an upper limit of 25% failure as an indication for change (WHO 1994).

Many questions remain. How should Tanzania set a cut- off level? Should the prevalence of RII or RIII resistance be considered, or the proportion of early clinical failures or of failures on day 14, or the use of cost-effectiveness assessments? The dynamic nature of the problem of resistance, and of the factors that contribute to its increase or decline, calls for a more dynamic assessment, taking into account all the factors that we have described above. Hence, the upper limit for changing policy should not simply be one number, but consider the efficacy of second and third-line antimalarials, together with other factors like treatment-seeking behaviour, public health impact, cost-effectiveness and the perceptions of health workers and policy makers. Decisions about limits should take into consideration the public health impact of resistance in terms of subsequent clinical episodes, effects of chronic infection like anaemia, severe disease and mortality. The availability of health and

demographic information systems in several African countries offers an opportunity to evaluate more rational approaches for setting upper limits in different epidemiological settings. A decision could be made to change the treatment policy for all the population, or different guidelines could be established for specific groups, for example women and children only. Such a policy would have its own unique implementation demands and must be considered in the light of the existing health infrastructure. In Tanzania, it would be logistically simpler to have a policy for all the population.

The decision-making process

The decision-making processes involved in changing policies for malaria treatment do not show a uniform pattern. There are big differences from country to country in the structure of health systems, and in the levels at which decisions on malaria control are made. Furthermore, changes in policy and policy implementation rarely result from a linear process of generating research, laying out policy options, choosing between alternatives, and finally evaluating the implementation of the selected option. Rather, changes come about through a process of iterative interactions among three "streams" of activity: defining the problem, suggesting solutions, and obtaining political consensus (Porter R.W.1995). After the generation of technical information, like data on efficacy, treatment-seeking behaviour, costs and cost-effectiveness, advocacy of the results to the stakeholders and those responsible for making decisions at various levels is required.

In Tanzania, a harmonious system for the transmission of research findings to policy makers is still lacking. Researchers complain that their findings are not considered in the decision-making process, while policy makers complain that they do not get a simple, understandable version of the results to translate into action. A decision to change drug policy has important implications for the Ministry of Health, the pharmaceutical sector, both public and private, public and private health practitioners, and the general population. Therefore, it is vital that the interests and concerns of all stakeholders are taken into consideration by all those involved in the process.

Case-studies - and the way forward

In Thailand, chloroquine (CQ) was replaced with sulphadoxine/pyrimethamine (SP) as first-line antimalarial in 1973. About ten years later, the efficacy of SP diminished, and a combination of quinine and tetracycline temporarily became the first-line treatment. Later,

this was replaced by a mefloquine-SP combination. These changes were made when parasitological resistance at RI level was 15%-20% (WHO 1994). In Africa, CQ has been the drug of choice for more than forty years. However, in 1994 Malawi became the first country to replace CQ with SP, and it was later followed by several other countries in Southern Africa, namely Botswana, Swaziland, South Africa and Kenya (White 1999).

The decision to change the malaria treatment policy in Malawi was based on a comparison of the efficacy of CQ and SP. In one study, 30% and 60% of children treated with CQ became symptomatic again by days 14 and 28 after treatment, but none of the children treated with SP were symptomatic during follow up. The improvement of haematological symptoms was significantly better in SP-treated than in CQ-treated children, and the RIII resistance level to CQ was 33% (Bloland *et al.* 1993). These data, together with others collected in 6 sentinel sites, formed the basis for changing the treatment policy. The main parameters considered were the reduction of clinical response in a 14-day period, poor haematological recovery, and a high level of in vivo parasitological resistance to CQ. In Malawi, CQ was replaced with SP at all levels of care, and the use of chloroquine restricted to sales on prescription only.

In Zambia in the 1990s, CQ clinical failure rate in six sentinel sites range from 31% to 48% with in vivo parasitological failure of 34% - 70% (using the 14 Day test, WHO 1996. SP tested in 2 sites indicate RII and RIII failures in 3% and 17% and only one case of clinical failure in at each site. Based on these results it was decided to maintain CQ as firstline drug and promote the use of SP for all cases not responding to CQ. SP was made available in all health facilities, whereas before it was available only on prescription and in hospitals (Barat *et al.* 1998).

There is consensus among Tanzanians that the problem of the high morbidity and mortality associated with the use of CQ as first line therapy needs to be addressed as soon as possible. The epidemiological and other information gathered so far also supports the view that Tanzania is long overdue in changing its antimalarial treatment policy (Kitua A 2000). So the question is not whether to change or not, but what the new standard treatment should be. In addition, clear guidelines need to be developed for deciding when the next change is necessary.

On the basis of the information currently available, an immediate switch from CQ to SP would be appropriate. Other drug options are not suitable either because of their costs (mefloquine, Halofantrine etc), or because only limited information is yet available on safety, cost benefit, ease of implementation and impact on epidemiological parameters of resistance (e.g Combination Therapy). It is certainly possible that the wide introduction and use of SP as a first-line treatment may compromise future strategies which are under development (Winstanley *et al.* 2000), and are dependent on antifolate compounds. These include the use of combinations of chlorproguanil and dapsone (Lapdap) or SP with artemesinin derivatives. But the high morbidity and mortality now means that delay because of possible future implications is not warranted. Furthermore, there is hope that a different range of options will be available in the future. New, cheaper efficacious compounds may be developed by initiatives like Medicines for Malaria Venture, and under the Roll Back Malaria initiative there may be a drop in prices of available compounds, and new strategies for funding malaria control.

Further work is needed on guidelines for malaria prophylaxis in children and expectant mothers in the new policy. The preparations for future policy revisions need to start now by developing new tools for assessments and decision making and refining available ones. For example, there is still room to improve on the costs and effects models and to validate them with the results of actual experience after the change of policy in Tanzania. New aspects of the health systems also need to be explored, for instance, the role of diagnostic and treatment strategies. For example, Integrated Management of Childhood Illness (IMCI) or the improvement of laboratory diagnosis of malaria. Improvement in diagnostic and treatment procedures may reduce unnecessary treatment and hence drug pressure.

Further developments are required in identifying molecular markers of resistance, and developing the necessary technology (e.g. DNA micro-array techniques) to allow the monitoring of the development and spread of resistance in large epidemiological studies. Mechanisms need to be developed for the advocacy of the concerns of policy makers to scientists, and the integration of these concerns in the research that is done. Ways must be found to identify solutions, and to create in all the stakeholders the political will to put them into practice. New strategies (e.g. combination therapy) need to be tested in the field. Lastly, training is needed to ensure that a “critical mass” of skilled personnel will be available to co-ordinate implementation, and maintain continuous monitoring of changes in all three dimensions – clinical, economic, epidemiological and health systems - over time.

It must also be remembered that as most malaria treatment is done at home, changing the first-line drug in the public health sector alone may not have a substantial impact. Promotion of SP alone at home, and restricting the use of CQ, might even be counter-productive because it might result in many cases of malaria not being treated at all. This might happen if SP is not perceived as efficacious, because although it is actually more effective than CQ its antipyretic effect is slower (Nyomongo 1999, Williams *et al.* 1999). Furthermore, though SP is commonly available in urban areas, it is not yet widely in available in rural areas (Nsimba 1999, Masele *et al.* 1998). However, if a new SP policy is implemented, the private sector can be expected to respond by making SP accessible even in rural areas. Information on SP and its appropriate use must be disseminated in the community and the private sector.

Fears of the inappropriate use of the drug on a wide scale, and an acceleration of the development and spread of resistance as a consequence, should not be ignored. Hence, a policy for home management and a suitable drug for use at home need to be developed. Ideally, the drug recommended for home use should be different from the ones used in the public sector. We propose that research be conducted to identify suitable compounds as a basis for home treatment. They should act rapidly, with high efficacy, low frequency of side effects and low potential for toxicity. The products would then be promoted and distributed mainly in the private sector using social marketing strategies. The distribution channels for home products should be investigated to enhance availability and correct use. Simple technology like blister packaging of the antimalarials may offer some solutions to the problem of incorrect use (WHO 1998).

Having a different drug for home use would reduce the potential of development of resistance to the drugs that are used in health facilities. Furthermore, if the drugs used in health facilities were not available on the home market, people would feel it was worthwhile to attend health facilities. Mothers and guardians do not want to waste a lot of time and money at the formal health facility, only to be given a drug (e.g. chloroquine) which they can easily get from a shop (Minja H. personal communication).

New treatment policies in practice

Malawi and Zambia used different approaches for changing malaria treatment policy. Malawi has replaced CQ by SP as the first-line drug in all health facilities, and restricts the use of CQ by making available on prescription only. Zambia has decided to maintain CQ as the first-line drug, and promote the use of SP for all CQ clinical failures. The Malawi approach has the advantage that operationally it is much easier; uniform health messages and information are disseminated to both the general public and clinicians. The approach is likely to cost about the same, and bring a substantial public health gain. However, the widespread use of SP may lead to a rapid spread of resistance

The Zambia approach may cost less in terms of SP costs to the provider. This will depend on the proportion of patients who come for retreatment. It may cost more for the patient in terms of financial and opportunity costs, and the public health gain may be lower. It may be difficult for patients to comply with health messages, as it will not be easy for individuals or staff of primary health facilities decide when to change to SP. Furthermore, considering that the CQ failure rate is high in Zambia - more than 31%- 48% (Barat *et al.* 1998) - so many patients will be treated with SP that in effect it will become the first-line drug. However, if CQ does continue to be used as well as SP, resistance to SP may spread at slower rate than in Malawi.

Conclusion

We have described a dynamic web of factors that need to be considered when reviewing policy. They are all interrelated. For example, changes in the health system and the economic situation may influence epidemiological pattern of the disease in a country, and the frequency of different forms of clinical presentation.

Considering all the options available, replacing CQ with SP in all health facilities, and the promotion of SP with proper health message to improve compliance, is the most appropriate policy for Tanzania at present. However, the change should be regarded as temporary, and preparations for further changes should be made. The main challenge of the National Programme is to ensure that effective malaria treatment and protective measures like insecticide-impregnated nets are widely available to all the people. Only by using all the measures available to us can we hope to reach the goal of "Roll Back Malaria", of reducing malaria mortality by half by 2010.

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PART IV : DISCUSSION

CHAPTER 11

Discussion

Morbidity and mortality in the Kilombero Valley

The studies described in this thesis confirm that malaria is a major public health problem in the study area. This is an area of very high perennial malaria transmission. Moderately severe anaemia was highly prevalent in young children before the start of the ITNs social marketing programme, with about half of all children found to be anaemic. Malaria parasitaemia prevalence was also high with 60% of children being parasitaemic. Initial mortality assessment in 1997 indicated that the children in the Kilombero valley had higher infant (95 per 1000) and childhood (14.3 per 1000) mortality rates (Schellenberg *et al.* 1999) compared to the Tanzania National average in 1996 (Demographic Health Surveys 1996). These findings made it essential that better preventive and curative malaria strategies be implemented.

Availability of treated nets

The use of untreated bed nets mainly for protection against nuisance mosquito was not uncommon before the start of the project. Initial work done 1996 indicated that 37% of all households had at least one net. A few ITNs were also available from initial short-term projects and programmes including the Rotary project (Fraser-Hurt & Lyimo 1998), and the UNICEF Child Survival Protection & Development (CSPD) programme. But most of the nets that were in use in 1996 were old and some were badly damaged, thus they provided little protection. The initiation of the social marketing programme resulted in a replacement of the untreated net nets with treated nets and increased overall ownership of nets. Relatively good coverage of ITNs in the main target group (children and expectant mothers) was achieved in this programme. About 61% of children under two years (Abdulla *et al.* 2000a) and 52% of children under five years (Abdulla *et al.* 2000b) slept regularly under a treated net. Among pregnant women 53% were using ITNs in 1998-1999 (Marchant *et al.* unpublished data). These findings are similar to results of earlier exploratory studies in same area, using similar delivery mechanisms (Fraser-Hurt & Lyimo, 1998) and in neighbouring Burundi (Van Bortel *et al.* 1996).

The sales figures of "*Zuia Mbu*" products indicated a seasonal pattern that can be explained by both the abundance of mosquitoes and the availability of spare resources. The figures indicated high sales at the start of the main rainy season and at the end of harvest in September to October. A total of 65,000 ITNs and 25,000 insecticide sachets for retreatment were sold between mid-1997 and mid-2000 (Mponda H. unpublished data). The rapid uptake of the treated nets clearly indicates the existence of a substantial market for nets. Preliminary assessment of the willingness-to-pay and ability-to-pay for the socially marketed products indicated that the majority of the population was both willing and able to pay the prices charged (Schellenberg *et al*. 1999). At the end of the two years only 17% of children under two were without any net. For this small proportion of non-users who can probably not afford a net, the existing welfare system could be used for assistance.

Impact of ITNs on malaria morbidity in children

The social marketing approach for distributing treated nets had a rapid overall impact on health outcomes in the community. The increase in the level of net ownership was accompanied by a decreasing prevalence of anaemia and malaria parasitaemia in the community. Overall, there was an improvement in mean haemoglobin levels in children under two years from 8.0 to 8.9 g/dl, and a reduction in the proportion of children who had haemoglobin of less than 8 g/dl from 49% to 26%. A decline was also seen in the proportion of children with parasitaemia or splenomegaly. The treated nets had an apparent protective efficacy of over 60% on the prevalence of anaemia, parasitaemia and splenomegaly (Abdulla *et al.* 2000a). Furthermore, there was a gradient in protection with those owning ITNs having less anaemia compared with those with untreated nets. When age-specific malaria parasite prevalence rates in children under two years of age observed in the cross-sectional surveys in 1997-1999 were compared with historical data from 1991 or 1993, it was clearly seen that children in 1997-99 had lower prevalences in all age categories, while not much difference was observed between 1991 and 1993. Hence it is likely that what was observed was a real decline in parasite prevalence and malaria disease, and not a difference due to long-term secular trends. These results over a decade increase the plausibility that the observed changes may be attributed to the intervention. The finding of an impact of ITNs on malaria morbidity in our studies further support the introduction and expansion of ITNs programmes to national level in Tanzania.

There are indications that the social marketing campaign has managed to make ITNs widely available even to those who live on the edge of the inhabited areas, where it has

been suggested that the risk of malaria disease is concentrated. The lack of significant spatial structure in the distribution of ITNs in Idete village is likely to indicate a homogeneous spread of ITNs in this village (Abdulla *et al.* 2000c). However this assessment was done in a small area with a small population, and a repetition of the evaluation on a larger scale with a larger population is required. This was also suggested by the larger cross-sectional survey we conducted, which indicated that children living far from the centre of villages had a significantly lower proportion of bed net ownership (Abdulla *et al.* 2000a).

ITNs in high transmission areas

Our studies have shown an impact of ITNs in an area of very high year-round malaria transmission. Concerns were raised by some authors that the ITNs will reduce transmission, and in doing so delay the acquisition of functional protective immunity in children living in high transmission areas. Theoretically, this could then increase the frequency of occurrence of cerebral malaria as severe form of disease, and hence not change the overall mortality burden in these areas in the long-term (Trape & Rogier 1996, Snow *et al*. 1997, Marsh & Snow 1999). However, following the discontinuation of malaria control trials in the past, no evidence for a delay or a "rebound" in mortality was found (Molineaux and Gramiccia 1980, Bradley 1991, Greenwood 1997). Data from Burkina Faso also did not show such effects in children under five followed up for four years after the intervention (Diallo 1998). Further, the indirect evidence presented to support the idea of a delay in child mortality in areas of high transmission has been questioned (Molineaux 1997, D'Alessandro and Coosemans 1997, Lengeler *et al*. 1997, Lines 1997). Recent analysis of mortality patterns of children under varied transmission intensity indicated that the long-term mortality burden in children living in high transmission areas is likely to be reduced by lowering transmission intensity, especially because of the reductions in infant mortality (Smith *et al*. 2001). It should also be recognised that transmission reduction through interventions will not necessarily result in a situation identical to naturally low transmission areas. The introduction of other measures for combating malaria and other public health problems will inevitably alter the environment within which the new and lower malaria transmission level exists.

Although the current debate does not warrant delaying the implementation of ITNs programmes this issue needs to be addressed scientifically and monitored. To address this concern a long-term follow-up (over 5 years) of children protected under ITNs is

currently on going in several settings including in the Kilombero Valley (Schellenberg *et al*. 1999, Smith *et al*. 2001).

Treatment of uncomplicated malaria

Antimalarial drug resistance is growing and spreading at an alarming rate. There are indications that the use of antimalarials for which resistance is wide spread increases mortality (Trape 1998). In Tanzania after reports of initial cases of resistance in 1978, an increase of admissions due to malaria but not other infectious diseases was observed in hospitals (Kilama and Kihamia 1991). Increasing chloroquine resistance in our study area was reported in 1980's and early 1990's (Koella *et al*. 1990, Mshinda *et al*. 1996). The results of our clinical study confirm the worry that chloroquine is no longer useful for the treatment of uncomplicated malaria in the study area, with only 35% of children having parasitological cure within 7 days of treatment (Hatz *et al*. 1998). Further work in Mlimba, an area 180 km away from Ifakara where the initial study was done, also showed similar levels of resistance (MOH 1999). This indicated that the problem of chloroquine resistance is wide spread and hence the need of an alternative antimalarial drug. Sulphadoxine/pyrimethamine (SP) was proposed as an alternative although resistance to this drug has also started to be reported in several places in Tanzania, with an average estimate of 14% treatment failures within 14 days (MOH 1999).

The mechanisms of *P. falciparum* resistance to antimalarials are still not clearly elucidated. It is known that the resistant parasites accumulate chloroquine less avidly and it is now thought that the phenomenon is conferred by changes in p-glycoprotein pumps that are coded by genes in chromosome 7 of *P. falciparum*. Resistance to SP is highly associated with mutations in the genes that code for enzymes dihydrofolate reductase (DHFR) and dihydropteroate synthetase (DHPS) (Winstanley 2000). The development of resistance is an evolutionary adaptive process in the parasites which is related to the spontaneous mutations in the parasites and selection of parasites with resistance genotypes by antimalarials. The importance of drug pressure (related to the parasite biomass exposed to a particular drug) in the mechanisms of resistance is further illustrated by experiments comparing rate of resistance development for SP, which has a long half-life, and chlorproguanil-dapsone which has a short half-life. More rapid development of resistance was observed with the long half-life drug (Nzila *et al.* 2000).

Lastly there is still a need for developing new compounds that have varied mechanisms of action, as the current armoury of antimalarials exploits very few targets in the parasite (Wistanley 2000). This leads to a high frequency of cross-resistance example between chloroquine and amodiaquine, or between pyrimethamine and chlorproguanil. Most of the new compounds (such as chlorproguanil-dapsone) are old products that are put together.

The focus of early diagnosis and treatment is to get the treatment initiated as quickly as possible after the malaria attack. Studies have shown that those children treated early in the attack have a better prognosis. Furthermore wide availability of antimalarials even at home was associated with low mortality in children (Trape *et al*. 1987). However wide-scale availability of drugs encourages the appearance of resistant parasites, by increasing the biomass of parasites exposed to the drug. For most of Sub-Saharan Africa a trade-off must be reached between wide spread use that meets the enormous need for antimalarial treatment with rational appropriate use that safeguards the useful life of the products.

Several more efficacious alternatives than chloroquine exist, for example the fast acting artemisinins. The cost of these compounds is high at present but it is envisaged that the costs could be reduced, especially with local production (for example: Tanzanian plantations of the Africa Artemesia Company). The main limitation of these compounds is the high recrudescence rates that have been reported with short treatment regimens (for example 3 days). The use of combination therapy for malaria (CT), which entails combining an antimalarial with an artemisinin derivative, reduces the chances of this happening. The artemisinin will lower the parasite biomass and hence reduce the bulk of spontaneous mutations in the parasites that are exposed to the selection pressure of the second drug. The ideal situation is to combine two drugs with (1) a short half-life, (2) different mechanisms of action, and (3) which have synergistic effect and matching pharmacokinetic profiles (White 1999). These CT treatments are usually more effective and are believed to have the additional advantage of delaying occurrence of resistance or even reducing transmission (White *et al*. 1999). Our results indicate that the combination of Artemether and Benflumetol (Co-artem®) was very effective in treating uncomplicated malaria with about 94% children having good clinical response within 7 days (Hatz *et al.* 1998). This combination was also found to be very safe and well tolerated in all the studies conducted so far (Bakshi *et al*. 2000). Other new compounds that are under development include chlorproguanil-dapsone which promises to be relatively cheap and has very short half-life and hence is unlikely to select for resistance (Winstanley 2000).

The decision on the choice of drug to be used for a particular country depends on a number of clinical, epidemiological, social economical factors, including also the health infrastructure. Consideration of all these factors allowed the identification of SP as an interim drug to be used as the first line therapy at health facilities in Tanzania (Mshinda *et al*. 2000). However, there is a worry that resistance to SP will rapidly develop as was seen in South-east Asia (White *et al*. 1999). Furthermore, compared to chloroquine it has no antipyretic activity, a factor which may give patients a feeling of poor response to treatment. Therefore, evaluation of other compounds and strategies including CT are in progress to get a long-term solution for the treatment of malaria in the formal health facilities.

The assessment of care at the household level, however has not been adequately looked into. This will entail having a product that is safe enough to be used repeatedly, with a rapid mode of action and a short half-life such that it induce have limited resistance selection. It will be wise to select a particular type of compound to be used at home and a different type with a different mode of action to be used at formal health facilities. Firstly, this will help to prevent the rapid selection of resistance to compounds used in the formal facilities, and secondly mothers will be encouraged to visit health facilities, if they know that the facilities provide medications that are not usually found at home. The implementation of such a home treatment strategy could then use social marketing techniques and organisational structures similar to what has been described for ITNs. The identification of a suitable branded product that will be promoted at home can be done with involvement of both the private and public sectors, including the national malaria control programme (NMCP).

ITNs and efficacious drugs for malaria control in Tanzania

Control of malaria in Tanzania requires a multi-sectorial and multi-disciplinary approach. Similarly, a combination of control strategies will be required to contain the problem of malaria. It is recognised that the use of ITNs confers only a risk reduction and not a risk elimination and effective treatment of cases of malaria is still required. Unfortunately, we don't have a better protective measure to-date. Candidate malaria vaccines are still a long way from being ready for wide-scale use. The overall transmission impact of the ITNs

programmes combined with appropriate use of an effective antimalarial may be dramatic if drugs such as artemisinin are used, as they may have an effect on transmission through their anti-gametocyte activity (White & Olliaro, 1998). Furthermore, ITNs may help in the effort of reducing the rate of development of antimalarial resistance by limiting the spread of the parasite, and therefore further enhance malaria control (Molyneux *et al.* 1999).

Evaluation of control tools

Studies described in this thesis give a good overview of the issues and approaches involved in the evaluation of interventions. The randomised clinical trial of Co-artem® was a Phase III evaluation where the main concern was to assess safety and efficacy under ideal conditions. Before this stage of evaluation the drug had been tested in animal models and volunteers to establish biological activity and safety for experimentation using human subjects. The high efficacy demonstrated in our study indicates that Co-artem® merits consideration as a suitable tool for implementation on a large scale for treatment of uncomplicated malaria. However, further Phase IV or implementation programme evaluations are needed before wide scale use can be advocated. Such programme evaluations are now being emphasised (Habicht *et al*. 2000), because the results of the phase III can not be easily translated in programme settings (Lengeler & Snow 1996). The coverage and compliance to treatment may be different in the routine use, and hence limit the effectiveness of the drug. Other factors related to the implementation of the intervention may also be markedly different from the randomised study. In Tanzania the majority of clinical cases of malaria are treated by semi-qualified personnel in dispensaries, using diagnostic algorithms rather than definitive diagnosis by microscopy (Massaga *et al*. 1999). Furthermore, the study population in Phase III is too small to be able to detect adverse effects which are rare, or take some time to manifest. Lastly, implications and interactions with other existing strategies is another concern that may be important to observe in a programme setting. Hence a careful assessment of the effectiveness, cost-efficiency, implementation strategy and the particular environment has to be made in order to ensure efficient and appropriate use of the drugs.

The many issues with phase IV evaluations are illustrated with the studies conducted to assess impact of ITNs. The ITNs evaluations were mainly aimed at demonstrating that the expected benefit of the intervention is retained when the intervention is delivered in a less controlled way. These studies highlight important issues for the evaluation of programmes.

Two methods of assessment were employed: cross-sectional and case control studies. Impact of ITNs was demonstrated using the cross-sectional approach but not the case-control approach. Attendance bias was the likely explanation for this difference, as those with ITNs attended more frequently for all the preventive and curative services offered at the dispensary (Abdulla *et al*. 2000b). It is likely that this observation can be explained by the high awareness of health issues and higher tendency to seek care at the dispensary for those owning ITNs, rather than more disease in this group.

Furthermore, the case-control approach was thought to be simple in its design and execution but in our study it proved to be difficult to implement and took a long period of time (over 18 months). The advantage of small sample size of the case-control approach is lost when evaluating a common disease like malaria. There is also a difficulty of finding suitable controls. Therefore, it is unlikely that persons with limited resources and skills in epidemiology, computing and database management, can repeat such an investigation. This makes the approach unsuitable for recommendation as a tool for routine programme evaluation.

The studies also highlight the need of collecting several pieces of information in order to get an elaborate picture of the effect of the intervention in the community. Our evaluation of ITNs involved repeated cross-sectional surveys and case-control studies. A comparison was also made with historical data collected a few years earlier which showed a lowering of parasitaemia prevalence after the ITNs social marketing programme was implemented.

The choice of appropriate study subjects is another crucial issue. ITNs work by reducing risk of infection and transsmission of malaria. The effects of this reduction are more likely to be observed in very young children (McElroy *et al*. 1994). For example, it has been observed that variations in transmission strongly affect the estimates of morbidity and mortality in very young children (Molineaux & Gramiccia, 1980). Therefore at a given transmission intensity, the age of the study participants is crucial in determining the level of protection. Our finding of high impact in children under two years of age is in line with other studies that included very young children (see Abdulla *et al.* 2000a for details). Hence our studies were mainly focused in children for whom the impact was expected to be apparent. Furthermore, in this group the burden of malaria anaemia is concentrated, hence they are more likely to benefit from the intervention.

Prevalence of anaemia as the main indicator in our studies was chosen as this is an area of high transmission, and malaria-associated anaemia is a major problem. It has been demonstrated that 60% of the anaemia in infants is due to malaria (Menendez *et al*. 1997). If such evaluations were conducted in an area of low transmission prevalence of parasitaemia may be more appropriate, as was done in Afghanistan (Rowland *et al*. 1997)

A decreased risk of admission to hospital for malaria was observed in children not using ITNs and living in areas with high ITNs coverage, compared to those in the control areas (Howard *et al.* 2000). This indicated that some protection is being conferred to those without nets and those with untreated nets. Therefore, the results of effectiveness evaluation in a programme will be reduced toward zero in high coverage rates, and it will therefore be very difficult to demonstrate impact (Abdulla *et al.* 2000b). It is often argued that it is essential to achieve very high ITN coverage in order to get the full benefit of ITNs (Lines, 1997). In our studies impact was observed even when the coverage was far from 100%. We could not assess changes in the observed impact at different coverage levels due to the small study population.

Lastly, for both the case-control and the cross-sectional approaches the main comparison was between those who have adopted the intervention and those who didn't. This is because of the lack of a contemporaneous control group in this programme setting. In this circumstance some control of confounding is performed in the analysis but there may still be some residual confounding. The measures used to control for confounding factors like social-economic status and health seeking behaviour may not be sensitive enough. The lack of a simple test to check for insecticide content of the nets (Drakeley *et al.* 1999) meant that this could not be verified as suggested by work in The Gambia (Muller *et al.* 1994; D'Alessandro *et al.* 1997). The reliance on reported ownership of ITNs meant that some misclassification was possible (Abdulla *et al.* 2000a). It can also be argued that those who adopt ITNs differ from those who don't by some unidentified factors that make their risk of getting malaria disease lower, hence causing an overestimation of the impact of ITNs.

It should also be recognised that the comparison of those who adopt versus those who don't essentially estimates the health benefit conferred to those who adopted the intervention, rather than how much the health outcomes have improved in a particular setting, estimated in control trials (Kirkwood *et al*. 1997). Therefore, the results of the randomised controlled trials can not be directly compared with the results of programme evaluations, unless there is a

control group as was the case in the Gambia (D'Allessadro *et al*. 1997). Inevitably specific indicators and programme evaluations approaches will need to be identified for different interventions. The results and indicators used in the Phase III trials may be different from those used in the Phase IV trials, and a direct comparison of the results of these two levels of evaluation cannot always be made. However, estimation and calculation of the cost-effectiveness or cost-benefit of reducing the burden of disease, especially using anaemia as an indicator can be done in both (Goodman *et al.* 2000).

Theoretically, it would have been advantageous to have a contemporaneous control group in our evaluations. One can argue that we could have implemented the ITNs in one district and observed the other as control. However, the problems with this design are many. Firstly, there would have been a variable uptake of the ITNs in the intervention area and possible leakage of nets into the control area. Secondly, it should be considered unethical to withhold an intervention with a proven benefit to a population, especially if mortality is evaluated. Finally, there are difficulties of comparability in an 'intention to treat' analysis of one intervention versus one control cluster. In this situation, analysis comparing those with ITNs and those without ITNs in the two areas will be similar to what we have done comparing adopters and non-adopters in the same area. An extension of such an idea is to have several clusters were the intervention is applied and several control clusters hence introducing some element of randomisation in the design. This also has the problem of variable uptake and possible "contamination" mentioned above. But it also has far larger cost and logistic implications since a large enough number of clusters is required for the analysis (Kirkwood *et al*. 1997). Social marketing of ITNs cannot be efficiently done at household or village levels and large units are therefore required. All these alternative approaches are less practical and will not usually be possible in many implementation programmes. Most programme implementers want to spend their money on implementing programmes rather than pay for elaborate evaluations. Therefore more research is required on simple methods and tools for programme evaluations.

Improved biomedical monitoring and evaluation tools

The assessment drug efficacy in clinical trials can also be improved. In areas of high transmission, the presence of parasites in peripheral blood cannot be taken as a proof of failure of the therapy. Microscopy can readily determine the parasite species and densities but can not distinguish between recrudecences and re-infections. The addition of molecular aids like polymerase chain reaction with restriction fragment length

polymorphism (PCR-RFLP) allows such distinctions and hence improves the evaluation of antimalarial drug efficacy (Irion *et al*. 1998).

More important is the role of such molecular techniques in the evaluation and monitoring of treatment strategy in malaria control programmes. Much work has gone in the delineation of the mechanisms by which parasites become resistance to antimalarials. The identification of markers of resistance can help in the explanation of problems in therapy but also as tools for assessing the performance of treatment strategy at population level. Examples are the mapping of the extent of the potential SP resistance problem in Tanzania using DHFR and DHPS mutations as markers (Mshinda H. pers. Comm). And the use of the same makers to detect the effect of artemisinin derivatives in a combination therapy strategy to delay the occurrence of resistance in a programme setting (Bloland P. pers. Comm). Additional approaches are still required to get the translation of evaluation results into policy. This entails compiling and summarising relevant information, as was done by modelling the effectiveness and cost-effectiveness of different malaria treatment strategies and drug regimens in Tanzania (Abdulla *et al*. 2000d).

From research to policy implementation

The results of all these evaluations are only relevant if the information is received by the end users (i.e. policy makers) and relevant policies are formulated. Policy makers need to be involved in the whole process of research from formulation of the relevant research questions to choosing the appropriate evaluation methods and implementation of the evaluation. Part of this is also establishing a good communication between the different stakeholders (Porter & Prysor-Jones 1997). The revision of the antimalarial treatment policy in Tanzania illustrates these issues. Research scientists had produced data that indicated that chloroquine was no longer a useful drug for treatment of uncomplicated malaria in Tanzania already in the 1980's. But the information was not well communicated to those who have the mandate to revise the National Policy. The review of the antimalarial treatment policy was initiated only after the policy makers were involved in the evaluations and provided with information that they required: representative antimalarial efficacy data from many parts of Tanzania (MOH 1999), and data on the cost implications of policy change (Abdulla *et al.* 2000d).

For the ITNs evaluations the policy makers and health managers both at local and national level were involved in the all the steps of the evaluation. Members of the District Health Management teams participated in regular planning meetings of the KINET project

implementation. Progress of the implementation was also communicated to the National Malaria Control Porgramme. Hence, there was a smooth move towards using the experience gained at implementing small district wide projects towards setting a plan for national implementation of ITNs (MOH 2000).

The up-scaling of an ITNs implementation strategy inevitably require the presence of other partners. Hence a completely different framework is required in which both public, non-profit, and private institutions participate. The issues of how best to introduce the treated nets in a wide scale are then to be discussed and the strategies tailored to the specific circumstances of the country or region. Sustainability of these malaria control initiatives make it necessary that they are integrated and recognised within the formal health system, resulting in a commitment at all levels of government and non-governmental organisations.

In Tanzania, much experience has been gained with the implementation of small projects. They had the dis-advantage of being small and were heavily subsidised. Subsidy allows equitable access to the ITNs for the majority of the population in rural areas who are generally poor and may not be able to afford the commercial prices of the ITNs. However, it introduces dependency on external support and limits the development of the commercial market for the ITNs. ITNs can be considered as a public health intervention and therefore the Government and its partners and supporters should contribute towards the implementation of the strategy. Virtually no other intervention in preventive health is entirely self-supporting: if ITN programmes are (1) feasible on a large scale and (2) efficient through low delivery cost per net or per treatment, they should be able to attract sufficient donor support in the context of the "Roll Back Malaria" initiative (Lengeler 1999). There are several ways that can be done to encourage the commercial market despite an element of subsidy, especially if it is a subsidy limited to specific target groups. These experiences and considerations then broadly categorise the roles of the different stakeholders in ITNs implementation. The private and commercial sector produce and distribute the ITNs, and the public sector promotes the growth of the market, encourages uptake of ITNs in communities, and ensures some level of equity.

Conclusion

Malaria control in the Kilombero Valley and Tanzania as whole requires improvements in both preventive and curative strategies. ITNs distributed through a social marketing programme setting were effective in reducing malaria morbidity, and plans are under way to implement the strategy nation wide. There is an urgent need to implement revised antimalarial treatment guidelines using SP as the first line drug. At the same time, continue to evaluate new drugs including Co-artem® in a programme setting, and try out new strategies such as combination therapy. The tools and instruments that assist in the monitoring and evaluation process, including molecular tools, need to be developed too.

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