CONTROL OF DISEASE DUE TO PERENNIALLY TRANSMITTED MALARIA IN CHILDREN IN A RURAL AREA OF SIERRA LEONE

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ABSTRACT

The effects of the community-wide use of lambdcyhalothrin-impregnated mosquito nets and fortnightly Maloprim^{R}/placebo prophylaxis, singly or in combination, were assessed in a randomised controlled trial as control measures to reduce disease due to perennially transmitted Plasmodium falciparum in children of Bo district, Southern Sierra Leone. Age-specific illness thresholds of 2000 Plasmodium falciparum parasites/ul for children younger than 24 months and a corresponding level of 5000 Plasmodium falciparum parasites for older children, together with fever, were used as case definitions of clinical malaria. Using an active case detection scheme, children were clinically screened and thick smears for parasitological diagnosis collected from those fulfilling any one or more of the set of sampling criteria. A series of cross-sectional surveys (pre-rain and immediately post rainy season) were also conducted during which, in addition to clinical and parasitological data, spleen size and haematocrit level were assessed for all children irrespective of health status. A 49% protective efficacy against cases of Plasmodium falciparum clinical malaria was demonstrated in children using the insecticide-impregnated mosquito nets. The impact of combining Maloprim^{R} prophylaxis with use of the lambdacyhalothrin-impregnated mosquito nets resulted in a 72% protective efficacy against disease due

to Plasmodium falciparum. The interventions *unexpectedly* demonstrated a significant impact on some of the traditional malariometric indices; reducing the average spleen rate and the geometric mean parasite density. It was found that children using the impregnated mosquito nets exhibited the largest increase in the mean haematocrit level documented during this trial (which lasted a year). These results provide additional evidences that synthetic pyrethroid-impregnated mosquito nets have the potential of serving as an alternative strategy for the control of disease due to perennially transmitted Plasmodium falciparum.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 PRE-INDEPENDENCE MALARIA CONTROL ACTIVITIES AND RELATED RESEARCH IN SIERRA LEONE

The Freetown peninsula, location of the Capital of Sierra Leone, was the site of some of the earliest malaria research and control programmes conducted in tropical sub-Saharan Africa. Even prior to Sir Ronald Ross's discovery that mosquitoes of the genus Anopheles transmitted malaria, British military medical officers were studying malaria infection in Freetown (Thin, 1896; Duggan, 1897; Wilson, 1898). In 1898, Ross led the first malaria expedition (organised by the Liverpool School of Tropical Medicine that went to Freetown with the express purpose of investigating the possibility of controlling malaria through better understanding of its vector's biology (Ross et al., 1900).

Between 1900 and 1960, many different control schemes were proposed and in some cases successfully implemented at great expense (Blacklock and Evans, 1925; Walton, 1947; Walton, 1948; Davidson 1947; Davidson, 1948). Right from the onset, control activities were adopted based on the findings of research. For example, when in 1913 Allen (quoted in Blacklock and Evans, 1925) found that some wells were an important breeding site of *Anopheles costalis* (now known as *An. gambiae*) almost all of the affected wells in Freetown

were immediately closed. Not all research findings were slavishly accepted, however. For instance, segregation of the non-immune (white) and the semi-immune (indigenous populations) as a method of malaria control advocated by Stephens and Christophers (1900) was rejected as impractical, as well as a tacit acknowledgement of defeat for overall malaria control.

Almost all of the malaria research and control programmes undertaken by the Colonial authority were restricted to the Freetown peninsula (Ross, 1901; Blacklock, 1921; Blacklock and Gordon, 1925; Macdonald, 1926; Thomson, 1945; Turner et al., 1946) with very little work being conducted in the interior of Sierra Leone. The few surveys conducted in the rural areas (Woods, 1914; Bulter, 1915) indicated that the malaria problem was probably higher than that observed in Freetown.

1.2 PRESENT MALARIA SITUATION IN SIERRA LEONE

Before 1993, information on the epidemiology of malaria in rural parts of Sierra Leone was limited (Mills, 1967; Kandeh, 1986) and usually consisted of anecdotal reports provided by clinicians working in those areas. Baseline parasitology and entomology data gathered by Barnish and Co-workers (1993a, 1993b; Bockarie et al., 1993) in the Bo district indicated that malaria transmission was perennial with the bulk of the resulting infections being Plasmodium

falciparum. As in the rest of the areas in the rain forests of West Africa, *Anopheles gambiae* species complex are responsible for most of the transmission, with *Anopheles funestus* playing an important role as a dry season vector.

Self-medication with chloroquine is almost universal in all parts of Sierra Leone as well as the rest of tropical West Africa, probably because the drug is well tolerated, widely available and cheap. One can only speculate as to the precise role of this drug pressure on Plasmodium falciparum resistance to chloroquine. What is certain, however, is that Plasmodium falciparum resistance to chloroquine is well established in Sierra Leone (Marbiah , unpublished observation) and growing. Alternate anti-malarial drugs, such as Fansidar^{R}, Mefloquine^{R} and Halofantrine^{R} are available over the counter throughout Sierra Leone but usually at very high prices that most people can ill-afford.

1.3 DETERIORATING MALARIA SITUATION IN SUB-SAHARAN AFRICA

Figures released by the World Health Organization indicate that 40% of the world population are at risk of malaria. Most of these people live in Sub-Saharan Africa. Annually, it is estimated that over 100 million people fall ill with malaria and of these a million, mostly children, do not survive their illness. Disease due to Plasmodium

falciparum malaria accounts for well over 90% of this morbidity and mortality (Molyneaux and Gramicia, 1980; Campbell, 1991; Marsh, 1992). It has been argued that this disease is one of the most serious obstacles to the socio-economic development of Sub-Saharan Africa (Breman et al., 1988).

The World Health Organization global malaria eradication campaign was never actively promoted or implemented to a national coverage in any country in sub-Saharan Africa (excluding the Southern tip) for logistical and financial reasons. Instead, the control of malaria morbidity and mortality through primary health care was recommended. It was thought that the early detection and prompt treatment of cases at the community level would be sufficient to control the disease or at least prevent severe episodes. Plasmodium falciparum resistance to chloroquine, which has been present in some other malarious regions for many years, is now present in every country in sub-Saharan Africa (Bjorkman and Philips-Howard, 1990). This is a very alarming development as it threatens the future usefulness of a cheap and well tolerated compound that has heretheto served as the mainstay of malaria control as implemented through primary health care in sub-Saharan Africa. Available alternatives to chloroquine are either too expensive or poorly tolerated. This problem with chloroquine has increased the need for new control strategies that are effective and sustainable at the community level.

1.4 MOSQUITO NETS AS AN ALTERNATE CONTROL STRATEGY

That insecticide-impregnated mosquito nets are now being seriously investigated as an alternate method in the control of malaria, in the setting described above, is not surprising, since mosquito nets have been used as a barrier against mosquito bites since the time of Christ (reviewed by Lindsay and Gibson, 1988). The use of mosquito nets in malaria control has been "rediscovered" several times during this century, since it was first advocated by Ross (1910) as a protective barrier against mosquitoes that transmitted malaria. There are reports of independent attempts to enhance the protective effect of bed and head nets by impregnating them with insecticides during the second World War (Blagoveschensky et al., 1945; Harper et al., 1947; Nauck et al., 1948). Although there are few details of these trials, it is thought that they were abandoned because the insecticides available then were considered as unsuitable for impregnating mosquito nets because they generally had a slow mode of action. With the advent of the quick acting synthetic pyrethroids, the evaluation of this strategy was once more taken up (Brun and Sales, 1976).

1.4.1 Mode of action

The principle underlying trials of insecticide-impregnated mosquito nets is that most malaria-transmitting mosquitoes tend to bite indoors and late at night. A person sleeping under an impregnated net is protected not only by the net acting as a physical barrier but also by the insecticide which enhances the effectiveness of the nets by repelling mosquitoes out of the room and killing those persistent enough to land on the net in their quest to feed. Various studies have provided ample evidence to support this hypothesis: reduction in man-mosquito contact (Snow and Jawara, 1987), insecticide impregnation of mosquito nets enhancing the effectiveness of nets; even torn or damaged ones (Lines et al., 1987; Hossain et al., 1989), and a beneficial effect to whole communities by reducing mosquito populations (Charlwood et al., 1987; Carnevale et al., 1988; Snow et al., 1988; Li Zuzi et al., 1989; Magesa et al., 1991).

1.4.2 Health impact

The logical extension of these promising findings has been the assessment of whether the effects of impregnated mosquito nets on malaria vectors have any measurable impact on malaria morbidity and mortality. Several studies conducted in different transmission zones have shown that impregnated mosquito nets do have protective effects as

assessed by indices such as the incidence of clinical disease (Procacci et al., 1991), prevalence of parasitaemia (Graves et al., 1987), spleen rate (Snow et al., 1988), and even childhood mortality (Alonso et al., 1991).

1.5 LITERATURE REVIEW

The design, conduct and result of trials evaluating the impact of insecticide-impregnated mosquito nets on malaria vectors and on malaria in humans have been critically reviewed extensively (Rozendaal, 1989; Curtis et al., 1990; Bermejo and Veeken, 1992; Sexton, 1994) and it would be difficult to attempt another case-by-case review without reiterating the points already highlighted. Two of these reviews (Rozendaal, 1989; Bermejo and Veeken, 1992) have similar concerns about what they considered as serious methodological problems in the design, conduct, and the absence of standardised case definition and therefore comparability of results from different trials. These concerns have been largely accepted and most new trials are designed and conducted in ways that can be said to have generally improved the comparability of results. However, there are additional areas that could benefit from further research and guidelines:

1.5.1 Standard definition of clinical malaria as an assessment index

As an example of differences in case definitions that make comparison difficult, Bermejo and Veeken (1992) cited the results of insecticide-impregnated net trials conducted in The Gambia (Snow et al., 1988) and Burkina Faso (Carnevale et al., 1988). The Gambian trial defined a case of clinical malaria as the simultaneous occurrence of recorded temperature greater than 37.5 °C and parasitaemia greater than 5000 parasites/microlitre; detected through an active case detection system, while Carnevale and co-workers based their case definition on self-referred fever cases (recorded temperature greater than 38 °C) and parasite density in excess of 10000 parasites/microlitre.

The different ways in which both studies recruited cases is of itself sufficient to limit a valid comparison of their results even if they had used identical parasitaemic criteria for defining a case of clinical malaria. What is debatable is whether it is wise to use an identical parasite density level in order to have a standardised case definition of clinical malaria, given the diversity in malaria transmission in different area. Is a standard case definition derived in such a manner necessary for the much desired comparative analysis of the effects of impregnated mosquito net trials?

In inhabitants of endemic areas, the age pattern of clinical malaria is related to the intensity of transmission

and the level of immunity engendered in response to that transmission pressure. It follows that in areas with different intensities of transmission as in The Gambia (season transmission) and in Burkina Faso (intense perennial transmission), the age-specific level of parasitaemia associated with illness and constituting the key component of the case definition of clinical malaria may be different.

This supports the view that the requirement for comparing the results of insecticide-impregnated mosquito net trials done in different settings is not simply a matter of standardisation in term of identical case definition, but rather a set of uniform criteria for the derivation of a parasite density level which in association with clinical manifestations constitute the case definition of clinical malaria that is area and age-specific (Smith et al., 1994).

1.5.2 Need to standardise method of deriving parasite density

All trials assessing the impact of insecticide-impregnated mosquito nets on the incidence of clinical malaria, have used a parasite density level to define illness threshold (Carnevale et al., 1988; Snow et al., 1988; Sexton et al., 1990; Alonso et al., 1991). There are several methods (Grenwood and Armstrong, 1991) routinely employed in determining parasite density and it would be advantageous to adopt a standard procedure thereby increasing the comparability of age and area-specific

illness threshold derived by a standard method as suggested above.

Field trials of malaria control strategy usually generate vast numbers of slides requiring several microscopists to cope adequately with the laboratory diagnosis of Plasmodium species and density level. With increasing reliance on parasite density level for case definition, it is essential that microscopy results derived as the combined efforts of several technicians are repeatable. So far, only one insecticide-impregnated mosquito nets trial(Snow et al., 1988) has reported a quality control of their microscopy results. These investigators noted a small number of false negatives from their original readings, and one can only speculate as to the contributory role of this factor in the contradictory results produced for some indices when more than one study was conducted in adjacent locations in some countries (Carnevale et al., 1988; Procacci et al., 1991).

1.5.3. Appropriate sampling unit

The issue of an appropriate sampling unit for assessing the effects of impregnated mosquito net trials do also need further urgent clarification. Several studies (Carnevale et al., 1988; Li Zuzi et al., 1989; Procaccci et al., 1991) have been criticised for comparing one intervention community with one control community. Since the community members are not independent variable, it is said that this

situation is analogous to basing a conclusion solely on the differential response between two individuals, one treated and the other untreated. On this basis, it is difficult to see how any statistically valid conclusion can be drawn from such a one-to-one comparison.

Because earlier studies (Lines et al., 1987; Snow et al., 1988) indicated that the use of impregnated mosquito nets by some people in a community, while others in the same community were without, may divert mosquitoes unable to feed on those with impregnated nets to those without, it became unacceptable for trials to randomise nets within a community. Another reason for treating an area said to have a distinct mosquito population (a community) similarly, is that impregnated mosquito nets have in some cases, demonstrated a "mass effect" (reducing the total mosquito density) in studies conducted in diverse areas; Tanzania (Megesa et al., 1991), Solomon Islands (Kere et al., 1993) and China (Li Zuzi et al., 1989), suggesting that the risk of transmission for inhabitants in a "community" is not unrelated. However, in most communities, the risk of malaria transmission is not homogeneous for all inhabitants initially. It varies greatly by households, being affected by such factors as distance of the individual household from the breeding site (Ross, 1899; Stephens and Christophers, quoted by Blocklock, 1925; Hackett and Missiroli, 1932), ease of access into houses (open eaves, etc.) (Magesa et al., 1990), types and level of protection used to prevent

people being bitten, and even mosquitoes' preference for some people (Khan et al., 1965; Khan et al., 1971; Wood, 1974; Dye and Hasibeder, 1986). These factors are usually similar within a household and it is difficult to imagine that the "mass effect" of a successful impregnated nets campaign would equalise the risk of transmission for all inhabitants in a community. It therefore seems reasonable to suggest that even if nets are distributed at the "community" level the role of the household as the sampling unit needs to be properly examined. The issue of the choice of a sampling unit in a trial of impregnated nets has immense implications for the cost of the trial and therefore require urgent attention.

1.5.5 Duration of trial period to take account of seasonality of transmission

Seasonal variation in mosquito density, malaria transmission and morbidity are among the earliest recognised features of malaria. However, in few earlier studies (Graves et al., 1987; Sexton et al., 1990) of impregnated nets, either the details provided are not sufficient for observers to determine whether the duration of follow-up took account of the seasonality of transmission or where reported, observations period was not long enough for the assessment to cover the full seasonal cycle in the study area. Restricting the follow-up period to the low transmission season only may bias the estimate of the overall impact of impregnated nets as a malaria control strategy in a

particular locality. This was demonstrated in Burkina Faso (Procacci et al., 1991), where curtains impregnated with permethrin were shown to reduce the incidence of malaria attacks, mean parasite density and prevalence, and splenomegaly but had no clear-cut impact during a period of more intense transmission. Even in areas with marked seasonal transmission, such as The Gambia (malaria transmission occurs for only four months during the rainy season), new trials should plan for a follow-up period that covers the entire seasonal cycle because the year-to-year variation in malaria transmission is usually unpredictable.

1.6 OBJECTIVES OF THE STUDY

The main objectives of this study include: (a). measuring the effects of synthetic pyrethroid-impregnated mosquito nets, singly or in combination with maloprim^{R}/placebo prophylaxis, on clinical malaria per child/week of observations, and (b) to determine also the effects of these interventions on other indicators such as parasite density and prevalence, spleen rate, and anaemia as measured by the haematocrit levels. The effects of impregnated mosquito nets on malaria vectors in the study area is also being investigated, but the results will be presented separately (Magbity et al., personal communication).

1.6.1 Supplementing impregnated mosquito nets

Several Studies conducted in sub-Saharan Africa (Snow et al., 1987; Snow et al., 1988; Procacci et al., 1991) have demonstrated that impregnating mosquito nets with synthetic pyrethroid significantly reduced most malariometric indices in areas with low to moderate transmission, or in the same area during a low transmission season but not during the high transmission season. A recent report from The Gambia (Alonso et al., 1991) indicated that combining Maloprim^{R} prophylaxis with permethrin-impregnated mosquito nets significantly reduced malaria morbidity in children using the combined interventions compared with those using treated mosquito nets alone. This represents an interesting avenue for augmenting the beneficial effects of treated mosquito nets. This study is therefore also an attempt to investigate whether combining Maloprim^{R} prophylaxis with insecticide-treated mosquito nets would significantly enhanced the protective effects of the later against childhood malaria in tropical west Africa where malaria transmission is perennial and intense, resulting in an impact similar to those seen in areas with low-to-moderate transmission.

1.6.2 Concern about the effects of the combined strategies on acquisition of immunity and related issues.

The possible effects of combining Maloprim^{R} prophylaxis and impregnated mosquito nets on the development of immunity in children is a serious concern to many people interested in malaria, especially those working in Sierra Leone. It is feared that the combined strategies may be so effective that children using it may not have the opportunity to develop the level of immunity existing in their age contemporaries living the same area but not involved in the programme. This is a valid concern but one which should not hamper this investigation. Firstly, it is not expected that combining impregnated mosquito nets and Maloprim^{R} prophylaxis would be so effective that transmission is completely interrupted to those involved. Even in those maintaining a meticulous compliance level, the opportunity for re-infection are so numerous (Bockarie et al., 1993) that they are expected to develop the age and area specific level of immunity. Secondly, no field trial or operational chemoprophylaxis campaign, has to my knowledge, ever achieved absolute perfection in the distribution and compliance with anti-malaria chemoprophylaxis (Greenwood et al., 1986; Greenwood et al., 1988; Kaseje et al., 1987; Allen et al., 1990a). The most that can be reasonably expected is that the combined effects of treated mosquito nets and Maloprim^{R} prophylaxis may, if effective, provide some protection against episodes

of clinical malaria, limiting the number of episodes or even their severity. In short, the use of these combined strategies is not intended to interrupt transmission to participants, but to reduce the disease burden. At present one can only speculate as to the means by which this may be accomplished: reduction in the average sporozoite load because the child is bitten by fewer infective mosquito (Magesa et al., 1991), or reduction in super-infection by fewer unfamiliar "strains" (Lines and Armstrong, 1992).

The other concerns are those regarding the development of side effects in children and resistance in Plasmodium species. Despite many years of chemoprophylaxis with maloprim^{R} in Gambian children, there has been no report of any resistance or untoward side effects noticed (Allen et al., 1990b). This is reassuring, but there are obvious differences in both the schedule of the prophylaxis and the locality and population necessitating a careful continuous monitoring of the situation in Sierra Leone.

1.7 ORGANISATION OF THE THESIS

This thesis is basically divided into two parts: pre-intervention pilot studies and the intervention phase. **Chapter 2** describes a comparative study of the acceptability of untreated-mosquito nets versus nets impregnated with permethrin, deltamethrin and lambdacyhalothrin synthetic

pyrethroid insecticides. **Chapter 3** presents investigations conducted with the sole purpose of developing an age and area-specific definition of clinical malaria as the key malariometric index for assessing the impact of the interventions. The chapters pertaining to the intervention phase are **chapter 4** (the design and conduct of the interventions), **chapter 5** (evaluating the impact of the interventions on clinical malaria and related malariometric indices) and **chapter 6** (summaries and conclusions).

CHAPTER 2

A double blind comparative study of the acceptability of untreated-mosquito nets versus permethrin, lambdacyhalothrin and deltamethrin-impregnated mosquito nets.

2.1 INTRODUCTION

The use of mosquito nets in the prevention of malaria was advocated by Ross (1910) early in this century. During the second world war, American and Soviet malariologists (Harper et al., 1947; Blagoveschensky et al., 1945) demonstrated that the protective effect of bed or head nets could be enhanced by impregnating with plant based repellents or the newly discovered DDT.

Gouch and his co-workers (1967,1971) demonstrated the potential of various repellent compounds for impregnating nets. The first community-wide intervention trial with pyrethroid-impregnated mosquito nets was organised in Mali by Ranque and co-workers (1984). Various synthetic pyrethroids have since been used extensively in malaria control trials (reviewed by Rozendaal, 1989).

A recent study from The Gambia reported that insecticide-impregnated mosquito nets reduce malaria-specific childhood mortality and have a beneficial, though less dramatic effect on morbidity (Alonso et al., 1991).

The advantages of impregnated bed nets are that they improve the personal protection provided by a damaged or badly used net, and that the odour of the sleeper in an impregnated nets serves as a bait attracting mosquitoes to the nets, where they may be killed (Curtis, 1992). Nets may be easier to implement and sustain than alternate vector

control measures, especially because of their immediate apparent benefit to the user in protecting from mosquitoes as well as other nuisance insects.

Malaria control by insecticide-impregnated mosquito net has not previously been assessed in the rain forest of West Africa under conditions of perennial transmission, and this investigation is part of the pre-intervention studies of a large community-wide intervention study of impregnated mosquito nets and maloprim^{R} prophylaxis, singly and in combination (Petersen et al., 1993).

This study compared the acceptability of three different synthetic pyrethroids: permethrin, deltamethrin and lambdacyhalothrin. The trials conducted in The Gambia used permethrin throughout, while deltamethrin had been used extensively in China and Francophone Africa.

As far as I am aware, lambdacyhalothrin has so far only been used once in Africa. In a malaria control trial in Tanzania (Njunwa et al., 1991), lambdacyhalothrin was among other insecticides tested and the investigators reported a time limited irritant effect related to the concentration of lambdacyhalothrin used.

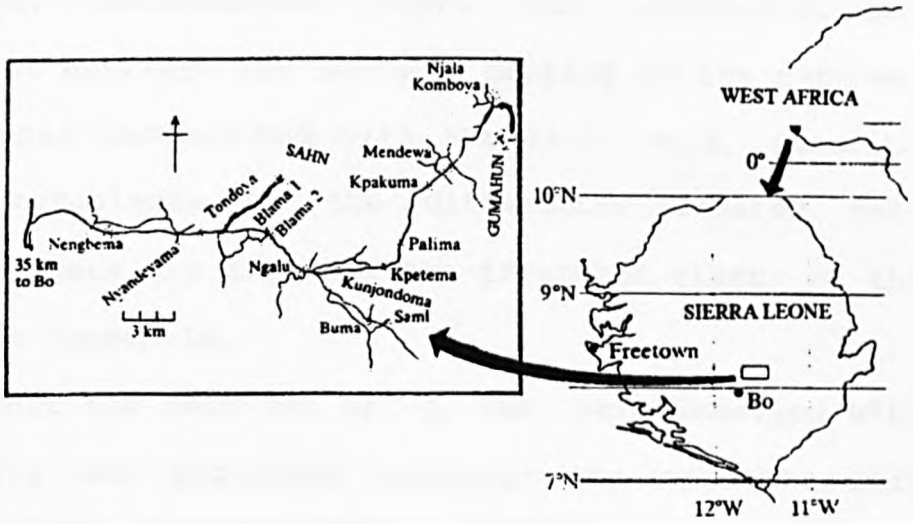
The aim of this pre-intervention study was to have a sample of our target community participate in the important decision as to which of the three synthetic pyrethroid insecticides, readily available to the study, to use for impregnating the mosquito nets during the intervention phase of this trial. It was thought that participation of

even a fraction of the target communities in this important decision would increase the likelihood of full co-operation of the entire study population.

2.2 MATERIALS AND METHODS

2.2.1 Study area and population

The base laboratory of this study is situated in Bo, 240 km East of Freetown, Sierra Leone, while the study area is about 40 km North of Bo (see map). The area is within the West African rain forest belt with perennial malaria transmission (Barnish et al., 1993b). The main vector in the study area is *Anopheles gambiae s.s* (Bockarie et al., 1993). The annual rainfall is between 2.5 and 3 m, with a marked hot dry season of little or no rainfall from November to mid-March, and a rainy season from April to October. The vegetation is secondary forest due to the extensive slash and burn cultivation of a subsistence economy. A census was performed in the selected trial village, Sahn, and every bed or sleeping arrangement enumerated. Each household was randomly allocated to receive either untreated mosquito nets or nets impregnated with one of the three synthetic pyrethroids. All beds within the household received nets impregnated with the same insecticide. The village had 95 households with a total of 726 beds and other sleeping arrangements.



Location of the Bo malaria study area.

2.2.2 Nets

Knitted nylon nets of 100 denier in four different sizes ranging from 9.8m^2 to 14.2m^2 were acquired from the Siamdutch Netting Co. Ltd., Bangkok, Thailand for the study.

2.2.3 Insecticides

Lambdacyhalothrin and permethrin were donated by ICI, UK, and deltamethrin was donated by Roussel Uclaf, France; all were supplied as emulsified concentrates(permethrin 500g/l; deltamethrin 25g/l and lambdacyhalothrin as 50g/l).

2.2.4 Impregnation

The impregnation was carried out using procedures similar to that used in The Gambia (Snow et al., 1988) to

achieve calculated concentration of: permethrin 500 mg/m^2 netting, deltamethrin 25mg/m^2 and lambdacyhalothrin 10 mg/m^2 of netting. The actually dipping of the nets was done by people unconnected with the field work, ensuring that both recepients of the differently treated nets and interviewers did not know the treatment status of the nets in each household.

Once the nets had dried, they were labelled with both washable and permanent markers; the washable mark was intended to monitor washing of the nets. Recipients were asked not to wash their nets as this would remove the insecticidal effect (Snow et al., 1987). The permanent mark coded the treatment on the net. There were six codes for each treatment group to ensure that interviewers remained unbiased for or against any of the insecticide.

2.2.5 Acceptability assessment

Acceptability was assessed by interviewing all adults present during visits by the interviewers to each household on day 7, 14 and day 28 after the nets had been successfully installed. The interviews were unstructured. Interviewees were asked to report what he/she liked or disliked about their net. A favourable outcome was registered when the respondent found the nets an improvement compared to before the nets were introduced; and an unfavourable statement was recorded whenever there were complaints about the nets. Two separate surveys were

conducted. In one survey, only the heads of households were asked about the nets installed in their homesteads, whereas the other survey involved all adults inhabitants present on the day of the interview. The interviews with heads of households did not inquire about whether any one had discontinued the use of the net on account of "unfavourable effects", but this question was put during interviews involving other adult inhabitants of the village. The issue of discontinuation of use of the nets was not a direct question, as it was feared that the respondents might be reluctant to admit to this directly. Instead, the question was phrased such that it was inquiring if the "unfavourable effects" were so severe or unbearable that the interviewee had considered abandoning the net altogether.

2.3 RESULTS

The results of the interviews conducted among head of households, are shown in **Table 2.1**, while that involving all other adults inhabitants is similarly shown in **Table 2.2**. The side effects of the nets, which according to respondents, had caused them to considered abandoning the nets were found only during the first 14 days after impregnation and installation of the nets. These side effects had completely disappeared by day 28 post installation (**Table 2.2**).

Table 2.1: The results of interviews conducted among head of households about reactions to the nets in their homesteads

Days after impregnation	Reported effects of nets			Total number interviewed
Day 7	Favourable	Unfavourable	Nothing unusual	
Placebo	5	3	17	25
Deltamethrin	16	7	0	23
permethrin	15	3	6	24
Lanbdacyhalothrin	17	3	3	23
Day 14	Favourable	Unfavourable	Nothing unusual	
Placebo	7	2	16	25
Deltamethrin	14	8	1	23
permethrin	17	2	5	24
Lanbdacyhalothrin	18	0	5	23
Day 28	Favourable	Unfavourable	Nothing unusual	
Placebo	7	1	17	25
Deltamethrin	15	3	5	23
permethrin	10	1	13	24
Lanbdacyhalothrin	10	0	13	23

On the positive side, those with treated nets were very enthusiastic about their nets, reporting not only a significant reduction in mosquito bites indoors, but the near elimination of bed-bugs, headlice and cockroaches. It is also apparent from the responses of even those using placebo-treated nets, that our study population greatly approves of the nets.

Table 2.2: **The responses of individual adults using the nets on what they like or dislike about the nets.**

Days after impregnation	Reported effects of the nets			Total number interviewed
	Favourable	mild side effects	Intolerable side effects**	
Day 7				
Placebo	57	2	5	64
Deltamethrin	37	8	2	44
Permethrin	46	5	2	53
Lambdacyhalothrin	46	2	1	51
Day 14				
Placebo	76	0	3	79
Deltamethrin	45	1	1	47
Permethrin	57	2	2	61
Lambdacyhalothrin	70	10	0	80
Day 28				
Placebo	86	3	1	90
Deltamethrin	50	3	0	53
Permethrin	60	3	0	63
Lambdacyhalothrin	67	1	0	68

**Intolerable side effects were those so severe that the respondent had considered abandoning the nets.

The negative ratings which were elicited from those with treated nets were predominantly about irritation and only a few were about any discomfort from reduced ventilation; this being found exclusively among respondents using placebo-treated nets. This seems to suggest that the discomfort from the irritant effects of the insecticides outweighed any ventilation problem, at least during the

first 14 days after net impregnation, thus causing it to be ignored by those experiencing the more serious irritant effects in the treated net groups. The results in **Table 2.2** also show a differences in the numbers of respondents in the different group who had considered the likelihood of discontinuing using the nets because of side effects. During the first interview, 7 day after impregnation and installation, only one of the three respondents in the lambdacyhalothrin group reporting an unfavourable effects indicated that they had considered abondoning the nets because of the severity of the side effects compared with two person each from the permethrin and deltamethrin group respectively. By day 14, there was no such report from the lambdacyhalothrin group, while respondents from permethrin and deltamethrin group were still indicating that they considered the side effect to be unbearable. During the final survey 28 day after impregnation and installation, one of the four persons reporting unfavourable effects, in the placebo-treated net group, still considered the side effect (reduced ventilation) severe enough to actually abandoned his net.

2.4 DISCUSSION

Mosquito nets are well known in our study area, but a survey found nets in only 6% of households and usually over a single bed belonging to the head of the household (Aikins

et al., 1994). The main reason given for the low frequency of mosquito net usage was cost. The newest nets in Sahn were at least 5 years old and cost the monthly wage of a secondary school teacher at the time of this acceptability survey. Differences in mosquito net acceptance and usage have been well documented among the different ethnic groups in The Gambia (Snow and MacCormack, 1986), but were not found in our study population.

The results clearly indicate that our study population found mosquito nets acceptable. Those using deltamethrin and permethrin impregnated nets reported slightly more unfavourable effects during first two weeks after impregnation and installation compared to users of lambdacyhalothrin impregnated nets, even though the difference was not statistically significant.

Snow and co-workers (1988) did not find any difference in reported unfavourable effects of permethrin compared to placebo, nor did Njunwa and co-workers (1991) reporting from Tanzania, mention anything similar to the irritant effects of permethrin such as found in our survey. However, the unfavourable effects reported in our study were mostly found during the first week after the nets had been impregnated and then immediately installed. This seems to suggest that the timing of the interview in relation to the impregnation of net should be taken into consideration, when evaluating reported side effects of impregnated nets.

Permethrin has the obvious advantage of having been widely used and hence more data should be available for comparison. However, it was decided to opt for lambdacyhalothrin instead, because our pilot study had indicated that it is slightly superior to permethrin and deltamethrin with regards to fewer reported side effects and the likelihood of abandoning the nets because of the severity of such side effects. In addition, lambdacyhalothrin requires a yearly impregnation in a low dose, which, at present prices, would mean substantial saving in the total cost of organising a community-wide campaign.

CHAPTER 3

Developing an area-specific definition of clinical malaria as the key malariometric index.

3.1 INTRODUCTION

In areas with stable and intense malaria transmission such as Sierra Leone, asymptomatic parasitaemia in children complicates the diagnosis of malaria (Marsh, 1992). Distinguishing clinical malaria from other common childhood diseases which happen to have coexisting malaria parasitaemia is highly desirable but may be difficult, if not impossible, with available facilities.

Several trials (Snow, 1988; Menon, 1990; Lyimo, 1991) involving synthetic pyrethroid-impregnated mosquito nets in the control of malaria have adopted an illness threshold which is generally defined as the simultaneous occurrence of parasitaemia above a certain cut-off value and symptoms or signs suggestive of malaria. It has long been recognized that because of variation in the transmission dynamics, the value of the parasite density adopted as pyrogenic or illness threshold must necessarily be area-specific (Miller, 1958; Earle, 1939; Trape et al., 1985;). However, it appears that the cut-off levels quoted in various reports (Baudon et al., 1986; Benassani et al., 1987; Velama et al., 1991) are arbitrary estimates of the pyrogenic threshold. Their values range from 1000 to 15,000 asexual parasites/ul, all referring to Plasmodium falciparum.

In The Gambia, Greenwood and co-workers(1987) proposed that probabilities of the attributable fraction, based on the relationship between fever risk and parasite density, and

estimated by the classical method (Walter, 1976) could be used to select an area-specific pyrogenic or illness threshold. However, in endemic areas with stable and intense transmission, the classical method of deriving the attributable fraction has been demonstrated to be inadequate because the relationship between the risk of fever and parasite density is non-monotonic over a certain range of parasite densities (Smith et al., 1994). Logistic regression models (Smith et al., 1994; Armstrong-schellenberg et al., 1994) have been shown to overcome this problem of non-monotonicity and have the additional advantage of being easy to adjust for covariates such as age and seasonal effects.

3.2 MATERIALS AND METHODS

This pre-intervention study was undertaken to develop an area-specific case definition of clinical malaria based on: (i) a simple, standardized frame for collecting specimens and referring participants to the Community Health Officer(CHO) for assessment and treatment as appropriate, and (ii) adopting an area-specific level of "critical parasitaemia" above which it would be rare to find asymptomatic children in the communities. Another simplification is that clinical malaria is characterized entirely in terms of Plasmodium falciparum, even though P. malariae and P. ovale occurred in the study area of Bo district, Sierra Leone(Barnish et al., 1993b). We have restricted our discussion to P.falciparum because it is

considered to account for well over 90% of the health problems posed by malaria in Sub-Saharan Africa (WHO, 1990).

3.2.1 Study area

This study was conducted in two parts: cross-sectional surveys conducted in nine of the 17 proposed study villages, and a weekly morbidity surveillance based in Sahn. Sahn is about 6 kilometres off the main road between Bo and Njala Komboya (see **map in Annex** for detail). Sahn is fairly large, in relation to surrounding villages, with ninety-five dwellings. Most of these houses have corrugated iron roofs. There are several swamps close to the village and they are sometimes used for rice cultivation. At the periphery of Sahn are several borrow-pits which were dug for the purpose of getting mud for sun-bricks as building materials. What role, if any, the swamps and borrow-pits play as breeding sites of malarial vectors is being investigated separately (Magbity, personal communication). Almost all villages in the study area do have borrow-pits with the swamps being limited to low-lying villages, so Sahn is not atypical.

A compound-by-compound census and enrolment revealed a total population of 2085 of whom 481 were under the age of 7 years. A sizable proportion of the adults spend days or weeks away in farming hamlets during the main farming activities such as planting and harvesting, while their "retired relatives" foster the younger children and maintain the homestead.

3.2.2 Morbidity surveys

Weekly morbidity surveys were initiated during the second week of August, 1991 and concluded at the end of May, 1992. During this time children under the age of 7 years and any new additions by birth or immigration were recruited for active surveillance with the permission of their parents or guardians. Each field worker was allocated between 60-80 children and was required to monitor them (from Monday to Friday) at the rate of 12-15 daily. The active surveillance system involved each child being presented to the field worker or located in the home, village school or farm and a standard questionnaire administered to the parents or guardians.

The presence of one or more of the following were used as criteria for taking blood samples:-

1.History of fever on day seen

2.History of fever during the last seven days

3.History of chill,rigors or headache during the last 7 days

4.History of vomiting or diarrhoea during the last 7 days

5.Recorded temperature greater than or equal to 37.5 degrees Centigrade.

These sampling criteria were selected because our previous experience of malaria morbidity surveillance in similar transmission circumstances and populations (Hogh et al., 1993) suggests that their inclusive nature would reduce the risk of missing "true malaria attack" among children with very high levels of parasitaemia but no fever at presentation.

Children found to be ill were referred to the Community Health Clinic for evaluation and treatment paid for by the study. This process of referring sick children to the community health Officer (CHO) is in keeping with our agreement with the Ministry of Health to support already established community-based drug revolving-fund schemes. The Ministry believe that if the research team provided a short term alternative service, this could undermine their efforts to develop a primary health care service supported by the communities. A community-supported primary health care service with a village-based CHO (para-medical worker) also benefitted the research team because it meant that ill children could receive prompt antimalarial treatment which if necessary would be re-assessed when the malarial microscopy results were available several days later.

3.2.3 Cross-sectional surveys

Two separate cross-sectional surveys (October, 1991, toward the end of the main transmission season and March, 1992, toward the end of low transmission season) were conducted in 9 of the 17 proposed study villages. Parents and guardians were encouraged to present all children aged 3 months to 6 years. Axillary temperature was recorded with an electronic thermometer and a brief history of health status during the past week noted. By contrast with the morbidity surveys, finger-prick blood samples were obtained for microscopy from all children irrespective of health status.

Children suspected of suffering from malaria were treated with chloroquine (25mg/kg).

3.2.4 Estimating the Attributable fraction

The attributable fraction is the proportion of cases in which illness is associated with raised P. falciparum density. This proportion can be estimated either by the classical methods (Walter, 1976) or by using logistic regression as proposed by Smith and co-workers(1994). In either case the derivation of the attributable fraction is based on the premise that the risk of fever or illness increases with parasite density. For example, suppose the incidence of fever among children with parasites is **L**, and that among children without parasites is L_0. The Relative Risk of fever in those with parasites compared to those without can be denoted by **R**, so that $L=RL_0$. Then, among those with parasites, the proportion of fever due to malaria is **(R-1)/R**. We can ignore those without parasites, since presumably none of their fever is due to malaria. However, among all cases of fever, the proportion due to malaria or the attributable fraction is **p(R-1)/R**, where **p** is the proportion of fever cases with parasites. This is the classical method of deriving the attributable fraction. In areas with intense and perennial transmission, this method underestimates the attributable fraction because there is a relative scarcity of low parasite counts in febrile children compared with afebrile children over a certain density range (Rooth and Bjorkman, 1992; Smith et al., 1994). The logistic

regression model overcomes this problem of non-monotonicity by relying on the parasite density distribution in febrile and afebrile cases. It aims to derive a relative risk of fever that smoothly increases with parasite density by modification of $\log(\pi/(1-\pi))$, where π is the probability of fever at a specified parasite density, x. The $\log(\pi/(1-\pi))$ or the log odds of fever, can be written as $A+f(x)$ where for a child with parasite density x, the Relative Risk of fever, R, is $\exp[f(x)]$. This is the simplest logistic model that denotes a linear relationship. The modification that best fits these data is that achieved by raising density to a power function where:

$$\log(\pi/(1-\pi)) = A+f(x^t)$$

This is equivalent to $R=\exp[f(x^t)]$. Note that the attributable fraction is then derived as previously: $AF=(R-1/R)$. The values for f and t were estimated from the data using the programme Egret^R with the best value being determined by the maximum likelihood technique.

3.3 RESULTS

3.3.1 Cross-sectional surveys

Table 3.1a depicts estimates of attributable fractions based on logistic regression power models which have been adjusted for possible confounders. The model adjusting for age-density interaction has the lowest deviance and highest

Table 3.1a: Mean attributable fraction estimated by logistic regression power models

Logistic Models	Fitted parameter(B)	t	LR statistic	P-value	Deviance	Mean AF
Unadjusted power model	0.005938	0.55	58.154	<0.001	1603.985	19
power model adjusted linearly for age	0.005882	0.55	1.547	0.214	1602.439	18
Power model adjusted for season as factor	0.006175	0.55	10.463	0.106	591.976	19
Power model adjusted for age-density interaction	0.00888	0.55	9.338	0.155	1582.638	23

attributable fraction, but the P-value of the Likelihood Ratio statistic indicates that for these data the best model

Table 3.1b. Estimation of the sensitivities and specificities of case defination

Diagnosis True Aetiology

	Malaria	Other	All
Malaria	$nc\lambda c$	$nc(1-\lambda c)$	nc
Others	$N\lambda-nc\lambda c$	$N(1-\lambda)-nc(1-\lambda c)$	N-nc
All	$N\lambda$	$N(1-\lambda)$	N

SENSITIVITY=$nc\lambda c/N\lambda$ SPECIFICITY=$1-[nc(1-\lambda c)/N(1-\lambda)]$

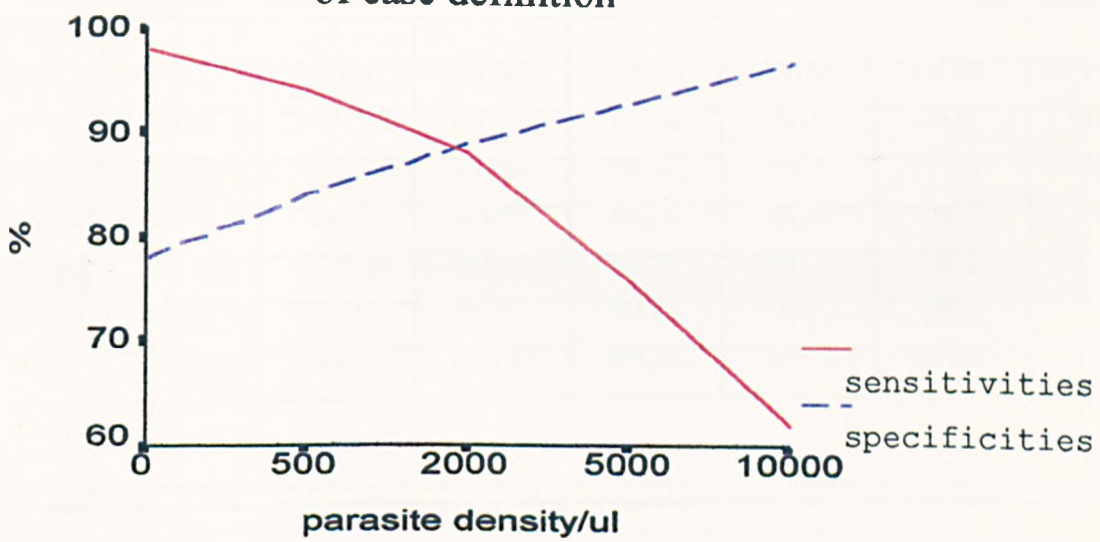
is the unadjusted power model which gives an attributable fraction of 19% [95% confidence interval(4%-28%)]. The

attributable fraction derived by the classical method is 17% and this underestimates the logistic regression figure of 19% as predicted by Armstrong-Schellenberg and colleagues (1994).

3.3.1.1 Deriving the illness threshold

Figure 3.1 shows the sensitivities and specificities of alternative case definitions for this data set. These figures are for all ages combined and were calculated from the attributable fraction probabilities as suggested by Smith and his colleagues (Smith et al., 1994.) (see **Table 3.1b**).

Figure 3.1: The sensitivities and specificities of case definition



3.3.1.2 Age-specific illness threshold

The results presented in **figure 3.1** suggest that a density cut-off in the region of 2000 parasites/ul (sensitivity of 83%, specificity of 89%) is a suitable choice for the illness threshold. However, it is doubtful whether

this level would apply to all ages as a standard diagnostic cut-off given that the level of parasitaemia tolerated (level at which residents of endemic areas are asymptomatic) is known to increase with age in children (McGregor, 1983; Petersen and Marbiah; unpublished observations).

The data displayed in **Table 3.2**, which shows the cumulative percentages of Plasmodium falciparum densities distribution by age in slide-positive afebrile children,

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Table 3.2: The cumulative percentages of P.falciparum density distributions by age in SLIDE-POSITIVE AFEBRILE children [number of children in ( )]

Age in years

Densities	1	2	3	4	5	6	7
1-499	82%(18)	62%*(58)	73%(76)	70%(85)	75%(70)	87%(90)	87.6%(221)
500-1999	86%(1)	78%(15)	83%(12)	71%(2)	76%(1)	88%(1)	88%(1)
2000-2999	86%(0)	91%(12)	83%(0)	79%(10)	78%(2)	88.5(1)	90%(5)
3000-3999	86%(0)	92%(1)	90%(7)	85%(7)	81%(2)	89%(1)	91%(4)
4000-4999	86%(0)	93.5%(1)	90%(0)	90%(6)	88%(7)	91%(4)	93.3%(4)
5000-9999	86%(0)	94.6%(1)	95%(5)	91%(1)	90%(2)	95%(2)	97%(10)
>=10,000	100%(3)	100%(5)	100%(5)	100%(11)	100%(5)	100%(5)	100%7)

---

represent an attempt to explore this result for differences in the level of age-specific asymptomatic parasitaemia. Note that the 90th percentile of the density distribution occurred below 3000 parasites/ul in afebrile children aged 1-2 years, while for their older comtemporaries it generally occurred at or above 3000 parasites/ul. This may be interpreted as supporting the view of a difference in the age-specific illness threshold

in this study population. While instructive, the 90th percentile of the asymptomatic parasite density level derived here cannot be taken as representing the precise level to adopt as the age-specific illness threshold for this study because it is based on a small number of children. However, this information is more useful than either the arithmetic or geometric means in exploring the effect of age on the illness threshold as both the arithmetic and geometric means are heavily influenceby outliers (data not shown).

The probable influence of age on the illness threshold has been accommodated in selecting the age-specific parasite density at which clinical manifestations are likely to occur in this population. For younger children, the vast majority (90th percentile level) who had asymptomatic parasitaemia were found with parasite density below 3000 parasite/ul. Therefore, an illness threshold at the cut-off of 2000 parasites/ul (sensitivity and specificity of 83% and 89% respectively) has been arbitrarily selected for children aged 2 year and younger, and the level of 5000 parasites/ul (sensitivity of 78% and specificity of 93%) similarly adopted for older children on the basis of a presumed difference in the level of parasitaemia tolerated with age in children. The sensitivities and specificities of the selected age-specific cut-offs are within acceptable range as derived by the logistic regression method using the combined data for all ages.

3.3.2 Morbidity surveys.

3.3.2.1 Extended criteria of taking blood films

Of the 14436 contacts made by field workers during the weekly morbidity surveillance, guardians were noted as the informants in only 8.3%(1201) of contacts. Indeed, parents presented their children on 13,235(91.3%) occasions out of 14436 contacts. In a close knitted extended kinship situation found in Sahn (and the entire group of study villages) where older siblings, relatives and grandparents may assist parents in looking after children, how reliable is the history of a child's health status given that a child is usually in the care of many different persons for a variable period of time?

Table 3.3: Attendent's subjective assessment of "fever on day seen" compared with recorded temperature>=37.5 C (Temp.>=37.5 C is febrile threshold of study)

	FEVER REPORTED ON DAY SEEN							
	YES				NO			
RECORDED TEMP.	<35.5	37.5-38.4	38.5-39.4	>=39.5	<37.5	37.5-38.4	38.5-39.4	>=39.5
INTERVIEWEES								
PARENTS	556	503	99	36	12000	27	1	5
GUARDIANS	81	35	17	1	1062	3	0	10

Parents:

positive predictive value=638/1194=53.4%

negative predictive value=12000/12033=99.7%

Guardians:

=53/134=39.6%

=1062/1075=98.8%

Of the five criteria for taking blood films, reports of "fever on day seen" can be objectively assessed against fever defined

by recorded temperature of 37.5 C or above measured with an accurate electronic thermometer(Therumo^{R}). **Table 3.3** is a summary of such an appraisal where the informants' subjective assessment of "fever on day seen" is compared with fever defined by recorded temperature of 37.5 C or above. The low positive predictive value of informants for reports of fever and recorded temperature in the febrile range is entirely consistent with the periodicity of clinical manifestations of malaria. On the other hand, the nearly identical negative predictive value of 99.7% for parents and 98.8% for guardians suggest that informants are generally reliable.

The value of extending the sampling criteria to include, history of fever during the last 7 days; chills, rigors or headache; vomiting or diarrhoea; is clearly illustrated by **Table 3.4** which shows the additional cases of parasitaemia above the illness threshold detected. Compared to sampling for fever alone, the additional criteria have a slightly lower yield, accounting for 47.7% (1792/3753) of the slides collected but only 26.8% of the 698 occurrences of "critical parasitaemia" found. However, the detection of 17% of children with parasitaemia above 100,000 parasites/ul would have been delayed had sampling been restricted to the usual practice of blood sampling for fever only.

Table 3.4: The distribution of Plasmodium falciparum densities observed during the morbidity surveys classified by sampling criteria

	P. falciparum densities distribution:density/ul								
Sampling criteria	0	1-999	1000-1999	2000-4999	5000-9999	10000-24999	25000-49999	50000-99999	>=100,000
fever*	870 (44%)	490 (52%)	19 (61%)	91 (61%)	134 (62%)	168 (73%)	110 (87%)	54 (90%)	25 (83%)
Extended criteria	1089 (56%)	461 (48%)	12 (39%)	59 (39%)	81 (38%)	63 (27%)	16 (13%)	6 (10%)	5 (17%)
Total	1959	951	31	150	215	231	126	60	30

The extended criteria for collecting smear included:

1. history of fever during the previous 7 days
2. history of chills, rigors or headache on day seen or during the previous 7 day
3. history of vomiting or diarrhoea during the previous week

* The usual criteria of fever is either history of fever on day seen or recorded temperatue above a given cut-off

3.3.2.2 Enumerating episodes

Table 3.5 shows the frequency of "critical parasitaemia" (age-specific illness threshold) and the number of such events persisting sequentially during consecutive weekly visits. There are two case scenarios here for calculating the incidence rate from these data. If one assumes that the occurrence of each critical parasitaemia noted during the weekly visits constitutes an episode of malaria, then the incidence rate of malaria would be 48.4/1000 child weeks-at-risk (698/14436). Alternatively, an episode in a child could be defined as a period of ill health due to clinical malaria which starts with the occurrence of critical parasitaemia and

continues until the child has recovered. This means that critical parasitaemia occurring sequentially in consecutive weekly visits constitutes a single episode. Note that by defining episodes in this manner we obtain the lower incidence rate of 42.8/1000 CWAR, which is however only 12% lower than that resulting from counting every critical parasitaemia as a distinct episode. Counting the occurrence

Table 3.5: The frequency of "critical parasitaemia" observed during the morbidity surveys and the number persisting sequentially during consecutive weekly visits.

Frequency of critical parasitaemia	Number of children	Total critical parasitaemia observed	Number of critical parasitaemia persisting during consecutive visits for:		
			2 weeks	3 weeks	4 weeks
0	173	0	-	-	-
1	115	115	-	-	-
2	67	134	10	-	-
3	35	105	3	1	-
4	23	92	7	1	-
5	11	55	8	1	-
6	9	54	3	2	1
8	3	24	3	1	-
9	3	27	3	3	-
10	5	50	7	1	1
Total	450	698	49	12	2

of every critical parasitaemia as an episode is probably incorrect because it is based on the erroneous assumption that complete and instantaneous parasite clearance always follows treatment with available antimalarials (Bjorkman et

al., 1991), and that the occurrence of every critical parasitaemia observed after treatment is therefore an independent event.

3.4 DISCUSSION

In endemic areas with intense and perennial transmission such as Sierra Leone, the essence of distinguishing malarial parasitization from disease is nothing new (Bagster-Wilson, 1938; Swellengrebel, 1950; McGregor, 1960). In these settings, malaria as a disease is a relatively rare event compared to the cumulative parasite prevalence of nearly 100% over a year (Bruce-Chwatt, 1963). This high level of asymptomatic parasitaemia limits the usefulness of "indices of parasitization" such as parasite rates, parasite density, spleen rates, etc in quantifying malaria as a health problem in inhabitants of endemic areas.

While desirable and necessary for measuring the malarial burden on a population in an endemic situation, malaria as a disease is difficult to define. There are no signs and symptoms exclusive to clinical malaria. A further complication (already mentioned) is that while fever and slide positivity are sufficient for a diagnosis of clinical malaria in non-endemic areas or naive persons in endemic areas, asymptomatic parasitaemia is very common among inhabitants of areas with stable transmission.

These difficulties complicate the characterization of clinical malaria in endemic areas. Efforts to address the methodological problems have recently received much attention, increasingly focused on the relationship between parasite density and the risk of fever (Delfini,1973; Rougement et al., 1991; Velema et al., 1991; Hogh et al., 1993). Although the intensity and length of exposure may modify this relationship (McGregor & Wilson, 1988; Baird et al., 1991; Petersen et al., 1991), it is generally acknowledged that the risk of febrile illness increases with parasite density. This implies that one can expect parasitaemia above certain cut-off values to nearly always be associated with a febrile illness and thus serve as a definition of clinical malaria. Implicit also in such a definition is that the cut-off selected is age and area-specific.

In this study, I have attempted to derive an age and area-specific definition of clinical malaria by exploring explanatory variables of the relationship between fever risk and parasite density. I have relied on variables that others have found useful (Smith et al., 1994; Amstrong-Schellenberg et al., 1994), while examining additional factors I consider pertinent to the construction of a definition of clinical malaria applicable to our study population.

I think that age is an important factor in the choice of the parasite density selected as an illness threshold, based on evidence that the level of parasitaemia tolerated increases with length of exposure, at least in children. This is the

basis of not relying exclusively on the sensitivity and specificity of various cut-off for my choice of case definition, especially as this data is pooled for different ages. The data presented in **Table 3.2** support this view by demonstrating that the level of parasitaemia tolerated in children increases with age. It is clear that ignoring this and depending on the sensitivity and specificity alone would have resulted in many false-positives among older children in this population.

The sampling criteria also have an important bearing on the proportion of children whose blood is sampled and accordingly affect the number of critical parasitaemia detected. The clinical manifestations of malaria are dominated by the febrile episodes that accompany the destruction of red blood cells during the host cycle of the parasite. The febrile episodes and other nonspecific symptoms that usually accompany it are characterized by a periodicity that tends to alternate with periods of freedom from any feeling of illness. This periodicity indicate that taking blood smears only from those children who have recorded temperatures in the febrile range (Temp.>=37.5 °C) at presentation may in fact result in the risk of withholding treatment from potentially serious cases. Indeed 17% of children with parasitaemia above 100,000 parasites/ul did not have fever on presentation and were detected only because we used additional symptoms other than fever for collecting blood smears for microscopy.

Finally, weekly morbidity surveys where the individual can be sampled repeatedly present methodological problems in terms of differentiating episodes. This is very important because of the error in rate calculation that may result from over-diagnosis. There are several ways in which situations leading to such over-diagnosis may conceivably arise: inadequate treatment with antimalarial drugs or treatment failure, super-infection, or inappropriate treatment due to errors in clinical diagnosis before laboratory results become available. These, singly or in combination, could result in prolongation of an episode over several weeks. A child with such persisting parasitaemia may have clinical manifestations and thereby be eligible for a blood smear. If the parasitaemia detected in such a child exceeds the illness threshold, he/she may be said to have an episode on each occasion if one ignores the preceding week. Such apparent clusters of parasitaemia above the illness threshold in a child can hardly be considered as independent events, a prerequisite for comparing rates of episodes.

In summary, alternate area-specific definitions of clinical malaria adjusted to account for the influence of age or length of exposure have been derived; children aged 24 months and younger are considered to have clinical malaria if they present with a P.falciparum asexual parasite density greater than or equal to 2000 parasites/ul, while their older siblings would be similarly categorized if they present with P.falciparum asexual parasite density greater than or equal to

5000/ul. I am convinced that the considerable effort required in deriving this age and area-specific definitions of clinical malaria as the key malariometric index for assessing this trial involving lambdacyhalothrin-impregnated mosquito nets and Maloprim^{R}/placebo prophylaxis is worthwhile for several reason.

Firstly, traditional malariometric indices or indices of parasitization are generally insensitive indicators of the effects of factors that at best would control rather than eradicate malaria. For example, the full impact of the enormous protective effect of sickle-cell trait against severe clinical malaria (Hill et al., 1991) would be easily missed if assessed only in terms of the traditional indices such as parasite prevalence, parasite density, etc,(Fleming et al., 1979). Several trials of impregnated mosquito nets have also shown similar results, for example in Tanzania (Lyimo et al., 1991), Burkina Faso (Carnevale et al., 1988), and The Gambia (Snow et al., 1987).

Secondly, there is considerable variation in transmission dynamics, sometimes even within the same geographical areas, resulting in differences in the degree of immunity and thus the level of parasitaemia tolerated with length of exposure or age. This certainly restricts the applicability of definitions of clinical malaria already developed for areas adjacent to Sierra Leone but with a lower transmission potential, such as The Gambia.

Finally, an area-specific definition of clinical malaria has public health relevance; assessment of different control strategies in term of malarial morbidity and mortality and the resources required to attain a certain degree of control. It also presents an opportunity to address the paucity of descriptive epidemiology of clinical malaria in an area with intense and perennial transmission.

CHAPTER 4

A randomised controlled trial of Lambdacyhalothrin-impregnated mosquito nets and Maloprim^{R}/Placebo prophylaxis: The design and conduct of the intervention trial.

4.1 INTRODUCTION

In Sub-Saharan Africa, Plasmodium falciparum is the cause of the most prevalent parasitic disease affecting the well-being of communities (Ghana Health Assessment Project, 1981; Stuerchler, 1989; Campbell, 1991). Even though no malaria eradication campaign was ever actively pursued to nation-wide coverage in any country in tropical Sub-Saharan Africa, serious setback in other malarious regions with less intensive transmission and better resources for eradication activities than available in Africa at the time, seems to justify the World Health Organization's reluctance to promote malaria eradicaton programmes for tropical Sub-Saharan Africa at the time. When the World Health Organization finally abandoned its global malaria eradication programme (WHO, 1969) it promptly started recommending the adoption of control strategies built around community-based primary health care in Sub-Saharan Africa. For many years, early detection and prompt therapy with antimalarial drugs (mainly chloroquine) remained the focus of this policy (Deming et al., 1989). However, the emergence and spread of P.falciparum resistance to chloroquine in almost all Sub-Saharan Africa (Bjorkman and Philips-Howard, 1990), has created an urgent need for alternative, effective, and sustainable control strategies (Greenwood et al., 1988; Campbell, 1991; Marsh, 1992).

The "rediscovery" of impregnating mosquito nets with insecticides (Lindsay and Gibson, 1988) represents an interesting interim tool with potential for community-based sustainable control practice, while the effort to develop the means of eradicating malaria continues.

Several studies, reviewed by Rozendaal, (1989); Bemojo and Veeken, (1992); and Sexton, (1994), have demonstrated significant reductions in malaria morbidity with synthetic pyrethroid-impregnated mosquito nets. The only trial that has so far measured the effects of impregnated mosquito nets on mortality reported that protection against malaria-related deaths was greater than the effects observed on morbidity in children in the same study area (Alonso et al., 1991). This group also reported that simultaneous chemoprophylaxis with Maloprim^{R} significantly reduced malaria morbidity compared with treated mosquito nets alone. While very exciting, these findings cannot be directly extrapolated to other areas for many reasons, including wide variations in malaria transmission between different areas and sometimes even in the same area from year to year, and other factors such as net acceptability, usage, etc. This study is therefore an attempt to investigate whether an impact of these interventions on malaria morbidity similar to those reported from The Gambia could be observed in children of rural Sierra Leone where transmission is perennial and more intense.

4.2 MATERIALS AND METHODS

4.2.1 Study design

The aims of this study were to: (a) measure the impact of treated mosquito nets, alone or in combination with Maloprim® prophylaxis, on clinical malaria per child/week of observation, and (b) to determine the effects these interventions also have on other indicators such as parasite density, spleen rate and the haematocrit levels. A separate study investigating the effects of the treated mosquito nets on vectors of malaria in the study area is being conducted (Magbity et al., personal communication) and while their results may be quoted as appropriate, their findings are not the focus of this thesis.

The basic unit of this study is each individual child between the ages 3 months and 6 years who was recruited for the weekly morbidity surveillance and cross-sectional surveys. Sample size estimates indicate that a weekly follow-up of 1200 children for a year would be required for a 90% probability of detecting a 50% reduction in the incidence of clinical malaria given the incidence of clinical malaria of about 2 episodes per child per year. It was decided that increasing this sample size to 1400 would compensate for a projected 10-15% loss to follow-up. However, the random allocation of each child to treated mosquito net or no net

was deemed impractical for several reasons. In this setting, several siblings usually share a "sleeping place"(mat or bed). It has also been suggested that the use of an impregnated mosquito net by one individual may have an effect on the risk of malaria for those sleeping nearby (Darriet et al., 1984; Lines et al., 1987). Finally, residents of the proposed study area indicated that individual randomisation of participants to impregnated mosquito net or not in the same household or village would probably present serious problems with compliance because those children allocated to the "no net" group were very unlikely to cooperate with the morbidity surveillance.

Community randomisation of nets was therefore adopted, involving the random allocation of nets between pairs of villages matched on such criteria as baseline parasitaemia, number of children, etc, to "treated net" or "no net". Each child recruited in participating villages was randomly allocated to Maloprim^{R} or placebo on a double blind basis.

4.2.1.1 Pairing and randomisation of treated nets to villages.

The 17 villages in the study area were paired off into eight groups on the basis of similarities mentioned above(see **Table 4.1**). Two of these villages(Blama I & Blama II) were so close (less than 300 yards apart) that it was thought prudent to combined them for pairing purposes because they were unlikely to have distinct and separate mosquito populations. At the end of the pre-intervention phase (**chapter 2/3**), all of our study villages started lobbying the

field team to be in the intervention group in the first instance. We realised then that the only way to maintain the cooperation of the villagers was to have them involved in the randomisation process so that we were not accused of some partiality in selecting those villages that received the treated nets.

Table 4.1: Similarities in the paired villages (number of children and P.falciparum prevalence)

Village	Village:study # in ( )	# of children(<=8 yr.)	P.falciparum
1	Nenbgema(2)	468	60%
	Njala Komboya(15)	428	60%
2	Bumbe(1)	99	58%
	Nyandeayama(3)	114	58%
3	Tondoya(4)	148	65%
	Buma(8)	161	67%
4	Blama I&II(5/6)	224	64%
	Ngalu(7)	239	65%
5	Kunjordorma(10)	86	66%
	Palima(12)	97	67%
6	Kpetema(11)	48	61%
	Kpakuma(13)	44	64%
7	Sami(9)	180	70%
	Mendawa(14)	169	64%
8	Sahn(16)	394	66%
	Gumahun(17)	370	64%

The Chiefs and Elders from all of the study villages accepted our invitations to gather at the base laboratory in Bo and participate in a lottery between matched-pair villages designed to decide which village of each pair would receive the treated nets during the first phase of the intervention study. This exercise, which was chaired by the District Medical Officer of Bo, was a success because it also provided

an opportunity for all the Chiefs to observe the processing of the blood smears, thus helping to allay the rumour that the blood collected from children for microscopic diagnosis of malaria and haematocrit determination was for sale to the Bo district hospital blood transfusion unit!

4.2.1.2 Randomisation of children to Maloprim or placebo.

The children were randomly assigned to Maloprim^{R} or placebo by Mr. Adam Gottschau (Statistician, Department of Biostatistics, Statens Seruminstitut, Denmark), who is completely unconnected with the field implementation of this study. Each child was assigned a letter code which represented placebo or Maloprim^{R} (appropriate dose for age). There were ten letter codes for active drug and a similar number for placebo. The tablets were packed in waterproof blister-packets containing six tablets each and labelled with the appropriate code by Mr. Gottschau before shipment to Bo, Sierra Leone.

Other than the code which indicated active or placebo drug (to which the field team and participants were blind), the packets were also labelled and colour-coded in three strengths as follow:

1. children aged 3-11 month-- for the active drug this means 6.25 mg pyrimethamine/125 mg dapsone or 1/4 adult dose;
2. children aged 1-4 year-- for active drug, this means 12.5 mg pyrimethamine/250mg dapsone or 1/2 adult dose;
3. children aged 5 years and older-- for active drug, contain 18.5 mg pyrimethamine/375 mg dapsone or 3/4 adult dose.

4.2.2 Conduct of the trial

4.2.2.1 Census validation and Sensitisation of the communities

The preliminary studies conducted by Dr. Guy Barnish and his co-workers were based in 15 of the 17 villages now involved in this present trial (Barnish et al., 1993a). In their census every dwelling in each village was numbered and inhabitants assigned a unique identification number of eight digits, consisting of their village number (first two digits), house number (next three digits) and their own number in their respective households (two digits), plus a computer generated check digit (one digit).

In early 1991, the unfortunate civil war in neighbouring Liberia was beginning to spread to the Southern province of Sierra Leone, resulting in instability and massive population relocation in the proposed study area. This delayed the commencement of this study by six months after the completion of the preliminary surveys by Barnish and co-workers (Barnish et al.,1993b). At the resumption of our study in July, 1991, we decided to undertake a re-census, especially as there would have been many births, deaths, and new migrations in and out of the study villages directly related to the upheaval mentioned above. Following this exercise, it was discovered that many of the expected participants were registered several times, either because their parents had moved to another participating village, or relatives of their parents had registered them as their own children according

to local customs. To minimise this duplication, we introduced Polaroid^{R} pictures as a supplement to the identification scheme devised during the preliminary study (Barnish et al.,1993a). The new scheme identified each child by their name, unique identification number based on the permanent residence of his/her biological parents, and a clearly labelled photograph with both parents and/or sibling(s).

During a familiarisation tour held in early 1991, Dr Guy Barnish had introduced me, together with Dr. Petersen, to the local officials of the Ministry of Health at the Bo district hospital, district and provincial headquarters. We also met the Chiefs and Elders of the study area, explaining that we were asking for their cooperation to institute an impregnated mosquito net study as a continuation of the preliminary study initiated by Dr. Guy Barnish. At the recommencement of the study in July, 1991, we again held meetings with the Chiefs and Elders of each community to re-acquaint them about our earlier discussions concerning an intervention trial of impregnated mosquito nets and seeking their approval and cooperation. A series of mass town meetings were subsequently held during which the outline of the trial was explained and the consent of all of the inhabitants sought for including their community into the trial. We particular stressed the need for some villages (not yet selected at that stage) to serve as controls during the initial phase of the intervention trial, when some communities would received treated mosquito nets while others were without, providing

the comparison necessary to determine the true effects of treated nets on malaria in their area. All of the targeted villages agreed to participate in the trial with the following provisos; (1) that the study continued to bear the cost of referring study participants and their siblings who were ill to the nearest Community Health Centre for diagnosis and treatment by the Community Health Officer, as was the case during the preliminary study (Barnish et al., 1993a) and (2) that at the end of the intervention phase, treated nets would be given to all the inhabitants of those villages that had served as controls.

It was further agreed that parents and guardians were free to withdraw their consent for their children to participate in the study at any stage during the trial without prejudice to whether they retained nets already installed or received nets at the end of the trial.

4.2.2.2. The weekly morbidity surveillance methodology

Despite the delay that occurred between the end of the preliminary surveys and the commencement of our intervention trial, we were fortunate to retain the services of almost all of the field workers who had previously worked with Dr. Barnish's preliminary surveys. As these Field Workers were familiar with the villages and had had a year of experience with smear preparation, labelling and storage of slides until processed at base laboratory, and completion of the pre-coded morbidity questionnaires, it was only a matter of orientating them to the new criteria for smear collection. The

preliminary study collected blood smears from those with a temperature greater than or equal to 37.5 °C (Barnish et al., 1993b). The new criteria for taking a blood sample were the presence of one or more of the following:

1.History of fever on day seen

2.History of fever during the last seven days

3.History of chills, rigors or headache during the last seven days

4.History of vomiting or diarrhoea during the last seven days

5.Recorded temperature greater than or equal to 37.5 degrees Centigrade.

These sampling criteria were selected for reasons already outlined in **chapter 3**. Each field worker was assigned the maximum of 80 children to be actively monitored weekly. They were also responsible for the fortnightly administration of Maloprim^{R}/placebo and monitoring compliance. A drug compliance card was devised, identifying each child by his or her identification number and a Polaroid^{R} picture, and detailing their treatment schedule (fortnightly timetable based on date of entry). This card was used to record the number of times the treatment was administered (see **Annex**). The Maloprim^{R}/placebo prophylaxis packet was stapled to this card according to the individual code and age group.

Each field worker was given a week's supply of pre-cleaned slides, cleaning swabs and lancets that were more than adequate even if he had to collect samples from all of

the children he monitored weekly. We hoped that by providing adequate supplies, **observation of the important rule; never to re-use the lancet for finger-pricking,** would be easily upheld. The slides collected were labelled with the name, identification number and date and then transported to the base laboratory daily or within 48 hours by the project drivers or field supervisors for processing.

4.2.2.3 Cross-sectional surveys(Clinical survey)

There were three cross-sectional surveys conducted during this study. The first survey was held in March, 1992 before the start of the rainy season which usually begins in April, and before the initiation of the intervention phase which was scheduled to begin during the first week of July, 1992. The second survey lasting four weeks began during the last week of October, 1992 and was planned to coincide with the end of the rainy season. The final survey was held in March, 1993. During these surveys, a brief history of the health status of each child attending was noted, an axillary temperature recorded, and in contrast to criteria for collecting blood specimens adopted for the morbidity surveys, a blood smear for microscopy and sample for haematocrit determination were collected irrespective of the health status of the child. The spleen size was also measured by examining older children in the standing position and infants supine and the result recorded according to Hackett's classification. The impact of the interventions on clinical malaria and related parameters as assessed by data collected

during both the weekly morbidity surveillance and the cross-sectional surveys are presented in later sections of this thesis but the methodologies are described in this section for completeness.

4.2.2.4 Slides processing and microscopy

All slides were transported to the base laboratory situated in the Bo District Hospital. The slides were processed according to the following procedures:

1. A fresh staining solution was prepared daily by diluting an appropriate volume of stock solution of Giemsa stain with distilled water and the pH adjusted with indicator paper. Our experience with available stock solutions of Giemsa indicated that a pH of 7.2 gives the best results contrary to the pH 7.4 which is usually recommended.
2. The slides were stained in batches in a staining trough for about 15-20 minutes.
3. After staining, they were gently flushed with tap water to remove excess stain and allowed to dry in the open.
4. The dried slides were then read under oil immersion, using a high power field with X10 eyepieces and a X100 objective (HPF) for the dual purpose of identifying Plasmodium species and quantifying the parasite density of each species per microlitre of blood. While the criteria used for the diagnosis of Plasmodium species are universally accepted, there are several methods used to quantify the parasite density. The method adopted in this study is the third method

described by Greenwood and Armstrong (1991) and practised during the preliminary surveys (Barnish et al., 1993b). This method involves examining a blood film systematically by scanning from side to side and top to bottom until 100 HPF have been viewed. The first stage is to determine the number of HPF containing one or more parasites. If each field examined contained one or more parasites, the second stage then requires that the average number of parasites per HPF in 100 HPF be determined. The conversion of count to parasite density per microlitre of blood was achieved by multiplying the number of positive HPF by 5 if the parasite count was scanty and some of the 100 HPF examined did not contain parasites or multiplying the average number of parasites per HPF by 500 when all 100 HPF contained one or more parasites. This conversion is based on the assumption that there is 0.002 microlitre of blood per HPF in a well prepared thick smear.

4.2.2.5 Pre-intervention house survey

During the Acceptability study(see chapter 2) it was discovered that the sizes of many of the "sleeping places"(beds or mats) used by our study population were larger than the largest size of net routinely available from our supplier (Siamdutch Mosquito Netting Co. Ltd., Bangkok, Thailand). We had to re-tailor many of the nets, increasing the largest size to approximately $16m^2$ compared to the $14.2m^2$ received from the supplier. In order to avoid the inconvenience and possible delay that could result from

having to re-tailor nets during the intervention phase, it was decided that information on not only the precise number of nets per household, but the sizes of nets and the number of nets in each size for each village was necessary.

Table 4.2: Pre-intervention surveys of dwellings in the study villages

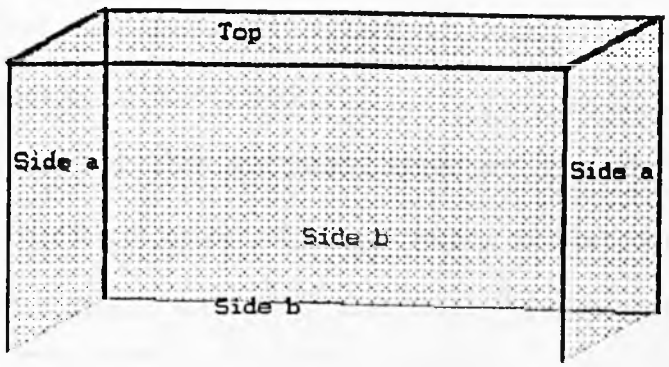
Village	Total population	# of dwellings	Total # of sleeping places	Ave.# person/sleeping place	Types of nets estimated by measurements of sleeping places		
					Small	Mediu m	Large
Bumbe(1)	289	18	111	2.6	21	50	40
Nengbema(2)	1352	73	550	2.5	105	250	195
Nyandeayama(3)	320	20	145	2.2	30	60	55
Tondoya(4)	467	27	192	2.4	32	100	60
Blama I(5)	454	32	194	2.3	32	90	72
Blama II(6)	215	12	98	2.2	28	40	30
Ngalu(7)	832	50	343	2.4	50	175	118
Buma(8)	506	43	223	2.3	48	101	74
Sami(9)	539	36	245	2.2	51	112	82
Kunjordorma(10	215	11	98	2.2	25	43	30
Kpetema(11)	152	12	61	2.5	7	36	18
Palima(12)	267	18	99	2.7	30	29	40
Kpakuma(13)	104	10	43	2.4	10	16	17
Mendewa(14)	513	36	232	2.2	42	105	85
N.Komboya(15)	1465	108	664	2.2	103	361	200
Sahn(16)	1410	95	709	1.98	109	351	249
Gumahun(17)	885	60	406	2.2	100	159	149

Types of nets: small=11.2 m^2 /medium=14.2m^2 / large=16 m^2 in surface area

This information was obtained by a 'House survey'(see **Table 4.2**) conducted in all 17 villages during which every "sleeping place" per household was enumerated and measured.

As had been expected, the measurements revealed that 35% of all the "sleeping places" in the study communities at the time of the surveys would required nets of $16m^2$ in size. This information was used to order nets specifically for every "sleeping place" and to also anticipate the insecticide requirement once the randomisation of a village in each matched-pair to nets was completed(see **section 4.2.1.1**).

Figure 4.1



Surface area

Size	length	height	width	side a	side b	Top	Total	H_2O*	Vol.EC10
small	180cm	150cm	130cm	2(130x150)	2(180x150)	130x180	11.64M*	300ml	1.2ml
medium	180cm	150cm	190cm	2(190x150)	2(180x150)	190x180	14.52M*	450ml	1.5ml
large	180cm	150cm	210cm	2(210x150)	2(180x150)	210x180	15.48M*	500ml	1.6ml

*Refers to the absorptive capacity

4.2.2.6 Impregnation of the nets.

The impregnation of the nets were carried out by mass-dipping in a fashion similar to that described from The Gambia (Snow et al., 1988). Our impregnation of nets was according to the following steps:

step 1. Determining the "absorptive capacity" of the different sizes of nets: The amount of insecticide retained by a net after dipping is proportional to both the concentration of the dipping solution and the amount of that solution that is absorbed by the specific netting material. We therefore determined the "absorptive capacity" of our three sizes of nylon nets by dipping each size in 500 ml of water, removing the net, wringing it and then measuring the volume difference in the bowl.

step 2. Calculating the surface area of the different sizes of nets: The surface area of each size of net was calculated by adding the surface area of the four sides and the top(see **figure 4.1**).

step 3. Determining the amount of insecticide required: We adopted the target dose of 10 mg/m^2 of lambdacyhalothrin (Icon,ICI) as recommended by the manufacturer who generously supplied all of the insecticides required through Dr. Graham White. The insecticide were supplied as EC10 which is equivalent to 100mg/ml of stock solution. The volume of this stock solution required to impregnate each size of net is illustrated in **figure 4.1**.

step 4. Mass dipping: Once the 'absorptive capacity' and amount of insecticide per net for each size of net was established, the impregnation was done by mass dipping. This was achieved by dipping sets of 10 nets of the same size at a time. For example, for the small size of net(surface area=11.64m^2, 116mg of lambdacyhalothrin/net) with an absorptive capacity of 300ml and requiring approximately 1.2 ml of the stock solution of ICON^R, the mass dipping of ten nets of this size would required 12 ml of the stock solution of the ICON^R diluted in 3 litres of water. Elbow-length rubber gloves and masks were provided to all involved in the impregnations.

Our earlier experience of impregnating nets during the acceptability study (chapter 2) indicated that using a shallow wide-brim bowl (i.e bathtub) rather than a deep one (i.e dustbin) was preferable because the persons dipping in such a shallow bowl could keep their faces to one side and therefore avoid the rapid onset of facial and upper respiratory tract irritation associated with dipping in a deep bowl where it was usually necessary to bend directly over the top of the insecticide to impregnate the nets.

step 5. Labelling: All nets were labelled with an identification number consisting of the village, house and a specific number assigned to the "sleeping place" in the household to which the net was allocated, using indelible ink. An "X" mark was also placed on each net with a water-soluble ink as a check on washing.

4.2.2.7 Distribution of the treated nets.

Because of the very high demand that had been expressed for acquiring the nets, a plan was devised to enhance the likelihood that the nets would remain in the villages allocated to receive them during the initial phase of the intervention. The first part of this plan involved the identification number marked on each net with indelible ink(see section 4.2.2.6). The second aspect involved handing out the nets required for each household in a village to the occupants (usually the head of household) through the Chief of the village. The need for the nets to remain in their assigned village and not be moved, especially to villages serving as controls, was stressed. Distributing the nets through the Chiefs and Elders also empowered them to stop inhabitants in their village who relocated to another village from taking the nets with them or even giving them away as presents to visiting relatives from non-participating villages. The occupants were also instructed not to wash the nets as this would removed the insecticide and rendered the nets ineffectual.

4.2.3. Monitoring adherence to the study protocol as an assessment of data quality

4.2.3.1. Data entry and quality assurance

There were basically two categories of data forms developed for this study: (a) interview forms: An example of

this type of form is the weekly morbidity surveillance form which was completed with answers to specific questions about the health status of a child given by their attendants (parents, guardians, older siblings). Even though this form is written in English, it was expected that most of the interviews would be conducted in Mende (local vernacular) by field workers (fluent in Mende and English) and the answers recorded in English. To avoid confusion that could easily arise from translating English words which may not have exact Mende equivalents, medically qualified English speaking indigenous Mende were asked to review the form and provide a Mende translation that would unambiguously convey the sense of the questions so that they would be understood by our study population. This Mende translation of the weekly morbidity questionnaires was then tested on our field workers and outpatients at the district hospital in Bo and found to be satisfactory. (b) observational forms: Forms such as the laboratory forms, House survey forms, etc, that were used to record the results of direct observation made by educated, English speaking field workers or laboratory technicians obviously did not need a Mende translation.

All data were entered directly onto the appropriate forms in the field or in the laboratory and then double-entered onto computers using a menu-driven system written in D-base III plus^{R}. All records were routinely checked for range and consistency. For example, every time an identification number was entered, its accuracy was

automatically checked by use of the check digit(see **section 4.2.2.6**) and any inconsistencies corrected. Accuracy in the identification number was absolutely essential in linking the morbidity data and the laboratory result of slide microscopy for the same individual for a particular week's morbidity survey. The performance of each field worker in such areas as the proportion of children meeting sampling criteria for whom smears were not collected, and Maloprim^{R} or placebo coverage rate was monitored from the data entry section of the study.

4.2.3.2. Direct supervision of the Field Workers

The one-to-one daily supervision of the field workers was done by me (NTM) assisted by three field supervisors, two of whom are trained community health nurses. Each field supervisor had a project motorcycle and was expected to cover every field workers in his/her assigned zone at least once a week. The three zones were organised as follows (see **map in annex**):

Zone 1. composed of villages 1,2,3,4,and 16. This zone was supervised by one of the community nurses who was based in village 16 and could therefore provide emergency treatment to seriously sick children who were later referred to the nearest community health centre located in village 2, about 10 kilometres away.

Zone 2. composed of villages 5,6,7,8,9,10,and 11. This zone also has a community health centre which is located in village 7(Ngalu). The Supervisor for this zone was based in

village 7 which placed him within equal distance of all of the field workers he monitored.

Zone 3. composed of villages 12,13,14,15,and 17. The villages in this zone are generally at a higher altitude, further apart from each other and generally more difficult to reach because of rough terrain and bad roads, especially during the rainy season. As the community health centre in this zone is located in village 15, the second community health nurse in the study was assigned to this zone and based in village 12 and thus able to provide treatment to sick children in villages 12, 13, and 14 who did not regularly use the facilities at village 15.

The supervision generally consisted of monitoring and assisting each field worker to ensure that everything possible was done to see that all children assigned to each field worker were visited each week, that the collection of blood specimens was done using the proper procedures (Bruce-Chwatt, 1980), specimens were labelled correctly, and that the distribution of Maloprim^{R}/placebo was according to the fortnightly schedule, and always ingested in the presence of the field worker and not given out to the childminder to be administered at a later time. When necessary, the supervisors covered for field workers indisposed by illness to avoid interruption of the weekly morbidity surveillance. A significant proportion of the time was actually spent ensuring the cooperation of the communities in such activities as providing nets to immigrants into "nets

villages", referring sick children to the community health centre and sometimes organizing transportation for gravely-ill adults to the Bo district hospital.

4.2.3.3. Monitoring usage and care of the treated nets

At mass meetings held before the distribution of the treated nets in each community, the study team asked for and received the permission of the inhabitants for our field workers based in their community to have unannounced periodic access to their homes to monitor usage of nets at night. It was agreed that such visits could occurred at any hour not later than midnight and during the morning, after the final call for the Muslim morning prayer (5.00AM). The houses to be inspected were randomly selected by the field supervisors who could do the inspection personally or ask the field worker based in the village to carry it out. A brief questionnaire was completed about the number of people, especially children, found to be sleeping outside their nets and their reasons for not using the nets on this occasion briefly noted. During these inspections and also during the weekly morbidity surveys nets were inspected for the presence of the water soluble "X" mark, the disappearance of which would indicate that the net had been washed.

A " mid-term" nets assessment was also conducted six months after the nets had been installed. A random sample of nets in each village was inspected for damage and the head of the household interviewed about such topics as whether the

nets were still effective, and whether he was willing to pay for the insecticide required for re-impregnation of the nets.

4.2.3.4 Repeatability of microscopy results

After microscopy, the laboratory technicians filled out a "laboratory result" form for each slide which was then submitted to be double entered onto the computer using a system similar to those already described (see **section 4.3.2.1**). As the laboratory did not retained a copy of the results, our quality control involved randomly selecting about 5% of the slides, from those collected and already read, for re-examinations usually four weeks after the slides were originally read.

4.3 RESULTS

The results presented in this section are those relating directly to the conduct of the intervention phase rather than its effects on malariometric indices. The impact of the interventions on clinical malaria and associated parameters are presented in the next chapter.

4.3.1 Matching and pairing the study villages

Figure 4.2 shows the total population of the study area and the distribution of the inhabitants by sex and age. Those under the age of nine years comprised 27% of the population, a figure identical to findings of a previous census (Barnish

et al.,1993a). The primary basis for pairing villages into matching pairs was the number of children present in the villages. As shown in **Table 4.1**, the villages in each pair were also very similar in terms of P. falciparum prevalence. It has been shown that the entomological characteristic of malaria vectors in the study villages, especially their density and seasonality, is related to the altitude at which the village is located (Bockarie et al., 1994). While this difference does not seem to unduly affect the malaria parasite prevalence in children living in villages located at high or low altitude, its effects on the intensity of transmission and thus incidence of clinical malaria is unknown (Smith et al., 1993). So, where possible, villages were paired-off on the basis of their location with respect to altitude. The villages in pair 8 (Sahn vs. Gumahun), pair 6 (Kpetema vs.Kpakuma), and pair 5 (Kunjundorma vs. Palima), are all at higher altitude(see **map in Annex**) and were paired-off on this basis, in addition to similarity in the number of children in the villages in each pair. The exception to this are both Nengbema and Njala Komboya which were paired-off despite their location at different altitude.

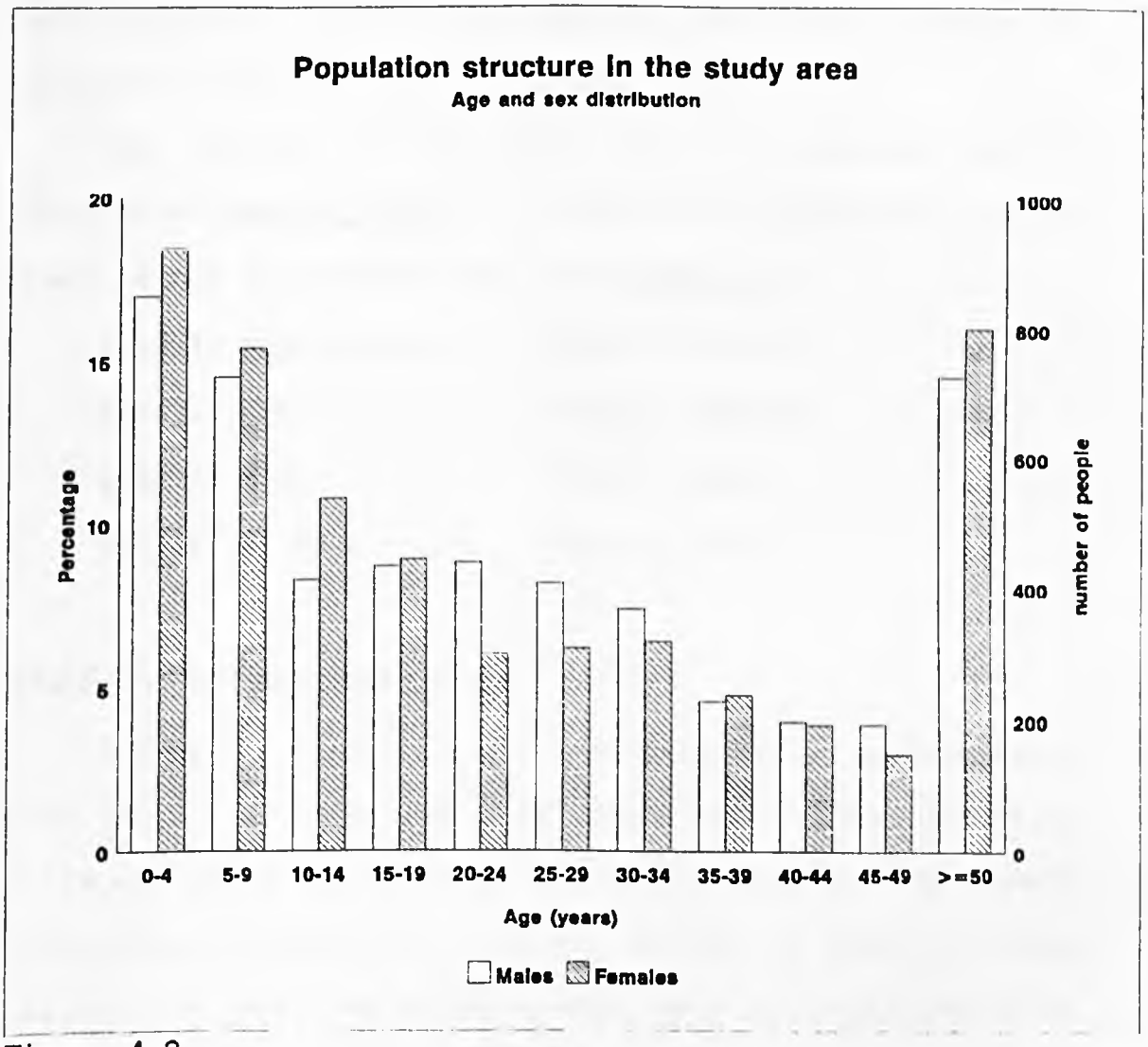


Figure 4.2

Both of these villages have community health centres and similar numbers of children. Assuming equivalent health-seeking behaviour of parents and guardians for their sick children, those based in villages with an established community health centre have the advantage of easy access compared to inhabitants who live some distance from these health centres. Such an advantage may affect prompt diagnosis and treatment which may conceivably affect the progression of

mild to serious clinical malaria or even the incidence of episodes of clinical malaria (Marsh, 1992).

The village in each pair that was selected by the lottery(see section 4.2.2) to receive nets during the initial phase of the intervention was (see Table 4.1):

Pair 1: Njala Komboya	**Pair 5**: Palima
Pair 2: Bumbe	**Pair 6**: Kpakuma
Pair 3: Buma	**Pair 7**: Sami
Pair 4: Blama I & II	**Pair 8**: Sahn

4.3.2 Pre-intervention house surveys

A total of 661 buildings, excluding barns, cooking huts, town hall, etc, are used as dwellings in the 17 study villages. Wattle and daub is the traditional and most common construction material of the walls of most of these buildings (63.2%), but most new building work uses sun-dried mud brick set either in mud or cement (34.5%). These mud bricks usually required extensive borrow-pits that may serve as important breeding sites for *Anopheles* (Bruce-Chwatt, 1980; Magbity, unpublished observation). The use of corrugated iron as roofing material is very wide spread (95.3% compared to 4.5% thatch) and is an important sign of affluence. However, only 112 or 16.9% of the houses have closed eaves and 26.9% of the 3185 rooms used for sleeping have ceilings. These open eaves and ceilings probably have an effect on vector-man contact (Njunwa et al., 1991) but as their occurrence seems equally

distributed in all of the study villages (data not shown) it may not affect the study outcome.

Measurements revealed vast variations in the dimensions (both width and length) of the sleeping places (beds and mats) in all the study villages. Of the 4413 sleeping places counted and measured, 7% (310) were mats, with lengths invariably longer than the 180 cm use as standard by the net manufacturer. 1202 or 27.2% of all beds were not only longer than the standard length of 180 cm but wider than the 190 cm used as the standard width of the largest nets. Experiments with several re-tailored nets indicated that the largest sleeping places could be accommodated by increasing the width of the nets to 210 cm, while maintaining the length at 180 cm. This is because the largest sleeping places, especially the mats were usually very narrow and the large net (210 cm in width) could be used crossways. The nets used in this trial were made to the manufacturer standard length and height of 180 cm x 150 cm, using our specification of 130 cm, 190 cm and 210 cm for the width of small, medium and large net respectively.

4.3.3 Nets: assessing care, retention and utilisation

Between October, 1992 and May, 1993, a total of 176 houses in the 8 villages with nets were visited on a total of 71 different occasions to inspect net usage. The results of these exercises are summarised in **Table 4.3**. The unoccupied nets found on inspections belonged exclusively to young adult

males and on no occasion were children found sleeping outside their nets. Among the varieties of reason given by these young men for not using their nets on the nights of inspection were: the nights were too hot during the dry season and the nets reduced ventilation (53%), they were not using the nets because it was the dry season and there were hardly any mosquitoes around (23%), or that they were too tired and forgot to use the nets (24%). A total of 9 households refused entry for the inspections because they claimed that they had been inspected previously (4 households), the inspection was being conducted too late at night (3 households), or that the visits were intrusive (2 households). A "mid-term" interview with the heads of households followed by inspections were conducted to ascertain that the nets had not been removed from their assigned villages. The nets were also inspected for damage and to ascertain whether they had been washed. Not only did all the nets stay in place, but we had given out 263 additional nets to people who had moved into the villages since the nets were distributed in June,1992. While 7 of the 372 Heads of households interviewed admitted that nets within their households had been washed, it was very difficult to assess the true number that had been washed because the deposition of soot on most nets made the water soluble ink marking almost invisible, even on nets that we were certain had not been washed because they were being used by the study team. Despite their darkened state most nets appeared well

looked after. Only 15(15 out of 2650 or 0.56%) of the nets in place had holes large enough to admit the fist of an adult.

Of the 2700 nets that had been distributed when we began re-impregnation in July,1993, only 6 (0.22%) were missing.

Table 4.3: The results of inspections conducted to assess net utilisation(Oct.,1992-May,1993)

Village	# households	Total visits	Total households visited	# nets in households visited	# found unoccupied	Mean occupancy rate	Range of occupancy rate observed during visits: Minimun	Range of occupancy rate observed during visits: maximum
Bumbe	18	5	10	55	8	90%	50%	100%
Blama	44	10	20(1)	138	18	85%	50%	100%
Buma	43	12	17(1)	89	14	84%	50%	100%
Sami	36	11	15(2)	98	15	85%	29%	100%
Palima	18	8	9	49	4	91%	75%	100%
Kpakuma	10	4	6	36	2	94%	83%	100%
Komboya	108	12	44(3)	268	48	82%	64%	100%
Sahn	95	9	46(2)	254	104	65%	45%	100%
overall	372	71	167(9)	987	213	84%	29%	100%

( ) indicate total number of households refusing entry for nets utilisation assessment

In fact two nets were truly missing as we were aware that 4 of the 6 nets missing had been destroyed when a fire caused by gasoline being stored in a house in Njala Komboya burned down two adjacent buildings.

4.3.4 Compliance with Maloprim^R/placebo

By the end of the follow-up period in July,1993, a total of 2095 children had been recruited and monitored by weekly morbidity surveillance. Despite our attempt to reduce loss-to follow-up by insisting that only those children whose parents are permanently settled in the study villages(people who have built a house or who have planted a food crop for that planting season) were recruited, 13% (273/2095) of the children attended less than 25% of the expected weekly morbidity surveillance surveys before moving out of the study villages to live with other relatives. Fortunately, excluding these 273 children from the analysis did not have any significant effect on the distribution of the remainder randomised to Maloprim^R/placebo (X^2=0.08,df=1,p=0.77).

The mean compliance with Maloprim^R administration was also similar among children in the "nets" compared to those in the "no nets" group (mean compliance=74.19% and 75.4% respectively; (X^2=0.03,df=1,p=0.87). The mean compliance rates were also very similar in the paired villages (data not shown) and not significantly related to sex (X^2=0.03, df=1,,p=0.87). There appears to be a significant difference in the level of mean compliance between children aged 24 months and younger and older children in the "nets" group (62.9% and 80.75% respectively; X^2=8.81,df=1,p=0.002), but a borderline situation with the "no nets" group(68.13% and 79.4% respectively; X^2=3.09, df=1, p=0.07).

In February, 1993, seven months after the intervention phase began, two children presented with hyperpigmented maculate lesions generally distributed over the face and upper trunk of the body. The possibility of an untoward drug reaction was immediately recognised and the participation of these children in the Maloprim^{R}/placebo chemoprophylaxis component of the study suspended. As these children did not have any other manifestation other than the skin lesion, it was decided that they would stay off the Maloprim^{R}/placebo chemoprophylaxis until their randomisation code with respect to active or placebo chemoprophylaxis was known at the end of the intervention phase in July, 1993. However, before July, 1993, a further 28 children developed the hyperpigmented maculae, with some children having generalised pruritus as the initial manifestations. The pruritus ceased within three to five days after suspension of the Maloprim^{R}/placebo while the hyperpigmented maculae gradually faded over several months. When the randomisation code for the allocation of these children to Maloprim^{R} or placebo was revealed, it emerged that all of these children had been on Maloprim^{R}. This was an unusual and unexpected finding as extensive experience with Maloprim^{R} as a malaria prophylactic both in West (Lucus et al., 1969; Menon et al., 1990) and Southern Africa (Harwin, 1972; Weber et al., 1975) had not reported such lesions previously. An investigation is now under way to determined if the observed "lesions" were due to Maloprim^{R}

and, if so, the circumstances under which its use would result in such side effects.

4.3.5 Consistency in the microscopy results

A simple assessment of quality control by re-reading slides as a measure of the reproducibility of the microscopy results is shown in **Table 4.4**. The 380 slides assessed in this exercise were a random sample of 5558 slides collected over half of the follow-up period of one year.

Table 4.4: Evaluating the consistencies of the microscopy results

			Microscopy at HPF(x10 eyepieces & X100 objectives)							
			Scanning 100HPF for parasites(1st.phase)				Determinig ave. count/100HPF(2nd phase)			
Month*	Total # slides	# re-read	Proportion with discrepancies:		Concordance rate		Proportion with discrepancies:		Concordance rate	
			count	positivity	count	positivity	count	discrepancies <5/HPF	count	discrepancies <5/HPF
Aug.	1221	54	0.26	0.19	74%	81%	o.24	0.04	76%	96%
Jan.	974	47	0.15	0.09	85%	91%	0.17	0	83%	100%
Feb.	1047	81	0.1	0.09	90%	91%	0.19	0.01	81%	99%
Mar.	748	51	0.18	0.16	82%	84%	0.16	0.02	84%	98%
Apr.	661	63	0.19	0.16	81%	84%	0.13	0	85%	100
May	907	84	0.1	0.07	90%	93%	0.15	0	85%	100%

*period= Aug.'92-May'93

Agreement between the original and quality control readings has been restricted to results relating to asexual Plasmodium falciparum parasites because clinical malaria is defined in term of reported P.falciparum density. A "similar"

count is defined as where the average parasite count per HPF in the two counts differs by less than 5 parasites. The mean concordance rate for parasite count was almost identical for both stages of microscopy (84% and 83% respectively). The mean concordance rate for positivity of 87.3% is acceptable given the constraints associated with reproducing microscopy results. There is a high similarity (mean concordance rate of 98.8%) in results when comparing the average parasite count per HPF between the original and quality control reading.

4.3.6 Assessing field workers adherence to surveillance methodology

The field workers involved in this trial were required to actively seek out their assigned quota of children weekly and then collect blood smears from those who fulfilled any one or several of a set of sampling criteria (see **section 4.2.2.2**). Sampling for a set of criteria rather than only one, as done previously (Barnish et al., 1993b), obviously requires a higher level of diligence and concentration from the field workers, increasing their work load and the likelihood of error. The data presented in **Table 4.5a** and **Table 4.5b** are a summary of the performance of each field worker in adhering to the surveillance methodology. There are two types of errors that can be exclusively attributed to the field workers: collecting samples from children who do not

fulfil the sampling criteria, commission error; and not collecting sample from those who should have been sampled,

Table 4.5a: Assessing field workers adherence to surveillance methodology

		fulfilled sampling criteria							
		yes				no			
		records indicate sample collected				records indicate sample collected			
		yes		no		yes		no	
field worker code	Total* number contacts	slides available	slides missing	number with slides	number without slides	slides available	slides missing	number with slides	number without slides
01	3694	818	35	0	1(1)	11	1	0	2827
02	4579	1046	51	0	18(1)	25	1	0	3437
04	3719	718	14	0	47(1)	13	1	0	2925
05	2908	1403	23	0	4(1)	17	1	0	1459
06	3092	413	22	0	4(3)	8	0	0	2642
07	2982	498	14	0	39(3)	10	0	0	2418
09	2220	352	4	0	11	5	0	0	1848
10	3252	697	9	0	2	6	0	0	2538
14	1744	368	13	0	12	26	0	0	1325
16	3153	610	4	0	16	2	0	0	2521
17	2890	545	17	0	14	12	0	0	2302
18	3795	666	19	0	29	23	0	0	3058
22	3354	1118	26	0	9(1)	27	0	0	2173
25	2692	315	8	0	13	3	0	0	2353
29	3086	513	22	0	12	12	0	0	2527
38	2319	337	4	0	0	8	0	0	1970
39	2831	579	14	0	10	5	0	0	2223
41	2856	783	24	0	2	6	1	0	2040
43	2332	401	16	0	3(3)	2	0	0	1910
44	1728	206	8	0	1	5	0	0	1508
Temporary staffs	3622	1174	32	0	16	10	0	0	2378
column total	62848	13560	379	0	263(14)	236	5	0	48391

*Number of contacts with children completing >=25% of expected visits

omission error. On the other hand, in the 379 instances where slides supposedly collected by field workers were missing, the exact source of the error is difficult to ascertain because several other people were involved: the slides may have been broken while being transported to the laboratory by

Table 4.5b: A summary table assessing field workers adherence to surveillance methodology (records of children who completed >=25% of expected weekly morbidity contacts).

Sampling criteria fulfilled	Slides available			Records indicate sample collected		
	Yes	No	Total	Yes	No	Total
Yes	13560	656	14216	13939	277(14)**	14216
No	236	48396	48632	241(5)*	48391	48632
Total	13796	49052	62848	14180	48668	62848

*records indicated that sample collected but slides missing

**records indicated that childminder(parents/guardians) refused permission for sample to be collected

the project driver or even broken or misplaced while being processed in the laboratory itself. Of the 14216 instances when children fulfilled the sampling criteria, the childminder (parents/guardians/siblings) refused permission for smear collection on only 14 occasions, giving a very satisfactory compliance rate of 99.9%.

Table 4.6 shows the distribution of 642 instances when smears were either not collected or were missing for children

fulfilling the sampling criteria by the study groups. This result clearly shows that the proportion of smears unavailable for microscopy was similar in the study groups (X^2=5.14,df=3,0.25< p >0.1).

Table 4.6: The distribution of "unavaliable slides" by the study groups

	Study groups				
Slides available	Mosquito net + Maloprim	Mosquito net	Maloprim	Control	Total
No	171(4.9%)	175(4.9%)	136(4.1%)	160(4.2%)	642
Yes	3293	3396	3189	3682	13560
	3464	3571	3325	3842	14202

X^2=5.14, df=3, 0.25<P>0.1

The data shown in **Table 4.7** provide an attempt to ascertain the quality of the data by weighing the probable impact of the type of error committed on the reliability of the number of outcome measures identified. Omission errors are more important than commission errors because of their potential to underestimate the key endpoint: clinical malaria. Therefore, they have has been weighted higher than commission error in the make-up of the error index. The reliability index was derived as (100-error index). A score of 100 would indicate a perfect reliability index where the surveillance methodology was invariably observed. On this reliability scale, our data from the weekly morbidity surveillance is good with an overall reliability index of 98.6 and all field workers scoring above 95.

Table 4.7: Assessing field workers adherence to surveillance methodology.

(Scoring the reliability of the data collected)

		Fulfilled sampling criteria							
Staff code	Total contacts	Yes	No	# of OE	# of CE	OER	CER	Error index*	Reliability index**
A	B	C	D	E	F	G	H	J	K
01	3694	855	2839	1	12	0.12	0.42	0.22	99.8
02	4579	1116	3463	18	25	1.61	0.72	1.31	98.7
04	3719	780	2939	47	14	6.03	0.48	4.18	95.8
05	2908	1431	1477	4	18	0.28	1.22	0.59	99.4
06	3092	442	2650	4	8	0.90	0.30	0.7	99.3
07	2983	554	2428	39	10	7.04	0.41	4.83	95.2
09	2220	367	1853	11	5	2.99	0.27	2.08	97.9
10	3253	708	2544	2	6	0.28	0.24	0.27	99.7
14	1744	393	1351	12	26	3.05	1.92	2.67	97.3
16	3153	630	2523	16	2	2.54	0.08	1.72	98.3
17	2890	576	2313	14	12	2.47	0.52	1.82	98.2
18	3795	714	3081	29	23	4.06	0.75	2.96	97
22	3354	1154	2200	9	27	0.78	1.23	0.93	99.1
25	2692	336	2356	13	3	3.87	0.13	2.62	97.4
29	3086	547	2539	12	12	2.19	0.47	1.62	98.4
38	2319	341	1978	0	8	0	0.4	0.13	99.9
39	2831	603	2228	10	5	1.65	0.22	1.17	98.8
41	2856	809	2047	2	7	0.25	0.34	0.28	99.7
43	2332	423	1912	3	2	0.71	0.1	0.51	99.5
44	1728	215	1513	1	5	0.47	0.33	0.42	99.6
Temporary staffs	3622	1222	2388	16	10	1.31	0.42	1.01	98.9
Total	62848	14216	48632	263	241	1.85	0.49	1.39	98.6

E=# of omission errors; F=# of commission errors; G=100(E/C)=omission error rate

H=100(F/D)commission error rate; J=[(2/3xG) +(H/3)]=Error index. K=(100-J)Reliability index

4.4 DISCUSSION

Conducting field trials in tropical Sub-Saharan Africa is, with a few exceptions, increasingly difficult because of deteriorating infrastructures and other social problems. The ongoing civil strife in Sierra Leone immensely compounded what is at best a difficult situation and increased the need to assess the quality of data collected under such trying circumstances. Such quality control should hopefully serve to reassure both investigators and observers about the reliability of the data collected and assist in an independent assessment of the results and conclusions derived from such studies.

For example, observers unfamiliar with traditional society in our study area would be excused for assuming that, because the trial provided treated nets free-of-cost to all inhabitants of the study villages, net coverage of the study population was adequate and need not be formally assessed. An untreated mosquito net trial, conducted prior to this study, in a district adjacent to our study area (Moyamba district) was inconclusive because most of the nets simply vanished before the trial period was over (Prof. H. Morgan, personal communication). We were able to retain almost all of the nets distributed (6 out of 2700 nets missing after one year) during the intervention phase in their assigned villages by involving the Chiefs, Elders and all of the inhabitants as custodians of the nets which we said were on loan to them for

the duration of the study. We also ensured that nets assigned to children were not commandeered for the use of visitors by providing spare nets to each village for such purpose. The drawback to such "collective ownership" involved responsibility for care of the nets such as repairing damaged nets, not washing them or willingness to pay for re-impregnation at the end of the study. An even greater difficulty involves assessing utilisation. I accept that inspections to assess net utilisation were inconvenient and probably intrusive, but interviews would have been most unreliable because while all inhabitants asked indicated that they used their nets every night, we found a mean occupancy rate of 84%, and on some nights as low as 29%. The villagers probably did not deliberately set out to mislead us during interviews assessing their usage of the nets, but probably felt that to say that they did not use the nets every night would lead us to remove the nets to other villages.

Large field trials investigating the effects of malaria control strategies usually require the services of several laboratory technicians to adequately cope with smear microscopy. Few such trials have reported the reproducibility of their microscopy results (Binka et al., 1994). Despite the constraints which conditions such as storage of slides and the interval between reading, quality of smears, stains, and microscopes may have on reproducibility of microscopy results, an indication of broad agreement between laboratory technicians is desirable, especially when case definition

relies on an illness threshold at a specific parasite density level (see chapter 3). Such agreement on the consistency of the smear results provided by the different laboratory technicians in our study indicated that the detection of our key end-point (clinical malaria) was not unduly affected by the proficiency or otherwise of our laboratory technicians.

The results of evaluating our field team's adherence to the surveillance methodology clearly indicated that the effort of intensive supervision and insistence on the highest standards were worthwhile by the comparatively few errors that occurred. Advance planning for such assessment should be a feature of field trials, particularly where an active case detection system is part of the study methodology. It is relatively easy and convenient for childminders to present sick children (when diagnosis and treatment are free), but this may seem pointless to both childminders and even some members of the study team when children are apparently healthy. Check "variables" that identify the individual members of the study team and monitor their achievement of a verifiable set of tasks are essential as a guide to the overall performance of the study team and thus the accuracy and completeness of the data collected. The use of such a system in this study was most beneficial in identifying not only the sources of our errors but in appraising the probable effect of the errors on the data collected. Errors exclusively attributable to field workers have been arbitrarily categorised as "omission" and "commission" errors

respectively. Omission errors occurred when smear samples were not collected from children fulfilling sampling criteria. This could potentially underestimate the number of cases of clinical malaria detected, with important consequences on the impact of the intervention measured if all such errors were restricted to children in a single arm of the study group. Fortunately, the distribution of instances in which slides that should have been collected are unavailable is equal in the study groups. Commission error, on the other hand, does not have such an effect because the smear results may be safely ignored. However, it may be regarded as an indication of the care with which other "variables" in the data have been collected. This is the basis of the arbitrarily designated error index (2/3 omission error rate + 1/3 commission error rate) which was used to score the reliability of the field workers in adherence to the study protocol.

Finally, I am unaware of any report of a similar "side effect" of Maloprim^{R} as that seen in children during this trial. In The Gambia, Maloprim^{R} has been used extensively as a malaria prophylactic with impressive results (Greenwood et al.,1988; Menon et al., 1990) in children (in some cases over several years), and yet they have never reported any side effect similar to those seen in this trial. While the study in Sierra Leone adopted the age-specific Maloprim^{R} doses used in The Gambia, it was administered continuously every fortnight because of the perennial transmission of malaria,

compared to The Gambia where it had been given for a few months in the rainy season when malaria transmission occurred. The other interesting phenomena associated with these "side effects" are that they only appeared, in those affected, after about six months of medications, and that 10 of the 30 cases were reported in siblings. This "familial clustering" suggests a genetic factor and may explain why the rash has not been described in other populations where Maloprim^{R} has been extensively used.

CHAPTER 5

A randomised controlled trial of Lambdacyhalothrin-impregnated mosquito nets and Maloprim^{R}/placebo prophylaxis: Evaluating the impact of the interventions on clinical malaria and other malariometric indices.

5.1 INTRODUCTION

Malariometric indices pertaining to parasitization (i.e. parasite rates, density, etc.) are relatively insensitive indicators, whether in quantifying malaria as a health problem in inhabitants of endemic areas or evaluating the efficacy of strategies primarily concerned with the control rather than the eradication of malaria (see **chapter 3**). Despite the difficulties and uncertainties associated with characterising the age and area-specific definition of clinical malaria in an endemic area (Smith et al., 1994), the lower incidence of attacks of clinical malaria or severe episodes in people heterozygous for certain haemoglobinopathies (Fleming et al., 1979, as compared with others in the same situation but without the haemoglobin abnormality, is a pertinent example of precedent that supports the suitability of clinical malaria as an appropriate index of the efficacy of a protective factor (Marsh, 1992). In endemic areas, the age pattern of clinical malaria reflects a balance between exposure to transmission and the acquisition of incomplete or partial immunity. The morbidity and mortality consequent on this process is the cost incurred in reaching some sort of balance with the parasite, a truce only maintained by continuous re-

infection. The price of this in the hosts, especially children and expectant mothers (particularly primigravidae), is unacceptably high. Control strategies, such as lambdacyhalothrin-impregnated mosquito nets and Maloprim^{R} prophylaxis, are by their very nature only expected to limit or reduce the burden endured by the host during the acquisition of a balance between parasite and host. Therefore, assessing the impact of such control strategies on the degree to which they reduce clinical malaria should be instructive in ranking their effectiveness in our dwindling armament for malaria control.

The definition of clinical malaria and the design and conduct of the intervention have been described in chapters 3 and 4 and are not featured here. The focus of this chapter is on assessing the effects of the interventions on clinical malaria and related parameters.

5.2. STATISTICAL METHODS

5.2.1 Unit of analysis

Each child recruited into the study was randomly allocated to one of four groups: **treated nets and Maloprim^{R} prophylaxis; Maloprim^{R} prophylaxis; treated nets;** and a **control group,** where nets were provided after the trial had ended. These groups are self-

weighting (various parameters equally distributed) and analyses for the effects of the interventions have compared them on that basis. The matched-pair communities have also been considered in the analyses under the assumption that the impact of the treated nets on malarial transmission and clinical cases in children in those communities receiving treated mosquito nets may not be independent (see **chapter 4**). A weighted analysis has been carried out when exploring for the effects of the interventions in the paired communities because of obvious difference in sizes.

Children participating in less than 25% of the weekly morbidity surveys conducted for a year have been excluded from the analyses (see **chapter 4**). The smear results for those who did not fulfil the sampling criteria have also been excluded.

The results of the weekly morbidity surveys were used to calculate the incidence rates of clinical episodes of malaria. Age-specific illness thresholds were used to derive alternative definitions of clinical episodes: (i) children aged less than 24 months were said to have an occurrence of "critical parasitaemia" when smears, collected because they fulfilled the sampling criteria, were found at microscopy to contained 2000 or more asexual *P. falciparum* parasites per microliter of blood on thick smear. An episode of clinical malaria began with the occurrence of critical

parasitaemia and continued until the child had recovered, that is, was free of clinical manifestations, and (ii) a similar situation held for children older than 24 months, but at a "critical parasitaemia" of 5000 asexual P. falciparum parasites or more per microliter of blood (see **chapter 3**). The incidence rates were calculated per 1000 child-weeks at risk and from these a relative rate derived for children in each arm of the study compared to the control group. Wilcoxon's signed rank test was used to compare the rates in the paired communities, weighted for differences in sizes in calculating the overall effects in "treated mosquito nets" versus "no nets" villages. The confidence intervals for the protective efficacies were calculated from the mean and standard error of the log rate ratios of each pair.

5.3 RESULTS

5.3.1 The impacts of the interventions on clinical malaria

The protective efficacies of the interventions on the incidence rate of clinical malaria observed during the weekly morbidity surveys are shown in **Figure 5.1** and summarised in **Table 5.1**. The effects of the exclusive use of treated mosquito nets or Maloprim^{R} prophylaxis on protection against clinical malaria are similar (49% and 42% respectively), while in combination

this is significantly augmented to 72%(X^2=273, df=3, P<0.001). Children in the control group had an average of 1.3 episodes per child compared to 0.65 episodes or 0.78 episodes for treated mosquito nets and Maloprim^R prophylaxis use respectively. Children using the combined strategies (treated nets and Maloprim^R prophylaxis) had an average of 0.37 episodes per child, a figure three time less than that observed in the control group.

Table 5.1: A comparison of the protective efficacies of the interventions on episodes of clinical malaria observed during the weekly morbidity surveys

Intervention	Number of episodes observed	Child weeks at-risk(cwar)	Incidence rate /1000cwar	Rate ratio	95% confidence interval	Protective efficacy
None	576	15269	37.7	1	-	-
Nets	309	16126	19.2	0.51	0.44, 0.58	49%
Maloprim	338	15205	22.2	0.58	0.51, 0.66	42%
Nets and Maloprim	169	16248	10.7	0.28	0.24, 0.33	72%

Table 5.2 shows the frequency of attacks of clinical malaria in children in different arms of the study. The data in this table indicate that there were significant differences in the study groups in the number of children with no episodes(X^2=94.6, df=3, P<0.001) or the number of attacks of malaria in those who experienced clinical cases of malaria. Only 11(2.3% [11/467]) children had

Fig.5.1: The impact of the interventions on the incidence rate of clinical malaria/1000cwar

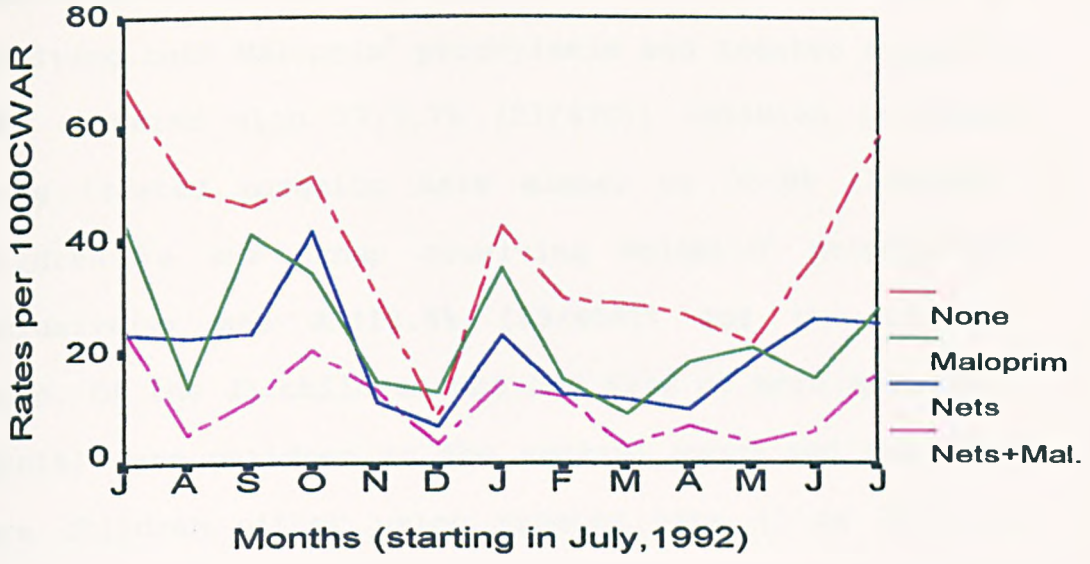


Table 5.2: The effects of the interventions on the frequency of attacks of clinical malaria

Number of Episodes	NONE	MALOPRIM PROPHYLAXIS	TREATED MOSQUITO NETS	TREATED NETS & MALOPRIM PROPHYLAXIS
0	177(39.3%)	242(55.5%)	291(61.9%)	339(72.6%)
1	126(28%)	110(25.2%)	102(21.7%)	95(20.3%)
2	64(14.2%)	49(11.2%)	50(10.6%)	22(4.7%)
3	44(9.8%)	21(4.8%)	11(2.3%)	8(1.7%)
4	19(4.2%)	8(1.8%)	9(1.9%)	3(0.6%)
5	10(2.2%)	4(0.9%)	5(1.1%)	0
6	7(1.6%)	1(0.2%)	1(0.2%)	0
7	2(0.4%)	0	1(0.2%)	0
8	1(0.2%)	0	0	0
9	0	1(0.2%)	0	0
Number/group	450	436	470	467

more than 2 episodes of clinical malaria in the group receiving both Maloprim^R prophylaxis and treated mosquito nets compared with 27(5.7% [27/470]) children in those using treated mosquito nets alone; or 35(8% [35/436]) children in the group receiving Maloprim^R prophylaxis exclusively; and 83(18.4% [83/450]) for the control group. Of the 33 children who had five or more episodes, 20(61%) were children in the control group and the rest were children either using treated nets (7 or 21%) or Maloprim^R prophylaxis (6 or 18.2%) exclusively. No child in the combined strategies group had more than four episodes (only three children in this group had four episodes). Seventeen or 51.5% of the children with more than four episodes of clinical malaria were from Gumahun (village 17) and it is remarkable that 13 or 76.5% of these children were registered as residents of houses that are adjacent to each other.

The number of episodes evident during a weekly visit and those persisting during consecutive visits have been summarised by intervention group and displayed in **Table 5.3**. The proportion of total episodes persisting for more than a week is very similar in the control, treated mosquito nets or Maloprim^R prophylaxis groups but differs significantly in children using both nets and Maloprim^R prophylaxis (X^2 =12.67, df=3, P<0.01).

Table 5.3: Categorising the duration of episodes by interventions

INTERVENTION	NUMBER OF EPISODES PERSISTING / CONSECUTIVE VISITS					Total
	1 WEEK	2 WEEKS	3 WEEKS	4 WEEKS	5 WEEKS	
NONE	501(86.9%)	56(9.7%)	12(2.1%)	4(0.7%)	3(0.5%)	576
MOSQUITO NETS	273(88.3%)	32(10.4%)	2(0.6%)	2(0.6%)	0	309
MALOPRIM	297(88%)	34(10.1%)	6(1.8%)	1(0.3%)	0	338
NETS & Maloprim	163(96.4%)	5(2.8%)	1(0.6%)	0	0	169

Table 5.4: The protective efficacies of the nets on clinical malaria and related malariometric indices summarised by the paired communities

VILLAGE PAIR	SLIDE POSITIVITY		HIGH PARASITAEMIA**		EPISODES OF CLINICAL MALARIA	
	rate ratio	protective efficacies	rate ratio	protective efficacies	rate ratio	protective efficacies
1	0.50	50%	0.54	46%	0.29	71%
2	0.91	9%	1.62	-62%	0.86	14%
3	0.56	44%	0.33	67%	0.63	37%
4	0.60	40%	0.50	50%	0.57	43%
5	.43	57%	1.07	-7%	0.77	23%
6	0.55	45%	1.44	-44%	0.38	62%
7	0.55	45%	0.33	67%	0.46	54%
8	0.94	6%	0.92	8%	0.49	51%
*PE	32.9% (25%, 50%)***		28.5%(-0.85%, 47%)		50.1%(21%, 51%)	
Wilcoxon Rank	P=0.0117		P=0.0910		P=0.0173	

** High parasitaemia=parasite density>=25,000 parasite /ul

*Overall protective efficacies=$\Sigma\frac{(\text{PROTECTIVE EFFICACIES} \times \text{COMBINED POPULATION OF VILLAGE PAIR})}{\text{Total population}}$

***95% Confidence interval

The overall protective efficacy of treated mosquito nets on clinical malaria in the paired villages was

50.1%(95% confidence interval 21%, 56%; Wilcoxon Signed Rank Test, P=0.0117) and is shown in Table 5.4.

Table 5.5: The frequency and distribution of *P. falciparum* densities observed in the study groups during the weekly morbidity surveys

PARASITE density/ul	INTERVENTION GROUP			
	NONE	NET	MALOPRIM	MALOPRIM & NETS
0	1928(52.4%)	2225(65.5%)	2111(66.2%)	2610(79.3%)
1-999	932(25.3%)	741(21.8%)	620(19.4%)	468(14.2%)
1000-1999	29(0.79%)	25(0.73%)	18(0.56%)	3(0.09%)
2000-2999	49(1.3%)	21(0.6%)	29(0.9%)	18(0.5%)
3000-3999	47(1.3%)	25(0.7%)	17(0.5%)	13(0.4%)
4000-4999	50(1.4%)	28(0.8%)	22(0.7%)	10(0.3%)
5000-9999	207(5.6%)	96(2.8%)	106(3.3%)	65(1.9%)
10,000-24,999	226(6.1%)	113(3.3%)	129(4.04%)	58(1.8%)
25,000-49,999	124(3.4%)	72(2.1%)	77(2.4%)	32(0.97%)
50,000-99,999	60(1.6%)	35(1.03%)	34(1.06%)	12(0.36%)
>=100,000	30(0.81%)	15(0.44%)	26(0.81%)	4(0.12%)
slides/group	3682	3396	3189	3293
% slides positive	47.6%	34.5%	33.8%	20.7%
% contacts when slides collected	24.1% (3682/15269)	21% (3396/16126)	20.9% (3189/15205)	20.3% (3293/16248)
contribution to total # slides	27.1% (3682/13560)	25% (3396/13560)	23% (3189/13560)	24% (3293/13560)

5.3.2. The impacts of the interventions on other malariometric indices

The frequency and distribution of P.falciparum densities observed in the study groups during the weekly morbidity surveys are shown in **Table 5.5**. It is clear that the groups are very similar in terms of their contribution to the total slides collected or the proportion of contacts in each group during which smears were taken. They however differ substantially in the slide positivity rate (X^2 =557, df=3, P<0.001). The seasonal variation in average monthly rainfall and P.falciparum geometric mean parasite density per microliter is displayed in **Figure 5.2** and indicates that during the rainy season, as the rainfall rises it tends to be followed by a fall in the geometric mean parasite density 6-8 weeks after the average monthly rainfall exceeds 500mm. Subsequently, the geometric mean parasite density seems to rise again some 6-8 weeks after the average monthly rainfall has declined below 500mm. This peak occurs during the middle of the dry season, two-three months before the onset of the next rainy season. The monthly incidence of clinical malaria demonstrated this same pattern (data not shown).

The results of the pre-intervention cross-sectional survey (March, 1992) and another survey held

a year later, 9 months after the trial started, are summarised in **Table 5.6**. During the pre-intervention survey, the children allocated to the study groups for the intervention phase were similar both in terms of the average spleen rate and mean packed cell volume (F=0.097, df=3, P=0.962; F=0.281, df=3, P=0.839 respectively).

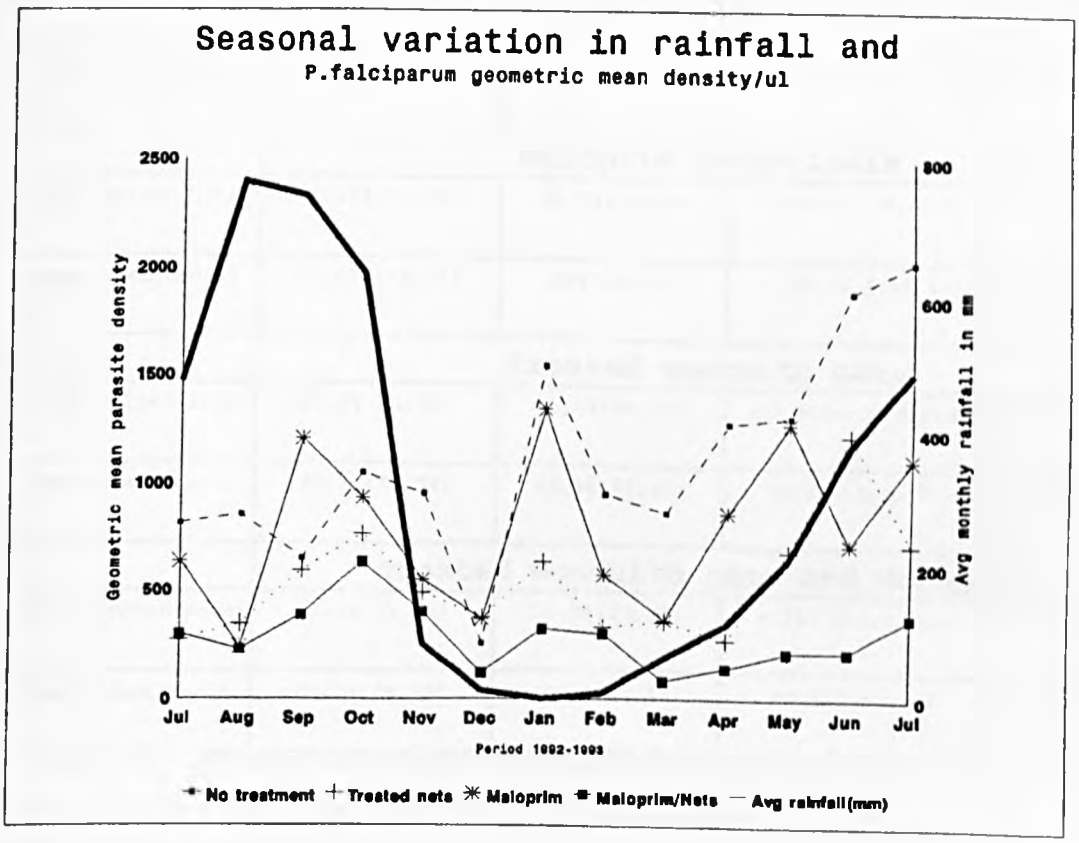


Figure 5.2

A comparison of the groups on these same indices from the March, 1993 cross-sectional survey revealed significant differences in the mean packed cell volume

(F=6.716, df=3, P<0.0001) and the average spleen rate (F=5.287, df=3, P<0.001) among the groups.

Table 5.6: Changes in the mean packed cell volume and the average spleen rate in the study group observed during cross-sectional surveys

parameters	Type of intervention			
	None			
	Mar.,92	Mar.,93	Change*	P value
Ave. spleen rate	45.45%(40,50)	46.11%(40,51)	+0.65%(-6.8,+8.1)	0.863
Mean haematocrit	36%(35,37)	38%(37,40)	+2.03%(+0.43,+3.6)	0.013
	Maloprim prophylaxis			
Ave. spleen rate	44.13%(38,49)	35.5%(30,40)	-8.65%(-1.3,-16)	0.022
Mean haematocrit	37.09%(36,37)	40%(38,41)	+3.25(+1.5,+5.02)	0.001
	Treated mosquito nets			
Ave. spleen rate	46.2%(40,51)	32.9%(28,37)	-13.3%(-5.8,-20.8)	0.001
Mean haematocrit	37.2%(36,38)	43.4%(41,45)	+6.2%(+4.4,+8)	0.001
	Treated mosquito nets and Maloprim			
Ave. spleen rate	45.2%(39,51)	34.2%(29,39)	-11%(-3.2,-18.8)	0.006
Mean haematocrit	37.2%(36,38)	42.2%(40,43)	+5.02%(+3,+7)	0.000

* + means an increase in the parameter at the March,93 survey

-indicate a decrease in the parameter at the March,93 survey

95% confidence interval in ( )

It is interesting to note that while the average spleen rate in the other study groups had declined compared to the rate observed during the earlier survey (March, 1992), the average spleen rate in the control group was

higher, even though by a small amount. Reduction in the average spleen rate and simultaneous increase in the mean packed cell volume is most clearly seen in children using nets exclusively. This finding is unlike the effect of the interventions on clinical malaria, where the combined strategies have a significantly better impact than the use of either control method alone.

5.4 DISCUSSION

The results of this trial indicate that the use of lambdacyhalothrin-impregnated mosquito nets in a forest area of West Africa with perennial Plasmodium falciparum transmission was effective in not only significantly reducing the incidence of clinical malaria in children using this control measure, but also the number of attacks they suffered. It was also demonstrated that the level of parasite densities associated with attacks of clinical malaria in those children using the intervention was significantly lower than comparable events in children in the control group.

The impact of lambdacyhalothrin-impregnated mosquito nets and Maloprim^{R} prophylaxis on the incidence of clinical malaria is greater than observed with the use of either control strategy alone. This

finding replicates results reported from The Gambia (Alonso et al. 1991), where in children using treated nets, the addition of Maloprim[R] prophylaxis had a spectacular effect on the incidence of clinical episodes of malaria. Unlike the transmission pattern seen in The Gambia, however, malaria transmission in this study area is perennial with the potential for children to suffer several distinct attacks of malaria throughout the year. The effect of the interventions on the frequency of attacks of clinical malaria has therefore been assessed. There were significant differences in the number of children having multiple episodes among the different study groups; with only 2.3% or 11 of 467 children using the combined strategies having more than 2 episodes compare to 5.7% and 8%, respectively for treated mosquito nets and Maloprim[R] prophylaxis, and 18.4% of children in the control group (see **Table 5.2**). The distribution of the number of children with more than four episodes by village suggests what appears to be clustering, with 51% of these children being resident of a single village; Gumahun (village 17). It is also quite peculiar that most of these children are from adjoining houses in Gumahun. A possible explanation of this phenomenon may be micro-epidemiological variation in factors affecting malaria transmission (Cattani et al., 1986; Molineaux, 1988; Day and Marsh, 1991; Lines and

Armstrong, 1992), as there is no evidence to suggest that these children were inadequately treated or did not respond to the anti-malarial treatment they received.

The interventions also appear to have an effect on the duration of episodes. Even though treatment failure cannot be categorically ruled out, the persistence of an episode over several consecutive weeks may be a manifestation of distinct episodes that are superimposed, though indistinguishable by the methods available to this study. If, as suspected, these prolonged episodes are indeed several distinct overlapping episodes, then the effect of interventions (especially the impregnated mosquito nets) in reducing the duration of episodes may have important implications for both the development of immunity and the outcome of cases. As far as the outcome of a case is concerned, a prolonged episode has nutritional and haematological implications, especially in children who may be anorexic and have concurrent destruction of their red blood cells during the schizogony phase of the malaria parasites. For instance, the likelihood of a child developing anaemia seems higher following many overlapping continuous episodes than the same number of episodes occurring but interspersed by gap during which the child can recover and replenish some of the lost nutrients and minerals essential for haemopoiesis.

Recently it has been hypothesised that disease occurs when a person living in an endemic area is exposed to a parasite that is antigenically distinct from those which they have encountered previously (Day and Marsh, 1991; Lines and Armstrong, 1992). This implies that partial immunity in people living in endemic areas is a function of previous exposure to the repertoire of antigenically distinct "strains" of parasites present in their immediate environment.

If this hypothesis is correct, then a possible explanation for the interventions reducing the duration of episodes is that of limiting super-infections with different "strains" of malaria parasites. Such a limitation may conceivably lead to delay occurring in being exposed to the variety of distinct "strains" of parasite available and result in changes in the age pattern of partial immunity and clinical disease.

However, there is some evidence which suggests that being exposed to malaria at an older age may be preferable. In his classic paper on the epidemiology of malaria, Schuffner (1919) noted an age-dependent immunity in people lacking a history of heavy exposure. He wrote, "Why do these persons (adults) behave differently from the others? Are they resistant simply because of age...?". Christophers (1924), working in India, also documented this age-dependent protection in migrants that paralleled that in natives. Recently,

Baird and co-workers (1991), working in North-eastern Indonesia, where malaria transmission is intense and perennial, interpreted their findings as supportive of age-dependent partial immunity, noting that first exposure as an adult seems to lead to the same level of partial immunity acquired as a cumulative product of many years of heavy exposure. One could infer from these findings that ameliorating or limiting the full effects of intensive transmission on vulnerable children may provide an advantage that is age-related.

The results presented in **Table 5.5** show the frequency and distribution of *P. falciparum* densities observed in the study groups during the morbidity surveys. The groups are similar in terms of their contribution to the total slides collected or the proportion of contacts in each groups during which slides were collected. This finding is very important because it clearly indicates that a potential source of errors and bias was effectively handled. A bias could have possibly arisen if many more or significantly fewer smears had been collected from any one of the study groups. For example, the number of children in each group who attended more than 25% of the expected visits or the number of total smears collected from each group are similar, indicating that the significantly different results noted for each group on parameters such as the slide positivity rate, the

distribution of parasite density, and other findings, truly represent actual happenings and were not unduly influenced by errors or bias occurring during the execution of the trial.

The geometric mean parasite density in this area appeared to vary inversely with the mean rainfall during the height of the rainy season; declining when the mean rainfall exceed 500mm and vice versa when it fell below 500mm. A lag period of 6-8 weeks has been noted as a feature of this pattern, with a peak in the mean geometric density occurring in January, a month of practically no rainfall in the usual seasonal pattern. This seems to suggest that the flooding associated with very heavy rainfall washes away the usual breeding sites of malaria vectors. The flood water usually starts to recede toward the end of the rainy season and beginning of dry season, leaving many puddles that are used by the vectors for breeding. This timing may have important implications for the implementation of an impregnated mosquito nets program in Sierra Leone or even other parts of tropical West Africa.

First of all, most of the cash crops (coffee, cocoa, rice, etc.) are usually harvested around this time, meaning that people may have money to pay for nets or re-impregnate those already available. Secondly, promotional campaign to persuade people to pay for an impregnated mosquito nets program may be

relatively easier when the escalation in relative mosquito abundance and nuisance coincide with cash availability.

The results from the cross-sectional survey conducted in March, 1992, before the intervention phase began, showed no differences in the mean packed cell volume or the average spleen rate in children allocated to different arms of the study. Following introduction of the interventions, significant differences emerged. The average spleen rate in the control group showed a small increase during the cross-sectional survey conducted 9 months after the interventions started. The largest changes recorded occurred in the group using treated nets exclusively, where the average spleen rate decreased by 13% and the mean packed cell volume increased by more than 6%.

CHAPTER 6

CONCLUSION AND SUMMARY

6.1 CONCLUSION

6.1.1 The impact of the interventions on Plasmodium falciparum induced clinical malaria

It is concluded from this randomised controlled trial of lambdacyhalothrin-impregnated mosquito nets and Maloprim^{R}/placebo prophylaxis conducted in Bo district, southern Sierra Leone, that the use of impregnated mosquito nets represents an effective means of augmenting existing strategies used in the control of disease due to perennially transmitted Plasmodium falciparum malaria. A 49% protective efficacy against clinical cases of P.falciparum malaria was demonstrated in children using lambdacyhalothrin-impregnated mosquito nets. The impact of combining fortnightly Maloprim^{R} prophylaxis with concurrent use of lambdacyhalothrin-impregnated mosquito nets was impressive, resulting in a 72% protective efficacy against P.falciparum induced clinical malaria.

It was also noticed that the interventions positively affected other attributes of clinical malaria; reducing the relative duration of episodes, the mean parasite density associated with episodes, and finally, in fewer episodes/child in children in the intervention groups compared to their contemporaries in the control group.

6.1.2 Effects on other malariometric indices

The results of this study also indicate that the interventions had effects on other malariometric indices similar to that seen on clinical malaria. Children in the intervention groups had significant reduction in their mean spleen rate and geometric mean parasite density, 9 months after initiation of the intervention. The highest increase observed in the mean haematocrit level, measured at the same time as these other parameters, was recorded in the group solely using impregnated nets.

6.1.3 Issues relating to the design and conduct of the trial

Studies of this kind involving several communities and field workers are challenging for many reasons, including the possibility of bias in design arising from erroneous assumptions or errors in implementation stemming from some or all of the field team not adhering to the established surveillance methodology. Much effort had been made to identify and reduce the possible sources of bias in this trial: an adequate supply of nets to all in the intervention community, spare nets so that the ones issued to children were not expropriated for visiting adults, monitoring washing, usage, quality control for repeatability of microscopy results, etc.,. In addition, training and unrelenting demand on a high standard ensured through supervision, seem to have

minimised the number of errors associated with adhering to the surveillance methodology. An attempt to ascertained the quality of the data by weighing the probable impact of the different types of errors indicated high consistencies in the outcome measures identified by different members of the field team.

However, several important factors which would conceivably significantly alter the results or provide explanation for findings, have not been taken into account, namely, the number of days that some children spend outside the treatment villages, sleeping in unprotected circumstances where they may have been bitten by infective mosquitoes and differences in transmission within a community because of such factor as the distance of dwellings from breeding sites, whether man-made or natural.

6.2 SUMMARY

1. Lambdacyhalothrin was selected for this trial by involving a segment of the study population in a double blind comparative study of the acceptability of untreated-mosquito nets versus nets treated with permethrin, deltamethrin and lambdacyhalothrin.

2. Area and age-specific illness thresholds derived by logistic regression power model were used to determine alternative definition of clinical episodes of malaria: I. children aged less than 24 months were said to have an occurrence of "critical parasitaemia" when smears, collected because they fulfilled the sampling criteria, were found at microscopy to contain 2000 or more asexual Plasmodium falciparum parasites per microliter of blood on thick smear. An episode of clinical malaria began with the occurrence of "critical parasitaemia" and continued until the child had recovered, that is free of clinical manifestations, and II. a similar situation held for older children, but at a Plasmodium falciparum density of 5000 and higher.

3. In an attempt to ascertain the quality of the data, errors committed by the field team were arbitrarily categorised as "omission" and "commission" errors and differentially weighted in derivation of a "reliability index", where a score of 100 would indicate perfect adherence to the surveillance methodology. On this scale, one could say that the quality of the weekly morbidity surveillance data gathered during this study is good, with an overall reliability index of 98.6(all field workers scored above 95).

4. The results of this trial provide further evidence that insecticide impregnated mosquito nets could be used

to augment existing malaria control strategies. Children exclusively using lambdacyhalothrin impregnated mosquito nets in this trial suffered 49% fewer episodes of Plasmodium falciparum clinical malaria compared to their peers in the control group. In combination with Maloprim^{R} prophylaxis, lambdacyhalothrin impregnated mosquito nets were even more effective, providing a 72% protective efficacy against Plasmodium falciparum clinical malaria. Other malariometric indices were also significantly affected. For instance, a 6% increase in the average haematocrit level was noticed in children using the nets solely, as well as a significant decrease in their mean spleen rate.

6.3 IMPLICATION OF FINDINGS FOR FURTHER STUDIES

Some of the findings recorded during this trial raise questions which would require further investigations before any firm recommendations can be issued:

1. Skin lesions observed exclusively in children using Maloprim^{R} prophylaxis need to be investigated. Were these skin lesions isolated "allergic reactions" or were there other manifestations undetected during this trial, which could hamper the use of this heretheto effective, safe and well tolerated drug (Allen et al., 1990b)?

2. How much did the movement of people, especially children, into areas where they slept without the protection of their insecticide impregnated nets influenced the results generated in this trial? This is a potentially important issue because in slash-and-burn shifting subsistence farming system found in large parts of the study area(and the rest of West Africa) people tend to have temporary farming hamlets away from their villages where dwellings are very rudimentary and usually offer no protection against access by mosquitoes. For example, if it was found that in communities with access to nets for everyone, a significant amount of persisting transmission occurred in such settings, then it would be advisable that people were encouraged to acquire spare nets for days when they slept outside their villages or took their nets with them to avoid being bitten by mosquitoes.

3. The role of borrow-pits as breeding sites close to dwellings needs to be investigated.

4. In order to be able to translate these promising results of the impact of impregnated mosquito nets on cases of *Plasmodium falciparum* into operations; it is urgent that studies be conducted that would seek to quantify present malaria losses not on humanitarian grounds alone but as economic problems and impediments to development. Such an evaluation could be very important

in shifting the perception of local authorities and individuals about the cost of preventing rather than attempting to cure cases of malaria after they have occurred. The availability of nets and impregnation kits through commercial outlets at prices that most people can afford, along with suitably focus promotional campaigns may go a long way in empowering people against malaria, eventually achieving better results than available with the present control strategy of early detection and prompt treatment used on its own.

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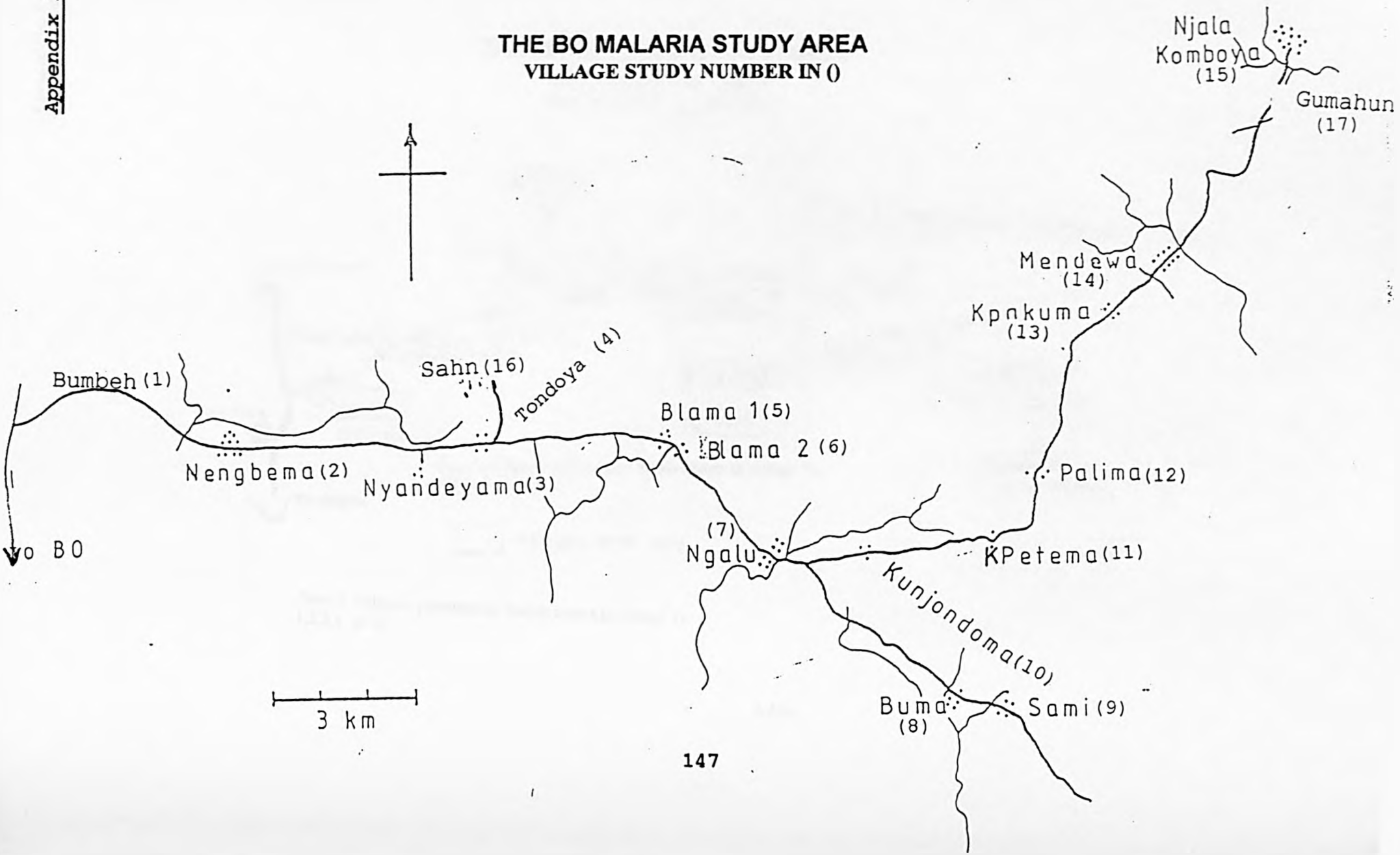
Appendix I

THE BO MALARIA STUDY AREA

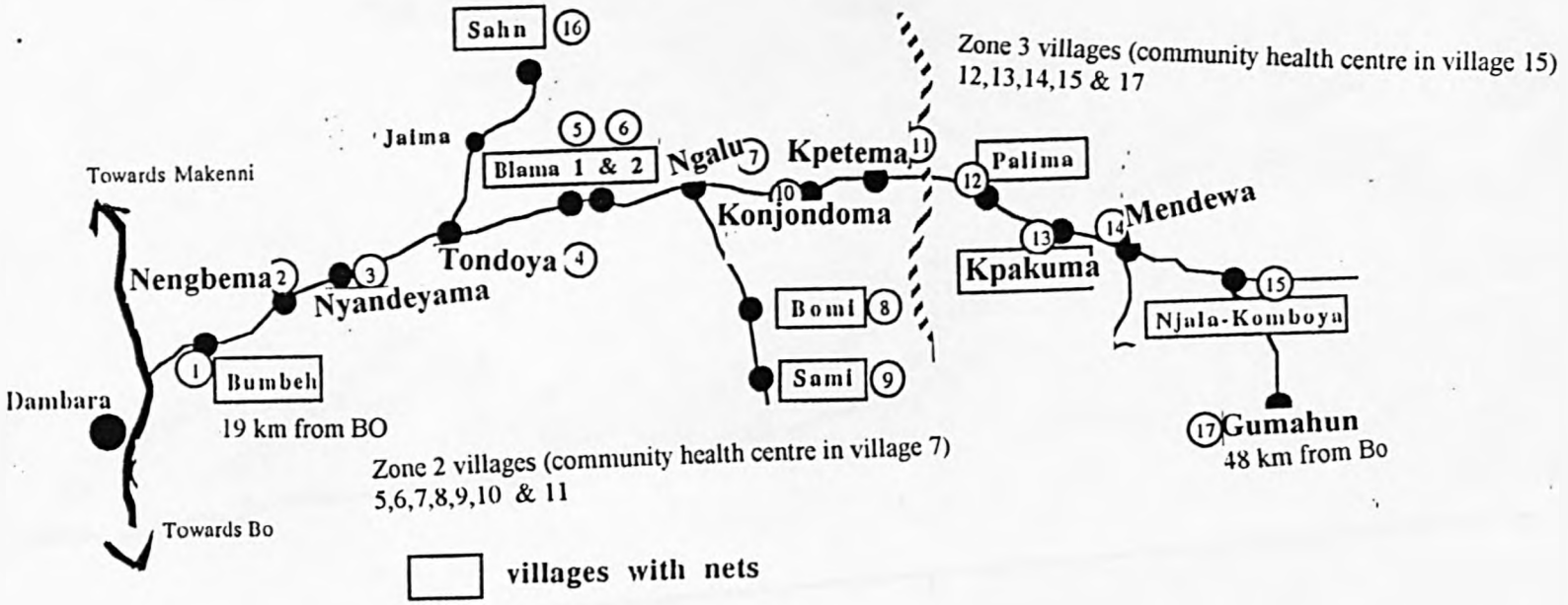
VILLAGE STUDY NUMBER IN ()



Appendix I

THE BO MALARIA STUDY AREA

Division of study villages into zones for supervision



Zone 3 villages (community health centre in village 15)
12,13,14,15 & 17

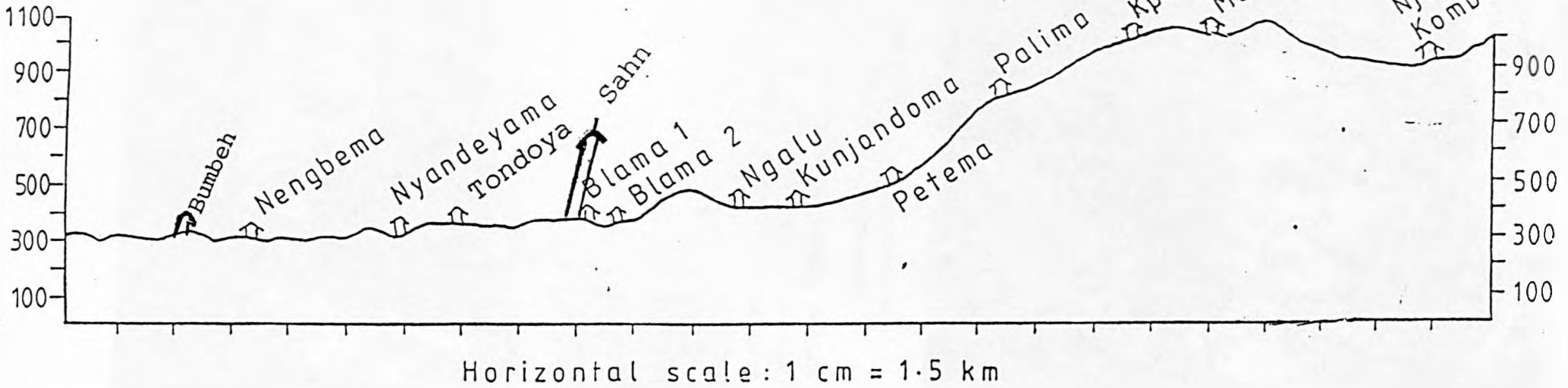
Zone 2 villages (community health centre in village 7)
5,6,7,8,9,10 & 11

Zone 1 villages (community health centre in village 2)
1,2,3,4 & 16

Appendix I

THE BO MALARIA STUDY AREA

Transect along road showing altitude in feet

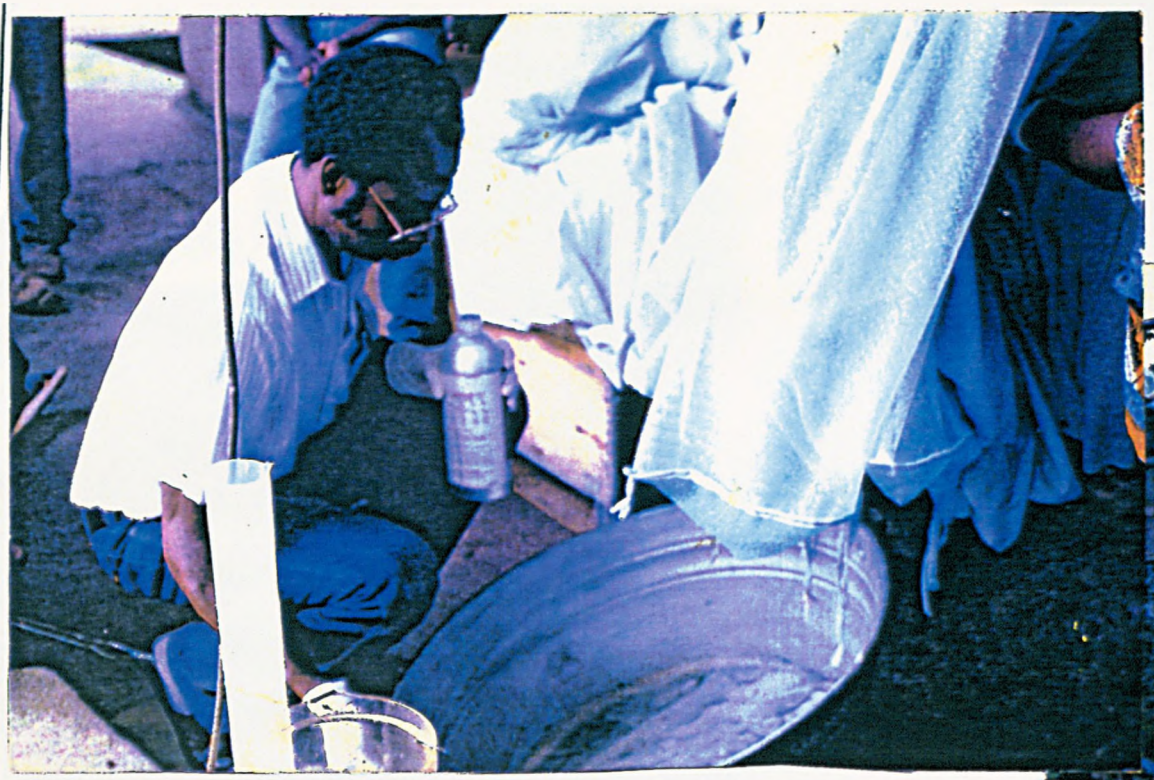


Horizontal scale: 1 cm = 1·5 km

Chiefs of the study villages in Bo to participate in a lottery to determine which villages in each 'matched pair' would receive the nets initially during the intervention phase.

Control villages received nets in July, 1993, at the end of the intervention study.

Members of the study team posing with the Chiefs after the lottery



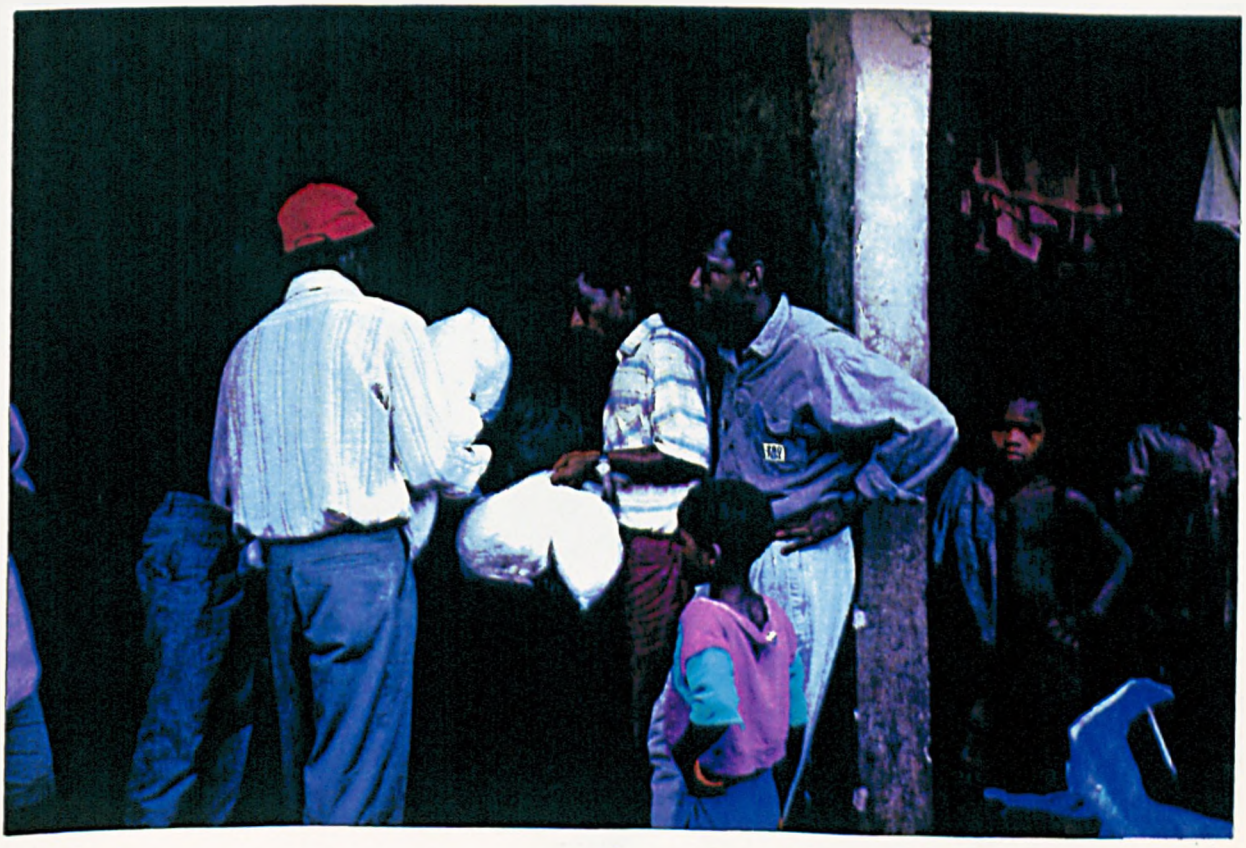
Dr. I. Ebojah of UNICEF(Freetown Office) assisting with nets impregnation. His involvement help ensured that the study team and participants in the 'acceptability study' were blind to the treatment status of the nets.

Volunteer assisting with impregnation. Nets were hung out in shade to dry

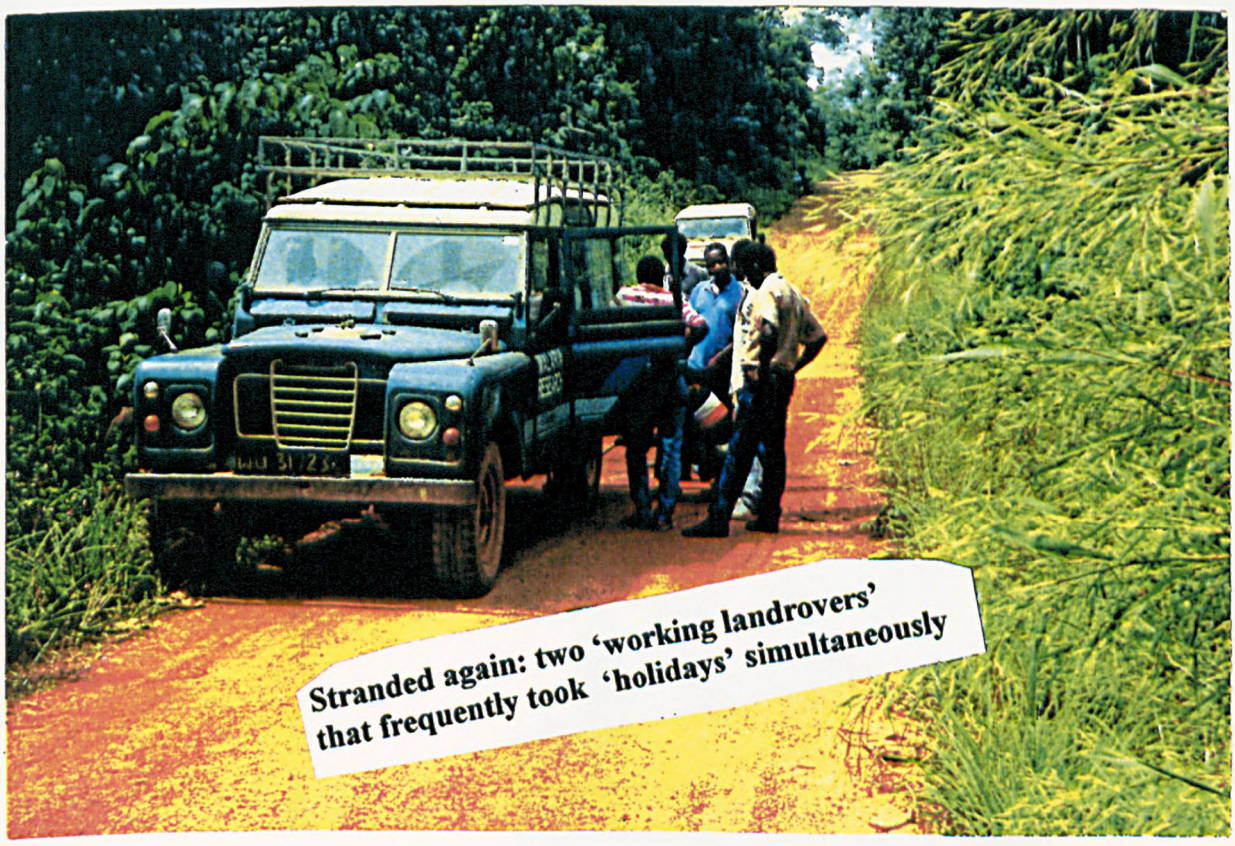
Ensuring that all 'sleeping places' in a household are supplied with nets

A pleased and proud owner

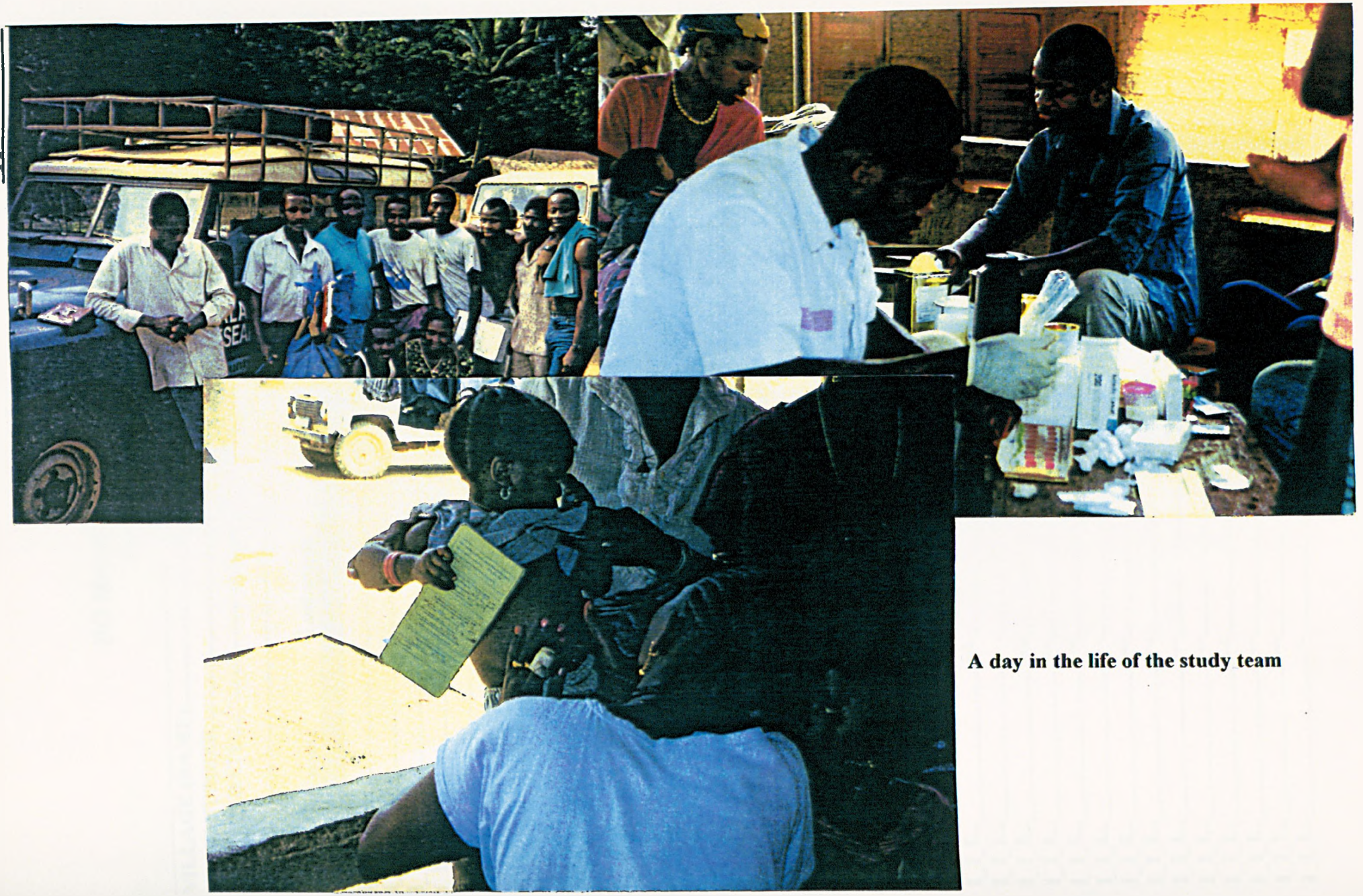
Nets being distributed through Elders/Chief of an intervention village in June,1992



**Community health centre in Ngalu(village 7)
typical of health centre in Bo disrtict**



**Stranded again: two 'working landrovers'
that frequently took 'holidays' simultaneously**



A day in the life of the study team

BO MALARIA PROJECT

Census form

VILLAGE (NAME)..[STUDY NUMBER]..I_I_I
HOUE NUMBER...I_I_I_I
SURVEY DATE...I_I_I..I_I_I...I_I_I

Pno.:	First name	Last name	Sex	DOB (mm dd yy)	M/S	Tribe
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I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I
I_I_I...	____________	....____________	..I_I.....	I_I_I..I_I_I.I_I_I	..I_I....	I_I_I

BO MALARIA PROJECT

FAMILY REPORT(I)

CHILD'S NAME_____

ID NEMBER.....I_I_I I_I_I_I I_I_I I_I IDNO

DATE(mm dd yy).....I_I_I I_I_I I_I_I DATE

INVESTIGATOR CODE.....I_I_I INCO

RESPONDENT (Mother=1; Father=2; Sibling=3; Usual minder=4; Other=5).....I_I RPOND

MOTHER PRESENT(living in village) (yes=1; no=2).....I_I MPRS

MOTHER ABSENT (from village) (yes=1; no=2).....I_I MABS

MOTHER DEAD (yes=1; no=2).....I_I MDEAD

MOTHER ID (if registered).....I_I_I I_I_I_I I_I_I I_I MID

FATHER ID (if registered)..... I_I_I I_I_I_I I_I_I I_I FID

SIBLINGS

1. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS1
2. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS2
3. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS3
4. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS4
5. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS5
6. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS6
7. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS7
8. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS8
9. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS9
10. NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS10
11.NAME_____ ID I_I_I I_I_I_I I_I_I I_I BRS11

BO MALARIA PROJECT
PRE-INTERVENTION HOUSE SURVEY

1. DATE.....I_I_I I_I_I I_I_I HDATE
2. VILLAGE/HOUSE No.....I_I_I .....I_I_I_I HHID
3. WALL MATERIAL.....I_I HWALL
   [legend: mud&stick=1; mud&brick=2; mud&cement=3; cement only=4]
4. ROOFING MATERIAL.....I_I HROOF
   [legend: corrugated iron=1; thatch=2; Others (specificy below)]

   .....

5. Are the eaves open (yes=1; no=2).....I_I HEAVES

FOR THE FOLLOWING QUESTIONS, WRITE NUMBER AS APPROPRIATE

---

7. NUMBER OF ROOMS USE FOR SLEEPING .....I_I_I HROOM
8. NUMBER OF SUCH ROOMS WITH CEILING.....I_I_I HCEIL
9. NUMBER OF BEDS IN THE HOUSE.....I_I_I HBEDS
10.NUMBER OF BEDS WITH MOSQUITO NETS.....I_I_I HNETS
11. NUMBER OF SLEEPING MATS(or other sleeping arrangements)..I_I_I HMATS
12. NUMBER OF BEDROOMS WITH SCREEN WINDOWS.....I_I_I HSW

FOR THE FOLLOWING QUESTIONS PLEASE INDICATE YES OR NO(yes=1,no=2)

---

13. WHICH OF THE FOLLOWING ANIMALS LIVE IN OR AROUND THIS HOUSEHOLD?

DOG.....I_I HDOG
PIG.....I_I HPIG
GOAT.....I_I HGOAT
SHEEP.....I_I HSHEEP
COW.....I_I HCOW

INVESTIGATOR CODE No.....I_I_I HINVEST

BO MALARIA PROJECT

BED-NET ASSESSMENT QUESTIONNAIRE

1.Date.....I_I_I_I_I_I_I MDATE
2. Village.....I_I_I MVILL
3. House Number.....I_I_I_I MHOUSE
4. Investigator Code.....I_I_I MINCO

This section should be completed from interviewing the head of the household.

---

5. How many bednets were supplied to you.....I_I_I MBED
6.How many of these bednets have been washed.....I_I_I MWASH
7.How many bednets have holes.....I_I_I MHOLE
8. Are the nets still effective(yes=1; no=2).....I_I MEFFECT
9. Are there bedbugs within your household(yes=1; no=2).....I_I MBUG
10. If yes, in how many beds.....I_I_I MNBUG
11. Do the children have headlice(yes=1; no=2).....I_I_I MLICE
12. Have you installed new beds or sleeping mats
in your households(yes=1; no=2.....I_I MNBED
13. If yes, how many.....I_I_I MNUMB
14. Are you willing to pay le.3500/net for nets for these
new beds or sleeping mats(yes=1; no=2).....I_I MNPAY
15. The nets would need to be reimpregnated by the end of July,1993.
Would you be willing to pay le.400/net for
the re-impregnation(yes=1; no=2).....I_I MREIMP

This section should be completed from observations made by the study team

---

16. Number of bednets presently installed.....I_I_I MBINSTA
17. Number of bednets with washable marks.....I_I_I MMARKER
18. Number of bednets with holes.....I_I_I MDAMAGE
19. If with holes, indicate the size of the largest holes.

Net Number	size of the largest hole	
1	I_I	NET1
2	I_I	NET2
3	I_I	NET3
4	I_I	NET4
5	I_I	NET5
6	I_I	NET6
7	I_I	NET7
8	I_I	NET8
9	I_I	NET9
10	I_I	NET10
11	I_I	NET11
12	I_I	NET12

[legend for hole size: 1 finger=1, 2 fingers=2; 3 fingers=3; fist=4]
20. How many of the nets in this household are almost white...I_I_I MWHITE
21 How many are darken by soot.....I_I_I MSOOT

CHILD REPORT
CROSS-SECTIONAL MORBIDITY SURVEY
BO MALARIA PROJECT

Code throughout: 9= no answer

Child name: _____
ID number.....I_I_I I_I_I_I I_I_I I_I Idno
Date(mm dd yy)..... ....I_I_I I_I_I I_I_I Date

Investigator code.....I_I_I Inco
Respondent (1=mother; 2=father; 3=sibling; 4=usual minder; 5=other).....I_I Rpond
Did this child receive the prophylaxis this week (yes=1; no=2).....I_I Trt

Status of the child
1. Is the child well today? (1=well; 2=sick).....I_I Well
2. If the child is sick, is he/she able to continue normal activities?(yes=1; no=2).....I_I Sana
3. Was the child well or sick during the last 7 days? (1=well; 2=sick).....I_I Well7
4. Temperature .....I_I_I, I_I Temp
5. Is the child being breast fed(yes=1) or not(2).....I_I Brf

Blood smear taken.....(1=yes; no=2).....I_I Bld
Blood in capillaries tubes for PCV determination.....(1=yes; no=2).....I_I Pcv
Spleen size.....Hecket's classification).....I_I Hct

6.Cough, sneeze, have a cold, sore throat or ear ache.....(1=yes; no=2).....I_I Urti
7. Cough and side pain and/or difficulty in breathing.....(1=yes; no=2).....I_I Lrti
8. Skin disorders(scabies,etc.).....(1=yes; no=2).....I_I Skin
9. Conjunctivitis.....(1=yes; no=2).....I_I Eye

CHILD REPORT
WEEKLY MORBIDITY SURVEY
BO MALARIA PROJECT

Code throughout: 9= no answer

Child name: _____
ID number.....I_I_I I_I_I_I I_I_I I_I Idno
Date(mm dd yy)..... ....I_I_I I_I_I I_I_I Date

Time of the day (1=before 12 o'clock; 2=after 12 o'clock).....I_I Extim
Investigator code.....I_I_I Inco
Respondent (1=mother; 2=father; 3=sibling; 4=usual minder; 5=other).....I_I Rpond
Did this child receive the prophylaxis this week (yes=1; no=2).....I_I Trt

---

Status of the child

1. Is the child well today? (1=well; 2=sick).....I_I Well
2. If the child is sick, is he/she able to continue normal activities?(yes=1; no=2).....I_I Sana
3. Was the child well or sick during the last 7 days? (1=well; 2=sick).....I_I Well7
4. Temperature .....I_I_I, I_I Temp
5. Is the child being breast fed(yes=1) or not(2).....I_I Brf

---

Blood film if any of the below listed conditions are present:

6. Temperature 37.5 or greater.....(1=yes; no=2).....I_I Htemp
7. History of fever today.....(1=yes; no=2).....I_I Fev
8. History of fever during the last 7 days.....(1=yes; no=2).....I_I Fev7
9. History of chills and/or rigors in last 7 days.....(1=yes; no=2).....I_I Crig
10. History of vomiting, diarrhoea or headache during the last 7 days(1=yes;no=2)....I_I Vh
Blood smear taken.....(1=yes; no=2).....I_I Bld

---

11. Cough, sneeze, have a cold, sore throat or ear ache.....(1=yes; no=2).....I_I Urti
12. Cough and side pain and/or difficulty in breathing.....(1=yes; no=2).....I_I Lrti
13. Skin disorders(scabies,etc.).....(1=yes; no=2).....I_I Skin
14. Conjunctivitis.....(1=yes; no=2).....I_I Eye

---

15. Malaria treatment by project today.....(1=yes; no).....I_I Mec
16. Treatment for malaria the past 7 days by anyone else?.....(1=yes; no=2).....I_I Elmd

.....if yes to 16, was it at:
17. Health centre(1); Drug peddler(2); Local herbalists(3); Other(4).....I_I Twho

---

Use of mosquito nets

18. Did the child sleep under a mosquito net last night? (1=yes; no=1).....I_I Bnet

Laboratory Report

E C Malaria Project, Bo, Sierra Leone

Date taken |_|_|_|_|_|_| Date Read |_|_|_|_|_|_|

ID Number |_|_| |_|_|_|_| |_|_| |_| IDNO

Laboratory Technician (initials) |_|_| LTI

Thick Film Results

P. falciparum

Asexual:	No. of positive fields per 100 HPF	|_|_|_| PF1
	if 100/100, no. of parasites per HPF	|_|_|_| PF2
Gametocytes:	No. of positive fields per 100 HPF	|_|_|_| PF3
Schizonts:	per 100 HPF	|_|_|_| PF4

P. malariae

Asexual:	No. of positive fields per 100 HPF	|_|_|_| PM1
	if 100/100, no. of parasites per HPF	|_|_|_| PM2
Gametocytes:	No. of positive fields per 100 HPF	|_|_|_| PM3
Schizonts:	per 100 HPF	|_|_|_| PM4

P. ovale

Asexual:	No. of positive fields per 100 HPF	|_|_|_| PO1
	if 100/100, no. of parasites per HPF	|_|_|_| PO2
Gametocytes:	No. of positive fields per 100 HPF	|_|_|_| PO3
Schizonts:	per 100 HPF	|_|_|_| PO4

P C V

Packed Cell Volume, PCV ..... |_|_| PCV

BO MALARIA PROJECT

PROPHYLAXIS COMPLIANCE MONITORING CARD

PHOTO IDENTIFICATION

NAME VILL HN PNo C

1._____ I_I_I /I_I_I_I/I_I_I/I_I

2._____ I_I_I /I_I_I_I/I_I_I/I_I

3._____ I_I_I /I_I_I_I/I_I_I/I_I

4._____ I_I_I /I_I_I_I/I_I_I/I_I

5._____ I_I_I /I_I_I_I/I_I_I/I_I

FOR PHOTO
REFER TO CARD#I_I_I: I_I_I_I: I_I_I

VISITATION:

	mm	dd	yy	P/A	DRUG	INCO
WK:						
1	I_I_I	I_I_I	I_I_I	I	I	I_I_I
2	I_I_I	I_I_I	I_I_I	I	I	I_I_I
3	I_I_I	I_I_I	I_I_I	I	I	I_I_I
4	I_I_I	I_I_I	I_I_I	I	I	I_I_I
5	I_I_I	I_I_I	I_I_I	I	I	I_I_I
6	I_I_I	I_I_I	I_I_I	I	I	I_I_I
7	I_I_I	I_I_I	I_I_I	I	I	I_I_I
8	I_I_I	I_I_I	I_I_I	I	I	I_I_I
9	I_I_I	I_I_I	I_I_I	I	I	I_I_I
11	I_I_I	I_I_I	I_I_I	I	I	I_I_I
12	I_I_I	I_I_I	I_I_I	I	I	I_I_I
13	I_I_I	I_I_I	I_I_I	I	I	I_I_I
14	I_I_I	I_I_I	I_I_I	I	I	I_I_I
15	I_I_I	I_I_I	I_I_I	I	I	I_I_I
16	I_I_I	I_I_I	I_I_I	I	I	I_I_I
17	I_I_I	I_I_I	I_I_I	I	I	I_I_I
18	I_I_I	I_I_I	I_I_I	I	I	I_I_I
19	I_I_I	I_I_I	I_I_I	I	I	I_I_I
20	I_I_I	I_I_I	I_I_I	I	I	I_I_I
21	I_I_I	I_I_I	I_I_I	I	I	I_I_I
22	I_I_I	I_I_I	I_I_I	I	I	I_I_I
23	I_I_I	I_I_I	I_I_I	I	I	I_I_I
24	I_I_I	I_I_I	I_I_I	I	I	I_I_I
25	I_I_I	I_I_I	I_I_I	I	I	I_I_I
26	I_I_I	I_I_I	I_I_I	I	I	I_I_I
27	I_I_I	I_I_I	I_I_I	I	I	I_I_I
28	I_I_I	I_I_I	I_I_I	I	I	I_I_I
29	I_I_I	I_I_I	I_I_I	I	I	I_I_I

VISITATION

	mm	dd	yy	P/A	DRUG	INCO
WK:						
30.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
31.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
32.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
33.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
34.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
35	I_I_I	I_I_I	I_I_I	I	I	I_I_I
36	I_I_I	I_I_I	I_I_I	I	I	I_I_I
37	I_I_I	I_I_I	I_I_I	I	I	I_I_I
38	I_I_I	I_I_I	I_I_I	I	I	I_I_I
39	I_I_I	I_I_I	I_I_I	I	I	I_I_I
40	I_I_I	I_I_I	I_I_I	I	I	I_I_I
41.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
42.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
43.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
44.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
45.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
46.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
47.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
48.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
49.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
50.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
51.	I_I_I	I_I_I	I_I_I	I	I	I_I_I
52.	I_I_I	I_I_I	I_I_I	I	I	I_I_I

code: [P/A]P =present; A=absent
[Drug]1=adminster; 2=nothing
[INCO]=investigator ID CODE

Field workers with their respective investigator codes

1 = James Boima
2 = Joseph Gborie
3 = John Kargobai
4 = Charles Gembeh
5 = Abdul Swaray
6 = Anderson Sesay
7 = Maada Gandema
8 = Thomas Saidu Alieu
9 = Gregory Bockarie
10 = Idris Lamin
11 = Prince Masuba
12 = Alex Momoh
14 = Charles Rogers
15 = Sulaiman Kaikai
16 = Anthony Kaigbesse
17 = Mohamed Kamara
18 = Prince Thomas
19 = Joseph Vandy
20 = Dr. N.T. Marbiah
21 = Elizabeth Koroma
22 = Sahr Bundor
23 = Edward Moiwa
24 = Elizabeth Musa
25 = Patrick Swaray
26 = Samuel Bailor
27 = Paul Dominic Luse.
28 = Emmanuel Bangali
29 = Sheik Mohamed Jeb.
30 = Mr. William Banya
31 = Francis Salia
32 = Samuel Yankuba
33 = Edward Magbity
34 = Francis Moriba
35 = Foday Mansaray
36 = Mohamed Fofanah
37 = Ago Lemoh
38 = Thomas Fullah
39 = Ahmed Sombie
40 = Ibrahim Aruna
41 = Moses Fatorma
42 = Ibrahim Bayon
43 = Lawrence Mamania
44 = James Faya
45 = Agnes Tommy
46 = Donald Scott Manga
47 = Francis Krim
48 = Edie Samai

Appendix IV

EVENTS CALENDAR

DATE	NATIONAL EVENTS	NUMBER OF YEARS AGO
1881-1884	Trade War in the Hinterland of Sierra Leone	101 - 105
1898	Hut Tax War	87
1898	Sierra Leone Railway Opened	87
1907	Death of Madam	78
1910	"Ngedenmeh" Famine and Kpangbama Impare Chiefdom Cannibal Case	75
1914-18	First World War	67-71
1918	Influenza Epidemic	67
1919	First Railway Strike	66
1920-25	First Motor Car	60-65
1922	First Agricultural Show(Kenema)	63
1925	Visit of Prince of Wales	60
1926	Second Railway Strike	59
1928	First Deluge(Flood)	57
1934	Locuts disaster	51
1936-37	Introduction of Native Administration in Sierra Leone	48-49
1939-45	Second World War	40-46
1945-46	Influenza Epidemic	40
1942-46	Quota Rice	39-43
1945	Third Deluge (Flood)	40
1947	Earth Tremor on Friday	38
1947	Paramount Chiefd Nominated to Legislative Council	38
1947-48	Return of Ex-Servicemen	37-38
1953	Coronation of Queen Elizabeth II	32
1954	Adult Sufferage Commission	31
1955	February - Freetown Riot General Strike	30

1956	Cox-George Commission	29
1957	First General Election	28
1959	Train Disaster in S-S Curve	26
1960	Constitutional Conference	25
1961	Independence	24
1961	Queen's visit to Sierra Leone	24
1962	Second General Elections	23
1963	First National Census	22
1963	First Governor General for Sierra Leone Appointed	22
1964	Death of Sir Milton Margai	21
1964	Introduction of Decimal Currency in Sierra Leone(Leones and cents currency)	21
1967	General Elections	18
1967	Coup d'etat Lansana Coup N.R.C. Government	18
1968	Overthrow of Juxon-Smith	17
1968	A.P.C. Government with Dr. Siaka Stevens as Prime Minister	17
1970	Fornah and Bash-Taqi resign from A.P.C.	15
1971	Declaration of Republic with Dr. Siaka Stevens as President of the Republic of Sierra Leone	14
1971	Coup d'etat (late J. Bangura & Ors.)	14
1971	Right Hand Traffic	14
1973	Last Railway Facing Out	12
1973	May: General Election - A.P.C - Unopposed	12
1974	July Arrest of M. Fornah and others (Abortive Coup d'etat)	11
1974	December: Second Census	11
1977	January: Student Strick	8

1977	March: General Elections	8
1978	Referendum - One Party	7
1980	July: Hosting of O.A.U Summit in Freetown	5
1981	Labour Congress Strick	4
1982	May: General Elections	3

Borrow-pits dug for bricks:
Creating breeding sites close to dwellings

Borrow-pits dug for bricks:
Creating breeding sites close to dwellings.

A summary of selected findings of the weekly morbidity surveys by village pair.
(Supplementary to Table 5.4)

Village pair	Village	Number of smears collected	Number positive	Parasitaemia >=25,000 parasites/ul	Number of clinical episodes	Total child-weeks at-risk
1	Nengbema(2)	1446	694	90	247	7797
	N. Komboya(15)	1297	314	23	61	6740
2	Bumbeh(1)	240	75	10	23	1346
	Nyandeyama(3)	402	136	11	45	2014
3	Tondoya(4)	360	156	19	56	2865
	Buma(8)	834	201	9	39	3142
4	Blama I&II(5/6)	1042	282	20	63	4665
	Ngula(7)	710	321	45	106	4483
5	Kunjondoma(10)	158	83	12	28	1284
	Palima(12)	458	106	16	33	2049
6	Kpatema(11)	269	149	13	43	1199
	Kpakuma(13)	81	24	3	9	654
7	Mendewa(14)	545	207	31	81	3456
	Sami(9)	664	141	7	34	3155
8	Sahn(16)	2078	711	82	219	10639
	Gumahun(17)	2976	1086	130	308	7360
Total		13560	4386	521	1395	62848

Appendix VI

The distribution of Plasmodium falciparum densities observed during the morbidity surveys, classify by age and sampling criteria.(supplement to Table3.4)

	Plasmodium falciparum densities distribution: density/ul																	
Sampling criteria	0		1-999		1000-1999		2000-4999		5000-9999		10000-24999		25000-49999		50000-99999		>=100000	
	<=24	>24	<=24	>24	<=24	>24	<=24	>24	<=24	>24	<=24	>24	<=24	>24	<=24	>24	<=24	>24
Fever	396 (47%)	474 (42.5%)	149 (53%)	341 (51%)	8 (67%)	11 (58%)	20 (55%)	71 (62%)	49 (69%)	85 (59%)	60 (79%)	108 (70%)	37 (95%)	73 (84%)	26 (90%)	28 (90%)	9 (82%)	16 (84%)
Extended criteria	447 (53%)	642 (57.5%)	137 (47%)	324 (49%)	4 (33%)	8 (42%)	16 (44%)	43 (37%)	22 (31%)	59 (41%)	16 (21%)	47 (30%)	2 (5%)	14 (16%)	3 (10%)	3 (10%)	2 (8%)	3 (16%)
Total	843	1116	286	665	12	19	36	114	71	144	76	155	39	87	29	31	11	19

wake up

doubt!
may paralyse
often hopelessly

to break out
avoid the thought
of nothing **new** to say

the Creator of the infinite
enlightens all

we only echo
a fragment of the **truth**
as all others have
or ever will

about understanding
a world still unfolding

nuahn tomanh marbiah
june 20,1994