THE IMPACT OF INSECTICIDE-TREATED BEDNETS USE ON MALARIA AND ANAEMIA ~~IN PREGNANCY~~ IN KASSENA-NANKANA DISTRICT, GHANA

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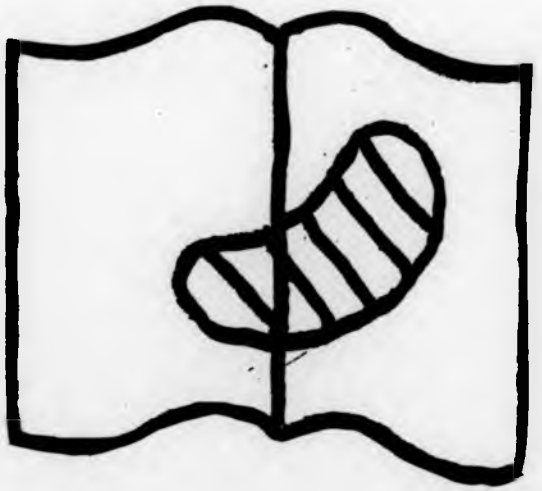

ABSTRACT

A study was conducted in Kassena-Nankana district, Ghana from April 1994 to April 1995 to assess the impact of insecticide-treated bednets on malaria and anaemia in pregnancy. A secondary objective was to assess the impact of insecticide-treated bednets on pregnancy outcome, although it was recognised that the sample size would be relatively small for this purpose. The study took place within a large-scale controlled trial designed to assess the impact of insecticide-treated bednets on child mortality. The study area was divided into 96 clusters of compounds and of these 48 clusters were randomly selected to receive the intervention (treated nets).

The endpoints of the study were haemoglobin levels, parasitaemia and parasite density and weight of newborns which were recorded within 7 days of delivery. All pregnant women were included in the study but the target group of main interest was primigravidae and secundigravidae. A total of 2812 pregnant women, of all parities, were enrolled into the study; 1961 (70 percent) women were seen at least once at a study clinic of whom 641 were seen for a second time between 28-40 weeks gestation.

At both clinic visits, blood was taken for haemoglobin determination and malaria parasitology. Chloroquine ELISA assays, using dried blood spots on filter paper, were performed for 64 percent of pregnant women at their first clinic visits. Data were obtained on 821 delivery outcomes, including 799 newborn weights recorded within 7 days of delivery. A cross-sectional survey was done to determine the distribution of haemoglobin levels and malaria parasitaemia in non-pregnant adult females. Focus group discussions were conducted to assess study women's attitudes to antenatal care and use of bednets.

Bednet use provided no protection against anaemia defined as (Hb<100 g/l), severe anaemia (Hb<70 g/l), *P. falciparum* parasitaemia (high: >2000 parasites/µl or low: >0 parasite/µl) or low birth weight. The characteristics of women in the treated and the no net groups were comparable. Net usage was lower than expected, especially in primigravidae.

Effective net use was as follows: primigravidae 42 percent (net coverage: 60 percent, use: 70 percent), secundigravidae 58 percent (net coverage: 80 percent, use: 72 percent), multigravidae 63 percent (net coverage: 86 percent, use: 73 percent). Below 10 percent of chloroquine ELISA assays were positive with no differences by treatment arms, parity or season. Odds ratios (ORs) for the different endpoints for those with nets in comparison to those without nets, based on an intention-to-treat (ITT) analysis did not show a statistically significant protective effect;

First clinic visit:	Anaemia	- 0.97 (0.86, 1.10)
	Severe anaemia	- 0.91 (0.57, 1.43)
	Low Parasitaemia	- 1.13 (0.54, 2.38)
	High Parasitaemia	- 0.98 (0.85, 1.12)

The following results were obtained when data for first and second clinic visits were combined (combined data) and restricted to one record per woman with at least 26 weeks gestation and including all second clinic visit records.

Combined data:	Anaemia	- 0.88 (0.70, 1.09)
	Severe anaemia	- 0.80 (0.55, 1.16)
	Low Parasitaemia	- 0.89 (0.73, 1.08)
	High Parasitaemia	- 1.11 (0.93, 1.33)

Low birth weight:	Adjusted (<2500g)	- 0.87 (0.63, 1.19)
	Unadjusted	- 0.88 (0.61, 1.24)

Analysis of protection at individual level showed similar results. Based on the findings of this study, insecticide-treated bednets are not recommended as a primary tool for malaria control in pregnancy in northern Ghana. Further operational research is required to assess the impact of insecticide-treated bednets combined with chemoprophylaxis and behavioural interventions on malaria in pregnancy.

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To God Be the GLORY. Forever and Ever. Amen !!!

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Chapter 1

Introduction

1.1 Organisation of the Thesis

The thesis is organised into 7 chapters. Chapter 1 covers organisation of the thesis, the introduction, the rationale for the study, objectives of the study and a summary of the design of the main trial in which this study was a supplementary trial [See Appendix I for more details on the main trial]. Chapter 2 covers a detailed review of the current literature on malaria and anaemia in pregnancy, control methods and their present strengths and weaknesses, and new methods being tested, with a focus on insecticide-treated bednets. Chapter 3 covers the description of the study design used, including the people and their culture, the study area and sample size determination.

Chapter 4 describes the field operations of the study detailing organisation of fieldwork, training, maternal and neonatal health services and data management. Chapter 5 details the results and findings of the study based on univariate and multivariate analysis. In chapter 6, the findings and limitations of the study are discussed. Chapter 7 draws conclusions from the design and results of the study, and ends with recommendations for further research.

1.2 Rationale for the Study

Malaria and anaemia in pregnancy constitute important public health problems in Sub-Saharan Africa (McGregor, 1984; McGregor, 1987; Mutabingwa, 1994). Malaria is implicated in prematurity, abortions, maternal anaemia and low birth weight, especially in primigravidae. Anaemia has several causative factors, one of the most important being *Plasmodium falciparum* malaria. In pregnancy, *P. falciparum* malaria and malaria-related

anaemia contribute significantly both directly and indirectly to maternal and perinatal mortality.

The key strategy to malaria and anaemia control in pregnancy in Sub-Saharan Africa is routine antenatal care provided at static health facilities. Occasionally outreach or mobile services complement this. In Ghana, this is achieved through malaria chemoprophylaxis using chloroquine together with folic acid and iron supplementation through self-administration. Early diagnosis and prompt treatment of presumptive malaria is another control measure, applicable not only in pregnancy but also in other situations (WHO, 1993a). In the case of anaemia, in-patient treatment is recommended below a defined cut-off point, usually set below 70 g/l (WHO, 1992a; WHO, 1993d). The above strategies have been only partially effective in routine programme settings. Poor accessibility and low coverage of health services mean that most women at high risk in rural Africa are seldom reached. Even for those with adequate coverage, poor compliance is a serious problem. Hence there is an urgent need to explore other forms of malaria control in pregnancy that are feasible and applicable on a community-wide basis in rural Africa, given that such are affordable, effective and culturally acceptable. Ideally, such interventions should require only limited inputs from the formal health services and be sustainable on a community-wide basis. Insecticide-treated bednets, if effective for malaria control in pregnancy, offer such an opportunity and challenge. However, very little work has been done on the use of insecticide-treated bednets by pregnant women.

Results from initial field trials and observational studies in children have shown a reduction in morbidity (Rozendaal, 1989; Curtis, 1992) and mortality (Alonso et al., 1991; Alonso et al., 1993; D'Alessandro et al., 1995) caused by malaria directly or indirectly through reducing man-vector contact. A recent meta-analysis of insecticide-treated bednets (Choi et al., 1995) suggested that they were effective in preventing clinical attacks of malaria, decreasing the incidence rate ratio by approximately 50 percent. Only field trials that measured the association between insecticide-treated

bednets and episodes of malaria infection and that had a concurrent control group were included in the analysis. The presumed mechanism of action of insecticide-treated bednets is through reduction of severity of parasitaemia and number of febrile episodes.

A large-scale insecticide-treated bednet trial in the Kassena-Nankana district of Upper East Region, Ghana was set up in 1992 at the Navrongo Health Research Centre (NHRC), one of the 3 field stations of the Health Research Unit (HRU) of the Ministry of Health (MOH), Ghana, with support from WHO/TDR, IDRC-Canada and UNICEF to assess the effect of permethrin-impregnated bednets on childhood (6 months to 4 years) mortality in 96 clusters, 48 with and 48 without nets. Meetings were held in the various chiefdoms in the study area to explain the trial design, demonstrate the use of bednets both indoors and outdoors and also to select clusters to receive insecticide-treated bednets by ballot. Compounds in 48 clusters were subsequently provided 31,000 brown coloured 100 denier nylon nets in June 1993. The women were taught how to impregnate the nets after a worker from NHRC had measured 20 ml of 50 percent emulsifiable concentrate of permethrin (50 percent EC, ICI, Public Health & Imperator 50, ZENECA, UK) and 500 ml of water per net into a plastic container. The nets had an average area of 12 m^2 and the target dose was 500 mg/m^2. The nets were re-impregnated in January and July 1994, and January 1995. At the end of the follow up period, in June 1995, insecticide-treated bednets were provided to the compounds in the 48 "no nets" clusters.

The trial was designed to have a power of 90 percent to detect a reduction of 30 percent in all-cause mortality associated with permethrin-impregnated bednet use in children aged 6 months to 4 years. The field trial also had a major entomological component. Details of the main trial are summarised in Appendix I. The results of the Navrongo bednet trial have been published recently (Binka et al., 1996). The Navrongo bednet trial offered a rare opportunity to assess the impact of insecticide-treated nets on malaria and malaria-related anaemia in pregnancy as a supplementary study

1.3 Objectives for the Study

The objectives for this study were as follows:

1.3.1 General Objectives

To assess the effect of insecticide-treated bednets on malaria and malaria-related anaemia in pregnancy in Kassena-Nankana District, Ghana.

1.3.2 Specific Objectives

i. To estimate the effects of insecticide-treated bednets on haemoglobin levels in primigravidae and secundigravidae,

ii. To estimate the effects of insecticide-treated bednets on malaria parasite rates, parasite density, and probable malaria illness in primigravidae and secundigravidae,

iii. To assess the influence of insecticide-treated bednets on birth weights

Chapter 2

Literature Review

2.1 Introduction

The literature review for this thesis has been organised into 6 main sections. **Section 2.2** provides a summary of the current global picture on malaria; **section 2.3** deals with the malaria situation in Ghana; **section 2.4** covers issues related to malaria and anaemia in pregnancy in Sub-Saharan Africa; **section 2.5** reviews strategies for malaria control in general, with greater emphasis on insecticide-treated bednets which is the focus of this work; **section 2.6** examines specific strategies for malaria control in pregnancy and finally **section 2.7** discusses some methodological issues related to statistical analysis of community intervention trials.

2.2 Global Malaria Situation

Malaria constitutes the single most prevalent and devastating disease in the tropics. Nearly 40 percent of the world's population is at risk (WHO, 1996a). The relentless spread of resistance to antimalarial drugs among parasites has compounded the seriousness of the problem. Appendix II shows the global malaria situation and reported drug resistance in 1993. New economic activities, especially the development of virgin territories and civil strife are additional aggravating factors (WHO, 1993a; WHO, 1993b). The malaria problem has been accorded global priority by the recent International Conference on Malaria in Amsterdam, the Netherlands (WHO, 1992b; WHO, 1992c).

The global malaria problem is concentrated mainly in tropical Africa where over 80 percent of all cases occur (WHO, 1996a). Estimates of malaria mortality vary from 1.5 to 2.7 million malaria deaths world-wide per year, the great majority of deaths occurring in

Africa. Approximately 1 million deaths among children under 5 years of age can be attributed to malaria alone or in combination with other diseases. In addition, malaria also contributes greatly to morbidity and mortality in other age groups especially in highland and desert fringe areas. Repeated and chronic infection sap productivity, causes chronic ill-health and affects pregnant women, resulting in severe anaemia and contributing to death in childbirth and to low birth weight babies. Stable malaria is typical in several areas of Sub-Saharan Africa. However in recent years, some of its most dramatic manifestations have been in areas previously relatively malaria-free due to high altitude or climatic factors unfavourable for malaria transmission (WHO, 1992d; WHO, 1993c). Due to a variety of reasons, mainly climatic change, several countries, including Burundi, Ethiopia, Madagascar, Namibia, Rwanda, Swaziland, Zaire and Zambia have experienced epidemics which have claimed several thousands of lives and have led to serious impoverishment of affected communities. Most of these affected countries have not had established malaria control programmes to deal effectively with these epidemics. The key obstacles to malaria control in Africa include: inadequate development and performance of peripheral health care services, lack of human, financial and managerial resources, and weak community involvement. Severe economic crises and civil strife in many African countries have worsened the situation.

2.3 The Malaria Situation in Ghana

Malaria is an important cause of morbidity and mortality in Ghana (MOH-Ghana, 1993). Malaria remains the single most important contributor to the number of "healthy days of life lost" in Ghana (GHAT, 1981). It accounted for 40 percent of all out-patient visits from 1985 to 1987 (MOH-Ghana, 1993), an increase on previous estimates of between 25 percent and 30 percent. In the 1992 annual report of the Ministry of Health, malaria remained the leading cause of outpatients' attendance and inpatient admissions and the

second most common cause of death nationally, surpassed only by anaemia (MOH-Ghana, 1993).

The malaria situation in Ghana has been reviewed recently (Ahmed, 1989). Malaria in Ghana is hyperendemic and unevenly distributed. Morbidity returns from health facilities indicate that most cases occur in the middle forest ecological zone followed by the coastal zone and the northern savannah zone. Between 1952 and 1954, Colbourne and Wright (Colbourne and Wright, 1955a; Colbourne and Wright, 1955b) carried out a series of studies on the epidemiology of malaria in Ghana. For the purposes of malaria transmission, they classified the country into 3 ecological zones; the relatively dry coastal plains, the forest belt, with a high rainfall fairly evenly distributed throughout the year, and the northern savannah with total rainfall similar to the coastal plains but seasonally distributed. This stratification has been modified recently with the addition of two new strata: urban malaria (as a result of rapid unregulated urbanisation) and development malaria associated with development activities such as irrigation, small-scale mining, and road construction (MOH-Ghana, 1991). Since the studies by Colbourne and Wright four decades ago, no malariometric studies have spanned all the zones.

In the coastal plains, the main vectors in the mid-1950s were *Anopheles gambiae* Giles and *Anopheles melas*. Infected bites per person per year were 21 in the suburban and 0.1 in central urban Accra. Parasite and spleen rates also showed differences between areas. Spleen and parasite rates in 1-4 year olds were both above 75 percent in the rainy season in suburban Accra compared to spleen and parasite rates of about 30 percent and 50 percent respectively in central urban Accra in the same age group. The parasite species was predominantly *Plasmodium falciparum* (98 percent). Fourteen percent of slides were positive for *Plasmodium malariae* alone or in mixed infections, mainly in the under five age group. The recognised definitions of endemicity were not applicable in the coastal savannah based on field studies.

In addition, malaria parasite rates have been declining in Accra as a result of rapid urbanisation (Chinery, 1984); 1921-31: 50 percent; 1952-54: 40 percent (Colbourne and Wright, 1955a); 1964: 12 percent (Ringelhaan et al., 1976); 1978: 2 percent (Gardiner et al., 1984); 1985: 1 percent (Osei et al., 1989). These changes may be due to population changes in major malaria vectors in Accra and increased availability and effective use of antimalarial drugs (Chinery, 1984). The findings of a study in the late 1970s showed that 40 percent of children aged less than 10 years in Ablekuma sub-district of Accra metropolis had no detectable antibodies against any of the three prevalent malaria species (Gardiner et al., 1984). A more recent study in the same area also noted that 70 percent of infants go through the first year of life without any malaria infection confirming the earlier observation (Osei et al., 1989). In rural parts of the coastal savannah, the picture is varied. In the Danfa project area, spleen rates were consistently above 45 percent but below 50 percent. Parasite rates were above 30 percent with low spleen rates in adults and little seasonal variation (Wurapa et al., 1978). Hence the situation could be technically described as "hyperendemic". This contrasts with the situation in Gomoa district of Central Region also in the coastal ecological zone. Parasite rates ranged from 36 percent to 79 percent in the dry season and from 66 percent to 96 percent in the rainy season (Itoh et al., 1986; Afari et al., 1993).

The studies in the forest belt were carried out in Bomfa (Colbourne and Wright, 1955a) in present day Ejisu-Juaben district, Ashanti Region. The vectors of malaria identified in this area were *A. gambiae, A. funestus, A. hargreavesi* Evans and *A. nili* Theobald. *A. gambiae* and *A. funestus* accounted for 95 percent of total "knock down" catches. The probable number of infective bites per person per year was 24. The parasite species was predominantly *P. falciparum* (90 percent). Slide positivity for *P. malariae* and *P. ovale* alone or in mixed infections were 12.6 percent and 3.5 percent respectively. The picture did not also fit the recognised pattern of endemicity. There was little seasonal variation in malaria transmission, parasite rates being slightly higher after the rains.

Malariometric studies in the northern savannah were performed in Yorugu village in Bolgatanga district in October 1954 and April 1955 (Colbourne and Wright, 1955b), in the Kusasi local council area of present day Bawku West district in 1960 (WHO, 1958) and in Kassena-Nankana district in 1991 (NHRC/MOH, 1991; Ghana VAST, 1990; Binka et al., 1994), all in the Upper East Region. The Yorugu study showed that *A. gambiae* was 1.5 times as numerous as *A. funestus* in the wet season, while in the dry season, *A. gambiae* was predominant with *A. funestus* being reduced to less than 2 percent. The parasite rates for under 5's were as follows; October 1954 - 94 percent, and April 1955 - 92 percent. There was little seasonal variation. The parasite species found were *P. falciparum* 74 percent, mixed *P. falciparum* and *P. malariae* infections 22 percent and the rest being *P. malariae* with very few *P. ovale* infections. *P. malariae* infections were predominantly in children aged between 1-4 years.

In the Pinotti study area in Kusasi local council area (WHO, 1958), parasite rates in children aged 1-4 years varied from 74 percent in March 1960 at the end of the dry season to over 90 percent in September at the peak of the rainy season. This was prior to the introduction of medicated salts. Sporozoite rates varied from 5-15 percent throughout the year with *A. gambiae* and *A. funestus* being the main vectors. The distribution of the three species of plasmodia found in the project area was; *P. falciparum* 82.2 percent, *P. malariae* 16.3 percent and *P. ovale* 1.5 percent. The pilot project, which was started in 1959, aimed at assessing whether or not under local conditions interruption of malaria transmission using chloroquine medicated salt was feasible. Two months after the introduction of medicated salt, the parasite rate fell to 6 percent in the study area in September 1961 compared to 86 percent in the control area. In 1964, this project was discontinued due to lack of co-operation from the local population due to noticeably bitter taste and irregular supply of medicated salt and the entrance of unmedicated salt into the study area.

In the Ghana VAST study area in Kassena-Nankana [Navrongo] district (Ghana VAST, 1990; NHRC/MOH, 1991; Binka et al., 1994), *P. falciparum* was present in 70.6 percent of all thin films, *P. malariae* in 16.9 percent, *P. ovale* in 7.9 percent and *P.vivax* in 1.4 percent. All slides were examined initially at NHRC, Navrongo and re-read at the Noguchi Memorial Institute for Medical Research (NMIMR) in Accra. A randomly chosen 10 percent sample was re-examined by the senior technician at the Malaria Reference Laboratory at the London School of Hygiene and Tropical Medicine. The *k* statistic between NHRC and Accra was 0.72 and between Accra and London was 0.52. The laboratory results on *P.vivax* are at variance with current knowledge which suggests the non-existence of *P.vivax* in West Africa (Miller, 1988). Majority of West Africans are Duffy blood group negative which offers absolute protection against *P.vivax* infection. These results require further investigation, preferably using polymerase chain reaction (PCR). The *A. gambiae* complex was the principal vector. The parasite rates varied from 53.5 percent in April to 94.2 percent in September. High rates of parasitaemia with marked seasonal variation were found (Binka et al., 1994), although the study period was only 12 months. This was in contrast to the findings by Colbourne and Wright (1955b).

Colbourne and Wright (1955) concluded from their studies that there was universal infection in the northern savannah and forest ecological zones by the second year of life with little seasonal variation in malaria transmission. In the suburbs of Accra, there is universal transmission but this is limited to half the year. The information on malaria vectors and parasite rates is summarised in Table 2.3a.

From 1961 to 1968, Ghana, with the support of WHO, started preparations for a malaria eradication programme (MOH, 1962). This programme was, however, stopped in view of the technical difficulties in achieving a breakthrough with malaria control as a result of the development of DDT resistance in anopheline mosquitoes on a global scale. Since 1968, there has been no official policy on malaria control in Ghana. The unofficial policy has been chloroquine treatment for presumptive malaria in health facilities, although self-

medication is common. Most health facilities do not have functional laboratories and hence are unable to do malaria microscopy. The few that have laboratories do not do routine malaria microscopy for febrile episodes.

Table 2.3a: Malaria Vectors and *P. falciparum* Rates By Season and Ecological Zone in Ghana

Ecological Zone	Malaria Vectors	Parasite Rates (%)	
		Wet	Dry
Coastal Savannah	*A. gambiae* *A. melas*		
*Urban Accra		<50	NA[1]
*Sub Accra		75	NA
*Gomoa		66-96	36-79
Forest	*A. gambiae* *A. funestus*	90	NA
Northern Savannah	*A. gambiae* *A. funestus*		
*Yorugu		94	92
*Zebilla		90	74
* Navrongo		85-94	53-77

[1] NA - Not available, *Sub Accra = Suburban Accra

The emergence of chloroquine resistance in Ghana threatens the effectiveness of this "unofficial" policy (Neequaye et al., 1988; Ofori-Adjei et al., 1988; Akanmori et al., 1989). In 1988, 10 percent of asymptomatic school children in Sunyani/Tano district in Brong-Ahafo Region in the forest belt of Ghana remained parasitaemic on Day 7 after supervised 25 mg/kg of chloroquine given orally. In the same study, 23 percent of sick children aged 0 to 4 years and 17 percent of sick children aged 5 to 10 years still had parasitaemia 7 days after a therapeutic dose of chloroquine given orally. However, these failures showed only RI and RII responses (Meima, 1989).

In the same year, a similar study carried out in 3 communities along the coast of Ghana indicated 19.4 percent resistance (RI-3.5 percent, RII-15.9 percent) (Afari et al., 1989). In a national survey on chloroquine resistance with a sample of 626 children aged 6-15 years

(Afari et al., 1992), 570 (91.1%) showed sensitivity to chloroquine and 56 (8.9%) responses were classified as resistant to chloroquine: RI (5.1%) and RII (3.8%). The resistance responses were commonest (17.1-22.7%) in the coastal zone, followed by the savannah zone (8.6-10.0%), and lowest in the forest zone (3.1-6.3%). The RII responses occurred mainly in communities in the coastal zone. There was no RIII resistance in any zone. The information on chloroquine resistance in Ghana is summarised in Table 2.3b.

Table 2.3b: Chloroquine Resistance By Ecological Zones in Ghana

Ecological Zone	Year of Study	% Resistance	Type of Response
Coastal Savannah	1988	19.4	RI/RII
	1992	17.1-22.7	RI/RII
Forest	1988	17.0-23.0	RI/RII
	1992	3.1 - 6.3	RI/RII
Northern Savannah	1992	8.6 - 10.0	RI/RII

In 1991, the Ministry of Health finalised a five-year (1993-1997) malaria action plan based on Primary Health Care (MOH, 1991). The components of the malaria control strategy were: medical care (early diagnosis, prompt treatment and adequate management of complications), vector control (using insect repellents, insecticide impregnated bednets and screens), health education and health legislation. This action plan is being implemented although the focus is on classroom-based training on case management and rational prescribing. Very little technical support or supervision is provided for malaria control at the district level.

2.4 Malaria and Anaemia in Pregnancy in Sub-Saharan Africa

In addition to febrile illness, malaria also causes abortions, prematurity, anaemia and low birth weight especially in primigravidae (Kortmann, 1972; Brabin, 1983; McGregor, 1984; Fleming et al., 1986). Anaemia in Sub-Saharan Africa is caused by nutritional deficiency and infections, among which malaria is important (WHO, 1979; Royston, 1982). Malaria is more severe and frequent in pregnant women than the same women before pregnancy and also in comparison with their non-pregnant counterparts (Gilles et al., 1969; Brabin, 1983; McGregor, 1984; Menendez, 1995). The susceptibility to infection and its clinical manifestation is determined by the level of pre-pregnancy immunity, which depends to a great extent on the intensity and stability of malaria transmission (Kortmann, 1972). In hyperendemic and holoendemic areas, primigravidae are more affected than other parities (McGregor, 1987).

In holoendemic areas in Western Kenya (Brabin, 1983) and in Papua New Guinea (Brabin et al., 1990a), the peak prevalence of *P. falciparum* parasitaemia was 13-16 weeks in all parities and 9-16 weeks in primigravidae respectively. In a holoendemic area of Tanzania, Mutabingwa and colleagues (1993a) also observed high parasitaemia prevalence rate in primigravidae in a study with a mean gestation of 15 weeks for all parities. The peak in parasite densities has also been reported to occur before the 24th or 25th week of gestation, a period of high infection rates (Kortmann, 1972; Bray & Anderson, 1979). The highest densities occurred in primigravidae.

Recent research findings from Kenya (Fried & Duffy, 1996; Williams, 1996; Fishman, 1996) have improved the current understanding of malaria in pregnancy and the reasons for its severity in primigravidae compared to multigravidae. It was observed that, outside the placenta, the blood of infected pregnant women contained a mixture of parasitized cells which could bind to either CD36 (an endothelial surface molecule) or CSA

(glycosaminoglycan chondroitin sulphate A). But in non-pregnant women, parasitized cells were bound only to CD36. Results from adhesion studies suggested that maternal malaria arose when the placenta selected for a parasite sub-population that could bind CSA. These findings explain why primigravidae, who are already immune to other forms of malaria, are particularly susceptible to maternal malaria. No immunity to gestational malaria will develop in a woman until she is directly exposed to the CSA-binding sub-population during pregnancy. Multigravidae are less susceptible due to the development of immunity from previous exposure in pregnancy. These findings seem to provide the first experimental evidence in support of McGregor's hypothesis (McGregor, 1984). Further research is being done to clarify the underlying mechanisms. These findings offer the prospects of potential targets for innovative therapeutic approaches to control gestational malaria.

Placental parasitaemia has been reported at rates of 20-34 percent and sometimes as high as 74 percent (McGregor, 1987). Prevalence tends to be higher in rural compared to urban areas. Placental parasitaemia may occur in the absence of febrile illness or peripheral maternal parasitaemia. High parasites in the placenta occur more frequently in primigravidae (McGregor et al., 1983). High rates of abortion and stillbirths have been reported during malaria epidemics and in non-immune women (McGregor, 1987). Maternal malaria may cause fetal death by interfering with transplacental transfer of nutrients, promoting hyperpyrexia or inducing intrauterine or intrapartum hypoxia secondary to severe anaemia (Menendez, 1995). Research findings from the Gambia have shown a lower incidence of stillbirths in primigravidae on malaria chemoprophylaxis compared to those on placebo (Greenwood et al., 1989; Menendez et al., 1994).

Maternal malaria may be associated with reduced birth weight, being most marked in first-born children (Kortmann, 1972; McGregor et al., 1983). This may result from impaired intrauterine growth, premature delivery or both. Intrauterine growth retardation is also often associated with placental infection and a subsequently diminished

physiological efficiency of the placenta in nutrients and oxygen transfer (McGregor et al., 1983; Menendez, 1995). Maternal hypoglycaemia associated with peripheral parasitaemia, in the absence of placental parasitaemia, may also be associated with reduced birth weight (Menendez, 1995).

In pregnancy, malaria makes a significant contribution to maternal anaemia. Primigravidae have more severe anaemia for a given level of parasitaemia compared to multigravidae (Gilles et al., 1969; Bray et al., 1979; Fleming, 1989a; Fleming, 1989b). The level of anaemia is usually disproportionate to that of parasitaemia (Abdalla et al., 1980; Weatherall et al., 1983; Abdalla, 1986; Clark, 1988). Anaemia in pregnancy, irrespective of underlying cause, has serious implications for maternal and neonatal health (WHO, 1992a; Brabin, 1992; WHO, 1993d). In a review of maternal deaths in Ibadan, Nigeria in the early 1960s, Lawson (1969) observed that anaemia during pregnancy accounted for 14 out of 89 deaths due to obstetric causes. Anaemia in pregnancy was predominantly haemolytic and in severe cases resulted in deaths from congestive cardiac failure. Malaria was presumed to be the major contributor. Several studies have been conducted on anaemia in pregnancy in Sub-Saharan Africa. The countries where such studies have taken place include Nigeria (Isah et al., 1985), Zambia (Fleming, 1989b) and Zaire (Jackson et al., 1991). Results from the Zambian study, cited above, on the aetiology of severe anaemia (below 70 gm/l) in pregnancy showed that 84 percent of the 37 study women had falciparum malaria, it being the sole cause in 22 percent, and complicated by folate deficiency in 49 percent and iron deficiency in 24 percent. In northern Nigeria, anaemia in pregnancy was more prevalent in primigravidae (52 percent) compared to grand-multigravidae (at least 5 previous pregnancies) (40 percent) despite a higher prevalence of iron deficiency in the latter; 35 percent in grand multigravidae compared to 18 percent in primigravidae. Haemolysis due to malaria was the most likely cause. Similar observations have also been made in Zaire.

Very little work has been done on malaria, anaemia and pregnancy outcome in Ghana. In the mid-1960s, a study on anaemia in pregnancy in relation to malaria infection of the placenta was done in Accra (Jilly, 1969). Its main findings were lower haematocrit levels in patients with parasitaemia compared to those without. The degree of anaemia was in close correlation with the extent of phagocytic activity found in the placenta. Premature delivery and false labour showed a much higher frequency in the parasitized group. The mean birth weight of infants born to mothers having parasites or pigments deposits in the placenta was 178 gm lower than that of those to mothers without signs of malaria infection. In an earlier study of anaemia in pregnancy in Accra in 1963, 20 percent of the women had haemoglobin levels between 8.0 and 9.9 g/dl and 2 percent had levels below 7.0 g/dl (Hathorn, 1963). Bruce-Tagoe and co-workers (1977) observed that anaemia (below 10 gm/dl) in rural southern Ghana was fairly common, particularly in children and 15-29 year old women. Malaria infection and low iron content diets were the major factors influencing haemoglobin levels, while hookworm infestation and high parity had little effect.

2.5 Strategies for Malaria Control

The goal of malaria control is to prevent mortality and reduce morbidity and socio-economic losses attributable to the disease (WHO, 1993b; WHO, 1993c). The major strategies for malaria control are:

- Case management
- Prevention and control of malaria
- Prevention and control of epidemics, and
- Integration into Primary Health Care.

This section deals with the broad principles of malaria control. **Section 2.5.2** of this chapter discusses in further detail strategies for malaria control in pregnancy and their limitations. Since the focus of this thesis is insecticide-treated bednets and its impact on

malaria and malaria-related anaemia in pregnancy, the literature review on other aspects of malaria control has intentionally been limited.

2.5.1 Case Management

Early diagnosis and prompt treatment is a basic element of any malaria control programme. Local case definitions need to be developed to facilitate diagnosis without microscopy and prompt treatment in peripheral health institutions using first-line drugs. Recent research findings from Malawi (Redd et al., 1996) have shown that a better clinical definition of malaria was feasible and resulted in a reduction in overtreatement. A revised malaria case definition of rectal temperature of 37.7^{0}C or higher, splenomegaly or nailbed pallor was 85 percent sensitive in identifying parasitaemic children and 41 percent specific. The corresponding sensitivity and specificity for the nationally recommended definition (mother's report of fever in the child) were 93 percent and 21 percent respectively. The revised case definition had 89 percent sensitivity in identifying parasitaemic children with haemoglobin concentration below 80 g/l and 89 percent sensitivity in identifying children with parasite density greater than 10,000 parasites/µl. For case definitions to be relevant and applicable, peripheral health staff require regular training, supervision and technical support. Further research is required in similar and different epidemiological settings to improve case definition of clinical malaria and also to review the consequences of misclassification of children requiring anti-malaria treatment.

With the rapid spread of chloroquine-resistant *P. falciparum* malaria throughout most malaria endemic regions, particularly in Sub-Saharan Africa, policies on first-line drugs need constant reappraisal based on local disease epidemiology. Adequate and regular in-service training, supervision and technical support to health staff in district and sub-district level health institutions are essential prerequisites in the successful implementation of this strategy. Major challenges with case management include

improving home-management of febrile illness in young children and teaching mothers to recognise early signs of impending danger (Mwenesi et al., 1995a) and clinical skills of peripheral health workers. A recent review of patterns of malaria treatment in Africa reinforces this point and calls for detailed studies on drug use and dosage patterns, with information on specific drugs used, especially in relation to home-management and self-treatment (McCombie, 1996).

2.5.2 Prevention and Control of Malaria

This section reviews in detail the strategies for prevention and control of malaria, namely chemoprophylaxis (**section 2.5.2.1**), vector control (**section 2.5.2.2**), prevention and control of epidemics (**section 2.5.2.3**).

2.5.2.1 Chemoprophylaxis

Chemoprophylaxis is no longer routinely recommended for children under 5 years of age in malaria endemic areas. Greenwood and colleagues (1988) in the Gambia have shown that treatment combined with fortnightly chemoprophylaxis with pyrimethamine/dapsone (maloprim®) reduced overall mortality, mortality from probable malaria and fevers associated with malaria parasitaemia in children compared to treatment alone which had no significant effect.

In a recent review on malaria prevention and prophylaxis, Shanks (1995) noted the wide variation in malaria chemoprophylaxis regimens between western countries reflecting historical precedents and lack of solid data on which to make informed decisions. Proguanil and chloroquine are recommended for travellers to West Africa, although increasingly mefloquine is recommended globally especially in areas with chloroquine resistant *P. falciparum* malaria. In South-East Asia, mefloquine resistance is becoming established and doxycycline is currently recommended (CDC, 1993). Recent research in

Kenya (Weiss et al., 1995) has shown that daily primaquine can be used successfully as a causal prophylactic regimen against falciparum malaria. However, this may have limitations in populations with high degrees of glucose-6-phosphate dehydrogenase (G6PD) deficiency, such as found in Sub-Saharan Africa.

The development of new anti-malarial drugs has been very slow and disappointing. Most pharmaceutical companies have little financial incentive to invest in drug development for management of diseases in poor countries. With the rapid spread of drug resistance in malaria parasites, the urgent need to develop new drugs with novel modes of action or modification of existing ones has been stressed (Olliaro & Trigg, 1995; Olliaro et al., 1996). The potential spread of multidrug-resistant parasites to Sub-Saharan Africa should be viewed with great concern. Such an eventuality in Africa will be a disaster of immense proportions. Chloroquine Chemoprophylaxis is recommended for pregnant women, especially primigravidae and secundigravidae, and certain category of patients, for example, those with sickle-cell disease. For non-immunes visiting malaria endemic areas, it is an essential requirement. Chemoprophylaxis should always be combined with personal protective measures like insecticide-treated bednets or insect repellents. **Section 2.6.1** deals in further detail with the literature on malaria chemoprophylaxis in pregnancy. In the light of the current antimalarial drug situation, more attention needs to be paid to strategies employing selective vector control as part of malaria control in Primary Health Care.

2.5.2.2 Vector Control

The measures available for control of transmission include the use of chemical insecticides, biological agents and environmental management. Residual insecticide spraying has been one of the oldest tools for malaria control, although it has never been widely used in Sub-Saharan Africa where the problem is at its worst. The proper use of insecticide is a complex matter involving huge expenditures in terms of insecticides,

trained manpower and sustained application. For vector control to be successful, selection of approach must be based on adequate knowledge of local malaria vectors and the relevant environmental, ecological, social, economic and health service features (WHO, 1993b; WHO, 1993c).

In South-East Asia, the major emphasis in all malaria control programmes continues to be vector control measures, of which the main strategy is residual spraying using DDT. However, the effectiveness of this approach has fallen due to vector resistance, non-cooperation of the population, organisational problems and escalating costs. Consequently, increasing emphasis is being given to prompt diagnosis and treatment of cases (Kondrashin & Rooney, 1992). In a recent review, Meek (1995) observed that choice of control strategy was often determined by epidemiological, economic and political considerations. Entomological information was often used to explain failures and to indicate alternative strategies. The review recommended more operational research as part of control programmes, taking account of local variation in environment and malaria ecology, in order to improve programme performance and efficiency.

Experience with vector control in Sub-Saharan Africa is very limited. Most national malaria control programmes are still in their infancy with priority being given to case management. Experience in the few projects in place and results from previous experiments suggest that vector control is feasible, given adequate resources and local expertise. In Yekepa, Liberia (Hedman et al., 1979), a mining company successfully controlled malaria in a holoendemic region over a period of nearly 20 years (1960-1979) using a combination of residual DDT spraying, regular larviciding with fuel oil and fortnightly chemoprophylaxis of workers using amodiaquine. A malariometric survey showed that spleen and parasite rates were 11 percent and 13 percent respectively in the operational area compared to 95 percent and 67 percent in the surrounding areas with no control activities. No adult vectors were found in the town. The annual per capita cost was

about 4-5 US dollars. Although successful, the replicability and sustainability of such efforts in rural settings is probably unlikely.

The Garki Project was jointly carried out by a WHO/Government of Nigeria research team from 1969 to 1975 on the epidemiology and control of malaria in the African savannah (Molineaux & Gramiccia, 1980; Molineaux, 1988; Goriup & Pull, 1988). The study area was the Garki district in North Nigeria in the Sudan savannah, where transmission of *P. falciparum* was intense and seasonal. The project's main objective was to study the quantitative local epidemiology of malaria before and after residual spraying with propoxur, either alone or with periodic mass drug administration.

Propoxur alone had a limited impact on transmission, and the impact on mortality was evaluated by comparison between unprotected control and intervention villages. Before intervention, there was no significant difference between the two groups of villages in terms of crude death rate (CDR), infant mortality rate (IMR) and death rate in the age-group 1-4 years. During the first year of intervention, all 3 rates decreased in both groups, and more significantly with respect to IMR in the intervention group. In second year, the rates increased in both groups but more significantly in the control villages.

The malaria vectors in the study area were *A. gambiae* s.s., *A. arabiensis* and *A. funestus*. The man-biting rates for *A. gambiae* s.l. and *A. funestus* were 174 and 94 bites/man/night (averages of 8 man-nights) respectively. The vectorial capacity (contact rate between persons through the vectors) reached a seasonal peak of about 40, i.e., 2000 times the critical value required to maintain endemic malaria. The cumulative entomological inoculation rate (EIR) reached a maximum of 145 sporozoite-positive bites in 1 year (out of which 132 were in the wet season). Indoor residual spraying with propoxur had a very limited impact on malaria. The very high baseline level of transmission and the relative exophily of local *A. gambiae* s.l were responsible for failure to interrupt transmission. The combination of indoor residual spraying with mass drug administration (MDA) using

sulfalene-pyrimethamine failed to interrupt transmission for any length of time. MDA probably reduced infant and childhood mortality. Although, propoxur spraying and MDA produced a high level of control, the study did not recommend MDA either alone or in combination residual insecticides in rural areas of the Sudan savannah on grounds of high cost. Data from the Garki Project was used to develop the Garki model of malaria transmission in tropical Africa, which simulates fairly realistically the epidemiology of *P. falciparum*.

From 1972 to 1976, WHO also carried out a research project in western Kenya, near Kisumu, to evaluate the impact of fenitrothion spraying on malaria transmission (Payne et al., 1976). The daily parasitological inoculation rate was reduced from 0.00958 infective bites per individual before treatment to 0.00037 after treatment (a decrease of 96 percent). In two years, general mortality decreased from 23.9 to 13.5 deaths per 1000 population and infant mortality decreased from 157 to 93 per 1000 live births. More recently, a malaria control programme set up as part of a large-scale socio-economic development project, including irrigation, in the rice-growing area of Rusizi Valley of Burundi has achieved modest success (Coosemans & Barutwanayo, 1989). From 1985 to 1987, indoor spraying was done once a year at the end of the rainy season. After the first year of treatment, the parasite index reached 52 percent of the expected value in the village treated with DDT and 41-62 percent in those treated with malathion. After a second treatment with malathion, the parasite index reached 30 percent of the expected value. In children aged 5 years and below, there was over 80 percent reduction in the prevalence of high parasite densities following DDT spraying and between 60-80 percent reduction after malathion spraying in the first year. The prevalence decreased further after spraying with only malathion in the second year.

However, from 1990 to 1993, a progressive resurgence of malaria was observed in most villages (Smits et al., 1995). Two villages in the area selected for detailed study showed that although the inoculation rates were similar in both, the peak of transmission occurred

at the end of April in one and 2 months earlier in the other. As a result, the strategy for vector control was modified to take account of the local variation in disease transmission. The study emphasised the need for control strategies, once outlined, to be reviewed regularly and modified according to current prevailing conditions. In addition, the timing of residual insecticide spraying was crucial in obtaining maximum benefit.

A biological agent, *Bacillus thuringiensis var israelensis* H-14 (Bti) effectively kills mosquito larvae. It is commercially available but its cost is prohibitive. Research workers in Peru have developed a kit that communities can use to produce Bti in coconuts with minimal instruction (IDRC, 1995). In tests, the Bti killed nearly all mosquito larvae in a pond and stopped breeding for 12 to 45 days, with a typical pond requiring two to three coconuts per treatment. The potential of Bti as a tool for malaria control has recently been demonstrated in Peru and Ecuador (Kroeger et al., 1995). In two study areas, Bti was applied weekly to mosquito breeding sites on the Pacific coast of Peru and Ecuador and in the Amazon area of Peru over periods of 10 and 7 weeks and adult mosquito densities monitored. The *Anopheles* adult density (based on human bait catches) was reduced by 70 percent and 50 percent respectively in the 2 areas.

Despite the prospects of using entomopathogens for malaria control, their current limitations include rapid sedimentation from the larval feeding zone, ultra-violet (UV) sensitivity and narrow host range. Porter (1996) has recently reviewed new genetic engineering approaches to overcome these limitations and allow stable expression of broad host range combinations of toxins in UV-resistant, buoyant recombinant bacteria. Although Bti is a promising tool for malaria control in Sub-Saharan Africa, especially in areas where vector habits and breeding sites have been well-documented, further research is required to clarify operational issues likely to enhance successful implementation.

2.5.2.3 Insecticide-impregnated Bednets: A New Tool for Malaria Control

Recent research findings indicate that insecticide impregnated bednets greatly reduce severe illness (Rozendaal, 1989; Curtis, 1992) and mortality (Alonso et al., 1991; Alonso et al., 1993; D'Alessandro et al., 1995) in malaria, especially in children. In Sub-Saharan Africa, most of these trials were conducted in the Gambia (Snow et al., 1987; Snow et al., 1988; Lindsay et al., 1989; Alonso et al., 1991), Burkina Faso (Carnevale et al., 1988; Procacci et al., 1991; Carnevale et al., 1992), Cameroon (Le Goff et al., 1992), Zaire (Karch et al., 1993), Kenya (Sexton et al., 1990; Beach et al., 1993) and Tanzania (Lyimo et al., 1991). Effects of impregnated bednets include lowering prevalence of heavy parasitaemias in children, fewer clinical episodes of fever, reduced spleen size, incidence and prevalence of malaria and reduced mortality.

Mode of Action

The mechanism of action of impregnated bednets has also been studied in some detail, although areas of controversy remain. Impregnated bednets exploit odour of sleeper to attract mosquitoes, kill vectors searching for blood meal, reduce vector entry, biting and resting indoors, increase vector exit rates and mortality, lower the sporozoite rates through reduced parasite survival in the mosquito and exert a mass killing effect if used on a community-wide basis. The results depend on community acceptability, proper use of bednets, type of bednet used, type of insecticide used and level of endemicity of malaria. Socio-cultural and economic factors may also play a critical role in the effectiveness of impregnated bednets (Rozendaal , 1989; Curtis, 1992).

Community Effectiveness and Social Acceptability

Although insecticide-impregnated bednets in different field trials have demonstrated an impact on malaria morbidity and mortality, these field trials have been carried out by researchers often outside the health care delivery system (Lengeler et al., 1996). When researchers in the health sector have carried out bednet programmes, this has often been done "under research conditions" and not programme conditions. This means that extra resources are available for research, and leadership is more capable and committed. Translating the findings of field trials into service delivery or routine programmes will require operational research involving actual service providers and community members.

A recent review noted that high theoretical efficacy of disease control, diagnostic accuracy, good compliance or adequate coverage cannot on their own lead to the final goal of community effectiveness (Tanner et al., 1993). The need to 'listen to the community' has also been emphasised in order to develop and sustain disease control programmes (Vlassoff, 1992). The reviews by Rozendaal and Curtis, cited earlier, both emphasised the crucial role human behaviour has played in the success of bednet research programmes to date. Rural agricultural activity peaks in the rainy season when anopheline mosquito densities also peak. In order to ensure adequate food stocks to tide over the next "hungry season", community members have to wake up early and sleep late as a result of essential economic and farming activities. In the case of rural women, domestic chores and child-care increase the burden. Consequently, in the case of pregnant women, insecticide-impregnated bednets may be less effective as a result of workload and domestic chores leading to sleeping late and waking up early.

The widespread use of bednets in the future, especially for child survival purposes, should be considered as part of integrated malaria control in Primary Health Care that includes other vector control measures, proper case management, appropriate chemoprophylaxis for high risk groups, surveillance and programme monitoring with attention to changing

epidemiological situations, developing technology and improved understanding of the pathophysiology of malaria (Sexton, 1994).

2.5.3 Prevention and Control of Epidemics

Factors associated with epidemics may be categorised broadly into two interlinked groups (WHO, 1993b):

- socio-economic and political factors leading to breakdown of the health care system,
- alteration of the ecological equilibrium due to natural events or changes resulting from human activities.

Areas prone to epidemics can be identified by epidemiological stratification that takes account of vectorial transmission capacity, environmental (including meteorological) conditions, social and economic conditions, population migration patterns and other factors. On the basis of this stratification, a limited set of locally relevant indicators of epidemic potential can be prepared for monitoring by local health and allied personnel and used to build preparedness and to lead to prevention at the community and higher levels. Highland areas in Sub-Saharan Africa, where malaria transmission does not normally occur, are prone to epidemics as result of climate change in relation to global warming (Martens et al., 1995). In a recent malaria epidemic in a highland area of Kenya, epidemic control measures used to contain the situation were case management, selective vector control and health education (Some, 1994).

2.5.4 Integration into Primary Health Care

For the long-term sustainability of malaria control, activities should be integrated into general health services based on Primary Health Care. Malaria control should be part of communicable disease control with regular exchange of skills and staff across programmes, especially at the periphery. A malaria unit at the national level of the health

system is required to provide the necessary technical and epidemiological support for programme implementation. Sufficient attention should be paid to disease surveillance, capacity building for malaria control and operational research to improve programme implementation (WHO, 1993b).

Development of community-based malaria control activities especially in relation to case management, chemoprophylaxis for high risk groups, selective vector control and use of insecticide-treated bednets is needed (Anonymous, 1988). The approaches to successful implementation will need to be field-tested in programme settings, rather than academic research settings, using a learning-by-doing approach that gradually builds up and sustains local capacity and expertise.

2.6 Strategies for Malaria Control in Pregnancy

2.6.1 Chemoprophylaxis

Chemoprophylaxis in pregnancy is recommended by WHO for prevention of malaria in endemic areas. Policies and recommended practices need to be based on sound local epidemiological data (WHO, 1993a; WHO, 1993b). These recommendations have been based on work done in Nigeria and Uganda (Morley et al., 1964; Hamilton et al., 1972). In addition, results from other studies in the Gambia (Greenwood et al., 1989; Greenwood et al., 1992), Nigeria (Fleming et al., 1986), Kenya (Steketee et al., 1987; Spencer et al., 1987), Tanzania (Mutabingwa et al., 1991; Mutabingwa et al., 1993a; Mutabingwa et al., 1993b), Malawi (McDermott et al., 1988), Zaire (Nyirjesy et al., 1993), Papua New Guinea (Brabin et al., 1990a) and Cameroon (Cot et al., 1995) suggest increased benefit with chemoprophylaxis compared with controls. Drugs used in these studies were maloprim in the Gambia, proguanil in Nigeria, chloroquine alone or in combination with proguanil in Tanzania and chloroquine alone in the rest. In areas with moderate chloroquine-resistant *Plasmodium falciparum* (CRPF) in Cameroon (Cot et al.,

1995) and Papua New Guinea (Brabin et al., 1990a;), chloroquine chemoprophylaxis in pregnancy was beneficial compared to controls. In the Papua New Guinea study, pregnant women who missed the routine antenatal clinic where weekly chloroquine prophylaxis was provided doubled their risk of *P. falciparum* infection.

However, a recent review on malaria chemoprophylaxis in pregnancy has suggested less benefit than previously assumed (Garner and Brabin, 1994) and further research into targeted chemoprophylaxis in first and second pregnancies and prompt treatment of febrile episodes were proposed. Recent research findings from Cameroon (Cot et al., 1995) suggested that supervised weekly chloroquine chemoprophylaxis in primigravidae reduced placental malaria infection and increased birth weight in the treatment group compared to the control group. The results of this study have to be interpreted with caution though due to a small sample size in relation to the endpoints and a loss to follow-up of nearly 50 percent. It also illustrated the logistical difficulties of using health facilities for research in rural communities.

Poor compliance is another serious problem with chemoprophylaxis (MacCormack and Lwihula, 1983; Kaseje et al., 1987; Heymann et al., 1990). Local beliefs and cultural practices are a major contributory factor to poor compliance. Chloroquine-associated pruritus is an associated factor. Maldistribution of health facilities in malaria-endemic areas, poor quality of care and regular shortage of anti-malaria drugs all contribute to make chemoprophylaxis a difficult practical proposition even if theoretically a good one.

The problems of drug resistance have limited the choice of drugs available for chemoprophylaxis. Further, health services seldom incorporate local cultural factors and beliefs into delivery of care. Despite numerous constraints, chemoprophylaxis is still recommended for pregnant women living in areas where malaria transmission is very intense and leads to parasitaemias, causing low birth weight and anaemia, or to a high risk of life-threatening malaria attacks. Malaria control in pregnancy should be guided by

national malaria control policy and implemented as a part of antenatal care. Chemoprophylaxis should be complemented by personal protection and, where feasible, by other methods of vector control.

A different approach to chemoprophylaxis, based on supervised intermittent treatment courses of anti-malaria drugs, which attempts to overcome the problem of compliance has been successfully tested in Malawi (Schultz et al., 1994). In this study, 3 groups of primigravidae and secundigravidae were provided chemoprophylaxis as follows: the first group was given chloroquine treatment followed by weekly chloroquine chemoprophylaxis (CQ/CQ), the second, sulphadoxine/pyrimethamine treatment followed by weekly chloroquine chemoprophylaxis (SP/CQ) and the third received a 2-dose sulphadoxine/pyrimethamine regimen (SP/SP) given once during the second trimester and repeated at the beginning of the third trimester. During the peak transmission season from April to July, the prevalence of placental malaria infection was as follows: CQ/CQ - 47 percent, SP/CQ - 37 percent and SP/SP - 10 percent.

In a similar but slightly modified study in western Kenya, primigravidae and secundigravidae were divided into 3 groups based on fever case management (CM), 2-dose sulphadoxine/pyrimethamine regimen (SP/SP) and a monthly sulphadoxine/pyrimethamine (SP-monthly). The prevalence of placenta parasitaemia was; CM - 25 percent, SP/SP - 4 percent and SP-monthly - 0 percent. The proportion of low birth weight in the 3 groups were; CM - 32 percent, SP/SP - 16 percent and SP-monthly - 0 percent (Parise et al., 1995). Operational research is required to define the best approaches to integrating such findings into routine antenatal care in rural Africa. No systematic research on malaria control in pregnancy has been conducted in Ghana to date, apart from this study.

2.6.2 Prompt Diagnosis and Treatment

Evidence from Burkina Faso showed no significant difference in birth weights between chloroquine chemoprophylaxis in pregnancy and prompt treatment of malaria episodes. This study recommended early diagnosis and prompt treatment for febrile episodes in pregnancy and possibly limiting chemoprophylaxis to only the first and second pregnancies (Cot et al., 1992). A possible explanation of the failure to observe differences in the two groups may be due to the reduced efficacy of chloroquine resulting from the spread of chloroquine resistance. Further, most pregnant women often have asymptomatic infections and hence may never get treated. However, evidence from the Gambia using data on children suggests that chemoprophylaxis is superior to prompt diagnosis and treatment (Greenwood et al., 1988). Recent work in western Kenya has shown the ineffectiveness of fever case management as a tool for malaria control in pregnancy (Parise et al., 1995).

Further research is needed to establish the efficacy of prompt diagnosis and treatment compared to regular chemoprophylaxis in different ecological settings. In addition, access to affordable health care in rural Africa remains a problem in many countries. Hence interventions that rely on regular contact with formal health services may be excellent in theory but of limited value in reality. Therefore, patterns of health care utilisation and health seeking behaviour should form part of any serious research effort aimed at improving malaria control in pregnancy using routine health services.

2.6.3 Insecticide-treated Bednets as a Tool for Malaria Control in Pregnancy

After nearly a decade of research on insecticide-treated bednets, very little work has been reported on the impact of insecticide-treated bednets on malaria and malaria-related anaemia in pregnancy. The possible explanations include the logistical difficulties of

conducting community intervention studies designed to answer the question, suppression of publication of results due to "negative findings" of little or no effect in hyperendemic communities or a combination of several factors.

Recent evidence from Thailand has shown that the use of permethrin-impregnated bednets in pregnancy marginally reduced malaria parasitaemia and more significantly malaria-related anaemia in women living in a mesoendemic area on the Thai-Burmese border (Dolan et al., 1993). Pregnant women in 3 adjacent study sites (3 refugee camps - Shoklo, Bomoklo and Maesalit) were allocated at random to receive either a single-size permethrin-impregnated bednet (PIB), or a non-impregnated bednet (NIB) or to a control group who used either their own family-size non-impregnated bednet (FNIB) or no net. The study period was from October 1990 to September 1992. The sample size was 307; PIB - 103, NIB - 100 and control - 104. However 74 women in the control group had nets (FNIB). In Shoklo camp, with the highest malaria transmission among the 3 sites, the risk of at least one malaria attack of malaria was 1.67 (95 percent CI 1.07 - 2.61) times higher in the NIB and no net group than in the (pooled) PIB and FNIB group (with allowance for parity).

Although not specified, analysis of data was based on protection at individual level rather than on intention-to-treat. Pooling PIB and FNIB groups drastically reduces the number of women in the control group. No differences were observed between the 2 groups at the other sites. Insecticide-treated bednets were associated with a reduction in anaemia in all camps and at all parities, independent of the effects of parasitaemic malaria. FNIB were also found to reduce anaemia compared to the NIB and no net group. Birth weights were lowest in the group not using nets and infant mortality was highest, but this difference was not statistically significant. Further, interpretation of the findings should be made with caution due to the small sample size and changes in analysis plan. Although compliance with bednet was high amongst study women, some complained of the small size of bednets (PIB and NIB) resulting in parts of their bodies being exposed during

sleep. Large size untreated nets, when properly used, were as effective as small size impregnated bednets. The study concluded that by reducing or preventing anaemia and its adverse effects on infant health, insecticide-treated bednet use during pregnancy could contribute significantly to improved maternal and neonatal health. The findings of this study have to be interpreted with caution.

The effects of bednet impregnation on pregnancy outcome in primigravidae in the Gambia National Impregnated Bednet Programme (NIBP) has been evaluated recently (D'Alessandro et al., 1996, in press). No bednets were distributed to pregnant women, rather the study investigated the effects of impregnation on bednets already in use. In this government programme, impregnation was done by village health workers. Data was analysed according to the treatment status of the community. Less than 50 percent of primigravidae used an insecticide-treated bednet. During the rainy season, the prevalence of *P. falciparum* was lower, less babies were classified as premature and the mean birth weight was 130 g higher in villages where treated bednets were used than in control villages. Mean haemoglobin levels and prevalence of anaemia (<80 g/l) were similar in the intervention and control villages. However, during the dry season the prevalence of anaemia was significantly lower in villages with treated bednets. These findings suggest that NIBP had some impact probably due to decreased risk of malaria infection.

Results from a recent study in Bo, Sierra Leone showed a modest impact of lambda-cyhalothrin-impregnated bednets on malaria in pregnancy and pregnancy outcome (David et al., 1996, in preparation). Use of net was associated with an increase in packed cell volume (PCV) in all parities; lowest in primigravidae and highest in multigravidae (range: 2.6-4.0 percent) and reduced *P. falciparum* parasite rates in all parities. A significant increase in mean birth weight was observed in multigravidae in net villages compared to controls. The results of this study have to be interpreted with caution. The analysis of the results was done at individual level whilst the study design was based on cluster randomisation using compact villages.

Preliminary findings from Kilifi, Kenya suggest little or no benefit of insecticide-impregnated bednet use in pregnancy, especially in primigravidae (Caroline Schulman, personal communication). The Kilifi study was designed primarily to assess the impact of insecticide-impregnated bednet use on childhood mortality.

2.7 Statistical Methods for Community Intervention Trials

Cluster randomisation, or group randomisation, has been used in the design of intervention studies when clusters rather than individuals constitute the unit of intervention (Hsieh, 1988). In a community intervention study, the unit can be a household, school, clinic, work site, city or any other unit appropriate to the delivery of the intervention. While some intervention studies necessitate cluster randomisation and cost less comparatively, cluster randomisation is usually less efficient and poses more statistical questions than individual randomisation. Reasons for cluster randomisation are diverse, but include administrative convenience, a desire to reduce the effect of contamination and the need to avoid ethical issues which might otherwise arise (Donner and Klar, 1994). For insecticide-treated bednets, community use may be more effective than use by individuals.

2.7.1 Analysis of Randomised Community Intervention Trials using Cluster Randomisation

Smith and Morrow (1991) advised that where communities rather than individuals were used as the unit of randomisation, analyses based on responses of individuals was inappropriate since it ignored the fact that randomisation was over larger units. The appropriate method of analysis is to summarise the response in each randomisation unit by a single value, and analyse these summary values as though they were the individual

values; i.e. the statistical test should be based on the variation between the community summary values, and not on the variation between individuals. Randomisation by cluster accompanied by analysis appropriate to randomisation by individual is an exercise in self-deception and should be discouraged (Cornfield, 1978).

Two recent reviews of cluster randomisation trials (Donner et al., 1990; Simpson et al., 1995) noted the continuing problem of poor design and analysis. In the earlier review of 16 non-therapeutic intervention trials, half of the trials used standard statistical methods with adjustment, taking into account between cluster variation, whilst the remaining half did not. The second review also noted the continuing problem of methodological issues associated with cluster randomisation. Fewer than 60 percent of the 21 trials reviewed took clustering into account in analysis.

Chapter Three

Intervention Trial - Study Design

3.1 The Kassena-Nankana District

3.1.1 The People and Culture

The Kassena-Nankana district comprises mainly the Kassena, who speak Kasem and the Nankana, who speak Nankam. Together they constitute 99 percent of the population. The rest are Builsas who speak Buli. Kasem and Nankam languages belong to the Grussi-Gurma sub-group of the Gur language. Ashanti Twi and Hausa are trade languages and widely spoken in the larger trading towns but not in the hinterland. English is the medium of instruction in schools and the official language.

There are 8 chiefdoms in the area: 4 Kassena - Navrongo, Paga, Chiana and Kayoro and 4 Nankana - Naga, Kologo, Mirigu and Sirigu. Some writers consider Ketiu and Kandiga as chiefdoms, however this is disputed since Ketiu is considered part of the Chiana chiefdom and Kandiga part of the Mirigu chiefdom. Historical origins of these people are embedded in myth and oral tradition. The Kassena migrated from modern-day southern Burkina Faso and the Nankana from among the Frafra in the southern part of the present day Upper East Region. Both groups have many features in common with other people of the Voltaic area. Much acculturation has taken place between the two groups with the Nankana having adopted some cultural usage and nuances of the Kassena while at the same time maintaining some aspects of Frafra culture, notably those relating to funerals and marriages (Senah et al., 1994).

Both groups, like other ethnic groups in the savannah region, live in compounds which are traditionally built and roofed with mud and are circular or rectangular enclosing a

yard. The flat mud roofs serve as places for drying grains and also as sleeping places during the hot season. Few compounds have aluminium roofing. Circular and rectangular rooms are for women and men respectively. The number of rooms and their sizes and the complexity of a compound structure vary according to the status and wealth of the head and the size of the domestic group. In some compounds, adult males are not allowed to leave the compound. Hence when they marry, they build extensions to the compound. In time such compounds grow into village "castles". However, most men on marriage establish their own compounds near the family compound in order to reduce sibling rivalry and accusations of witchcraft which are common occurrences. With time, the main compound acquires a satellite of compounds and grows into a village.

Both communities are highly patriarchal and descent is based on patrilineal reckoning. Society is based on hierarchies of clans and lineages that control access to land and exercise authority in marriages, funerals and religious and social ceremonies. The people are mainly traditionalists who revere their ancestral gods. Sacrifices are made at all ceremonies; births, marriages, funerals and festivals, and also to determine the cause of any disease or mishap. Soothsayers, traditional healers and community elders who usually conduct these ceremonies also play an important role in social organisation, conflict resolution and mediation in the community. Perceptions of disease are linked with culture, social organisation and religion. Polygamy is universally accepted and widely practised. A compound is thus made up of a number of nuclear and extended families who are related to the head of compound either by blood or through marriage. The family structure is hierarchical with the compound head at the apex. He is the most senior male in the compound - the one everyone calls "father", except in a chief's compound. Women are politically and economically marginalised. Their level of participation in decision-making and access to means of property acquisition is highly restricted by cultural usage and nuances.

3.1.2 The Study Area

Kassena-Nankana district is one of six administrative districts of the Upper-East Region of Ghana. It lies between latitudes $10^{o}30'$ and $11^{o}00'$ North and between longitudes $1^{o}00'$ and $1^{o}30'$ West. Its borders are Burkina Faso in the north, Sissala and Builsa districts in the west, Bolgatanga and Bongo districts in the east and Bolgatanga and West Mamprusi districts in the south. Appendix III shows the map of Ghana, with administrative regions. There are 2 main seasons, a wet and dry season. The wet season is short, with an average rainfall of 850-1000 mm, most of which falls between June and September. The mean monthly maximum temperature ranges from $29^{o}C$ to $38^{o}C$ and the minimum $17^{o}C$ to $27^{o}C$ (ICOUR, 1995). The population of the study area for 1994 was estimated at 130,000 (data from Navrongo Demographic Surveillance System-NDSS).

Malaria is hyperendemic in the district. Although not widely used, bednets are familiar to the people in the district. A bednet is called "born goro" in Kasem and "dorsi futo" in Nankam, which literally translates as "a mosquito house". In a recent survey, however, in 4 percent of 6,000 compounds, at least one member of the compound owned a bednet (Ghana VAST Report - third dosing round. 1990). In an exploratory study on acceptability of bednets in the study area, no cultural barriers were identified (Gyapong et al., 1996). Antimalarials are freely available in the open market but traditional herbal treatment is the main source of treatment for febrile illness (Ghana VAST Survival Study Report, 1991, unpublished).

The district has a large irrigation project at Tono, near Navrongo and several dug-out dams which provide water for drinking and farming during the prolonged dry season. The people are mainly subsistence farmers who grow cereals for domestic consumption and raise some poultry, sheep, goats and cattle . Over 90 percent and 80 percent of the female and male population respectively are illiterate.

The district has a hospital at Navrongo, 3 health centres and limited outreach clinics. Since 1994, the Navrongo Health Research Centre (NHRC), in collaboration with the Kassena-Nankana District Health Management Team (DHMT), and with support from the Population Council of the USA, has initiated a Community Health and Family Planning (CHFP) operations research project (Binka et al., 1995a) with the setting up of 4 community-based clinics at Naga, Kologo, Kanania and Kayoro on a pilot basis. An additional 12 community-based clinics are planned when the project scales up in 1996. Appendix IV shows the study district and distribution of treated and no net clusters in the study area.

3.2 Study Design

This study was a supplementary and independent field trial done in the context of the large-scale cluster randomised intervention study which assessed the impact of insecticide-treated bednets on childhood mortality (described in Chapter 1). The study area was divided into 96 contiguous clusters of compounds, half of which were randomly assigned to receive insecticide-treated bednets. All compound members in intervention clusters were to be supplied with a net, and in cases where there was a shortfall of nets, priority was given to women and children. The current study was designed to assess the impact of insecticide-treated bednets on malaria and anaemia in pregnancy and on birth weights by comparing pregnant women (all parities) from 48 "insecticide-treated bednets" and 48 "no-net control" clusters in Kassena-Nankana district, Upper East Region, Ghana from June 1994 to April 1995.

The original intention was to compare primigravidae from treated and control clusters. However this was modified due to the strong ethical objections of the Research Team at NHRC. The reasoning was that it was improper in a rural setting to recruit only primigravidae into a study. Difficulties were likely to arise due to the lack of appreciation of the rationale for the study and hence reduce community cooperation. Further, all

pregnant women in the community needed care without discrimination. The final reason for modification was the timing of the main trial. The end of the trial was fixed for the end of June 1995 and not enough primigravidae would have been recruited to satisfy sample size requirements by that time. As a result all pregnant women were enrolled into the study and were seen at least once.

3.3 Study Population

3.3.1 Recruitment

Women were recruited on a continuous basis by fieldworkers moving from compound to compound in each cluster enquiring about pregnancies. All fieldworkers covered a specified number of clusters and were expected to visit each compound in a given cluster at least once a month. A pregnant woman who had been recruited was not considered a study participant until she had visited the clinic at least once.

3.3.2 Registration and Enrolment

Pregnant women identified by fieldworkers were interviewed using a questionnaire, provided they were local residents. Details obtained included their address, year of birth, obstetric history, last menstrual period, illnesses over the past one month, whether they owned or shared a net, and whether they slept under a net the night before the day of interview. Completed interview forms were checked by Field Supervisors for completeness and consistency. The completed forms were submitted to the Field Office of the study for further checks. If no queries were raised on a form, the pregnant woman was registered and given an identity (ID) card by the Field Office with the following details on it:

* her study number (a unique identifier)
* exact address and location (based on cluster code and compound number),

Table 3.2: **Primigravidae and Secundigravidae enrolled by Trial Arm**

Parity	Treated Net	No Net	Total
1	204 (50.3)	202 (49.7)	406
2	168 (50.9)	162 (49.1)	330
Total	372 (50.5)	364 (49.5)	736

(Row percentage in brackets)

* year of birth (based on local calendar of events),

* name of husband/next of kin

* date of enrolment

Field Supervisors collected ID cards every day from the Field Office and passed them on to Fieldworkers to be given to the pregnant women. When a pregnant woman was given her ID card she was referred to a study clinic with time, day and place specified. Those seen at study clinics for the first time were enrolled into the study. A detailed clinical examination was performed at the first clinic visit. Diagnosis of pregnancy was based solely on history. Gestation was estimated by determination of fundal height on clinical examination. Primigravidae and Secundigravidae were given an appointment for a second clinic visit between 30 to 36 weeks gestation. In between study clinics, pregnant women were encouraged to attend routine antenatal clinics organised in their locality by midwives.

3.4 Sample Size

3.4.1 *Plasmodium falciparum* Parasitaemia

For *P. falciparum* parasitaemia, sample size determination was based on the assumption of a 40 percent reduction in parasite rate in the intervention group compared to the controls. The parasite rate was estimated at 50 percent in the control group. The required sample size was estimated at 320 per group, with a power of 90 percent at the 5 percent significance level, allowing 15 percent for clustering and 10 percent loss to follow up. The sample size estimates were based on a total for both primigravidae and secundigravidae per group. For the treated group the actual sample was 372 compared with 364 for the control group as shown in Table 3.2.

The formula for the sample size determination was based on test of proportions (Smith & Morrow, 1991) and given below:

$$n = \frac{(Z + Z\beta)^2 (p_1q_1 + p_2q_2)}{(p_1 - p_2)^2}$$

where

n = sample size in each group

Z = SND corresponding to the 2-sided significance level (p = 0.05, Z = 1.96) [SND - Standard Normal deviate]

Zß = SND (one-sided) corresponding to 1 - power (power =0.90, Zß = 1.28)

p_1 = estimated proportion of parasitaemia in pregnant women in the control group

p_2 = estimated proportion of parasitaemia in pregnant women in the intervention group

q_1 = $1 - p_1$

q_2 = $1 - p_2$

3.4.2 Anaemia

Sample size estimation for anaemia was also based on a prevalence of 50 percent in the control group, with a projected reduction of 40 percent in the intervention group. The same assumptions in 3.4.1 above applied.

3.4.3 Birth weights

For birth weight, sample size determination was based on the same formula, except that 40 percent was replaced by one-third reduction in proportion of low birth weight in intervention group compared to controls. The proportion of low birth weight in the

controls was estimated at 30 percent. This led to a required sample size of 500 births in each arm, requiring 1000 births.

3.5 Attitudes on Antenatal Care and Use of Bednets

Planned focus group discussions on bednet use in the study area were modified to include guide questions on the use of bednets by pregnant women. In addition, focus group discussions were held in Sirigu and Kandiga (representing Nankam-speaking areas) and Paga and Chiana (representing Kassem-speaking areas) to determine the attitude of study women to study clinics, antenatal care and factors influencing their clinic attendance.

Chapter 4

Intervention Trial - Field Operations

4.1 Fieldwork

4.1.1 Field Office

A Field Office was set up to oversee the implementation of the study headed by the author. He was assisted by a Field Co-ordinator (a UST-trained graduate sociologist recruited locally) and 2 Field Supervisors. A Laboratory Technician was seconded to the study from the main trial. The Navrongo Hospital also seconded 2 full-time midwives to the study. Two data entry clerks were recruited for the study but for administrative purposes were considered part of the Navrongo Health Research Centre (NHRC) Computer Centre. A driver was also provided by NHRC. The Field Office had the sole and primary responsibility for the proper conduct of the study. All completed forms from the field or study clinics were logged in, checked and certified for completeness and accuracy first by the Field Co-ordinator and by the Field Study Director. Checked forms were then logged in at the Computer Centre where one of the Data Entry Clerks signed for them. These were then assigned individual form numbers and batched for data entry independently by the two Data Entry Clerks. At each point in the process, registers/log-in books were kept on the flow of all forms at both the Field Office and the Computer Centre. This ensured that each form could be traced without difficulty. Data collection tools used in the study can be found in Appendix V.

The Field Co-ordinator also prepared activity reports for the weekly Inter-Departmental meetings (IDM) of NHRC. He also represented the study at such meetings since the Field Study Director was out in the field most week days running study clinics. Weekly staff meetings were held between Field Supervisors and the Field Office to check on progress

of work, to discuss any problems cropping up and to resolve them. Issues discussed included performance of fieldworkers and supervisors, in-service training, maintenance of transport and equipment, organisation of the occasional entertainment for field staff and staff welfare issues (including remuneration and promotions). The Field Office organised refresher training for all staff once a month to update and maintain the requisite skills of staff for fieldwork and study clinics.

4.1.2 Organisation of Fieldwork

Organisation of fieldwork followed the conventions at NHRC. Meetings were held with the Head of NHRC and other research scientists to discuss the research protocol and organisation of fieldwork, training, data management, supervision, laboratory work and other pertinent issues. Fieldwork procedures had to be approved by the Technical Committee of the NHRC, including tools for data collection and the intended use of data collected. These meetings provided a good insight into the operations of NHRC. A special seminar was organised by the Technical Committee at which all the points agreed on at the earlier meetings were further discussed and concluded.

4.1.3 Community Entry

The research team visited the chiefs and elders of Navrongo, Paga, Chiana, Ketiu, Kayoro, Sirigu, Mirigu, Kandiga, Kologo and Naga to introduce the research project to them and to solicit their support. At each point, the research team was warmly received. The chiefs were particularly happy that a research team made up of a doctor, 2 midwives and support staff would be running study (mobile antenatal) clinics in their communities. Each chief and his elders was given a calabash of cola-nuts and a bottle of schnapps, in accordance with local customs. The research team also took advantage of these visits to introduce the project to medical assistants and midwives in various health facilities in the district.

4.1.4 Training of Fieldworkers and Midwives

NHRC has laid down procedures for staff recruitment, training and selection of field staff. These procedures were followed in the recruitment and selection of field staff. An advert was put up at vantage points in Navrongo and other large settlements in the districts inviting individuals to apply for positions as fieldworkers. The closing date was one week after the appearance of the advert. Sixty applicants were invited for a written and oral test after which 30 were selected for training. The training was based on a written manual. A period of 10 working days was allowed for training which took place at NHRC. Supervised field practice was done in clusters close to NHRC. Trainees were taken through:

- the rules and regulations of NHRC, including remuneration and disciplinary procedures,
- job description of fieldworkers and field supervisors
- map reading and identification of compounds in clusters
- interviewing techniques
- planned field activities in relation to research on malaria in pregnancy
- practice sessions on use of data tools, including translation and reverse translation into Kassem and Nankam, and explanation of scientific terms
- supervised field practice on compound tracing and interviewing

Finally, 18 trainees were selected as fieldworkers, 6 of whom were selected for further training as Field Supervisors.

All midwives working in health facilities outside Navrongo Hospital and 4 midwives from the hospital were trained in 2 batches for 7 working days each, based on a locally produced manual. Their training covered both classroom and bedside teaching with hands on practice, and took place at NHRC, Maternity Ward and the Ante-natal Clinic at Navrongo Hospital.

They were taken through

- rationale for the research
- organisation of research with emphasis on special study clinics (antenatal)
- antenatal care
- management of malaria in pregnancy
- management of obstetrical referrals
- weighing of newborns
- gestational age assessment (Dubowitz method) (Dubowitz et al., 1970)

See Appendix IX for staff list on field study.

4.1.5 Field Supervision

Six trainees undertook a 7-day intensive training on field supervision focusing on:

- Checking of forms for completeness and consistency
- Re-interviews, sit-in interviews, spot checks
- Maintenance of registers on pregnant women enrolled and new deliveries
- Logging of forms at Field Office
- Updating of motorbike riding skills
- Completion of transport log books
- Report-writing
- Organisation of antenatal clinics
- Maternal anthropometry
- Neonatal anthropometry
- Organisation of zonal meetings

After the course, all passed a written test. Four were assigned to the field, one each for West, North, East and South Zones to work with three fieldworkers each. Each Field Supervisor was assigned a motorcycle. The remaining two were assigned to the Field Office to assist the Field Study Director, Field Co-ordinator and Laboratory Technician.

In addition, they also assisted with organisation of study clinics and fortnightly zonal meetings with field staff.

Field supervision entailed regular daily visits to all fieldworkers to check on their work. Field Supervisors did re-interviews on study women already interviewed to check on the accuracy of data collected and sat in interviews to check on correct interviewing techniques and interaction with study women. In addition, checks were made on visits made by field staff to check on new deliveries. Field Supervisors also carried out weighing of newborns and their subsequent follow-up at Day 28. These activities were monitored at weekly meetings at the Field Office. The Field Co-ordinator also undertook field visits to check on the quality of field supervision. Appendix VIII shows a photo from the June 1996 TDR News on training of field supervisors.

4.2 Organisation of Maternal and Neonatal Health Services

4.2.1 Antenatal Clinics

Seventeen study clinics were organised at vantage points in the district for antenatal care and data collection. These clinics were timed, whenever possible, to coincide with the outreach clinics of the health centres. Midwives, Community and Public Health Nurses from the nearest health facility always joined the Research Team to run them. The organisation of the study clinics followed the same pattern as the routine antenatal clinic. In summary, a pregnant woman went to a registration desk where her records were traced from the ANC register and her attendance recorded. If it was her first visit, she was given a home-based antenatal card and her detailed family and obstetric history taken. At the registration desk, the pregnant women enrolled in the study (not all pregnant women were eligible for enrolment: some came from Burkina Faso and neighbouring districts outside the study area) had their axillary temperature and blood pressure (in the sitting position -

left arm) taken and their weight and height recorded. The relevant sections of clinic visit forms were completed. They were asked about their general health, including any febrile illness in the past 7 days, including day of clinic visit. From the registration desk, they waited for their turn in front of the "examination room".

4.2.2 Clinical Examination

Clinical examination was done in private in a separate room, or where this was not practical in some villages, screens were used to ensure privacy. The waiting area was about 5 metres from the examination room. In the examination room, the forms were checked and completed. Examination covered the eyes, chest, cardiovascular system, extremities and the abdomen. During abdominal examination, gestation was assessed manually and the lie of the foetus determined. Symphysio-fundal height and abdominal girth at the umbilicus were measured using an inelastic tape. All women were treated for any diseases detected or presented. The Research Team provided free treatment for all febrile illnesses and also iron and folic acid supplementation. No chemoprophylaxis was provided pregnant women because it was not the standard practice in routine antenatal clinics in Kassena-Nankana district. Chloroquine for antenatal care was not available despite an official policy of free chloroquine chemoprophylaxis for all pregnant women (see **section 6.3.3**). From the examination room, the pregnant women went to the laboratory area to have their haemoglobin level determined and blood film (thick and thin) made for malaria microscopy.

4.2.3 Laboratory Examination

4.2.3.1 Collection and Storage of Specimens

All women seen at study clinics had their haemoglobin levels determined by finger prick method using a Hemocue® (Be et al., 1991; Linegar et al., 1991; Hudson-Thomas et al..

1994). The Hemocue® system utilises the principle of oxidation of haemoglobin to hemiglobin by sodium nitrite and the subsequent conversion of hemiglobin to hemiglobinazide by sodium azide. The reagents for these reactions are contained within a small disposable microcuvette of approximately 10 microlitres in volume. A venous or capillary sample is introduced into the microcuvette by capillary action and, after reaction with the reagents, the absorbance is read in the Hemocue® photometer at 565 and 880 nm. The haemoglobin concentration is then displayed as a digital reading. The results were recorded on both the clinic visit forms and laboratory forms. At the start of each clinic, each Hemocue® was calibrated with the standard cuvette provided by the manufacturer for the particular machine. The manufacturer recommended that if the reading was outside a range of ± 3 g/l of the standard, the machine should not be used. However, this problem never arose in 10 months of 3-4 clinics per week.

Blood was taken from all study women for the preparation of thin and thick blood films for malaria microscopy. Both thin and thick films were prepared on the same slide. Each slide was labelled with a unique laboratory number. This was also recorded on both the laboratory and clinic visit forms for each study woman. The thin film was fixed with methanol and both films were air-dried. The slides were then packed in slide boxes which were labelled with the venue and date of the study clinic. For each study woman, blood spots were also collected on filter paper and air-dried. These were stored in small self-seal poly bags and labelled with their study and laboratory numbers.

After reading, the slides were packed in slide boxes, which in turn were also packed in a larger box and placed on a shelf in the NHRC laboratory. The filter papers with blood spots were stored in the freezer compartment of a fridge in the NHRC laboratory. The Laboratory Technician ran the laboratory for the study, assisted by the 2 Field Supervisors assigned to the Field Office. Once a month, the Field Study Director printed out a listing of women seen at study clinics with their laboratory and study numbers. Together with the laboratory team, checks were made on all labels of filter papers and blood films.

4.2.3.2 Slides Processing and Microscopy

Blood films collected at study clinics were processed at the NHRC Laboratory within 24 hours. Thin smears were fixed with methanol in the field, after which both thin and thick smears were stained with Giemsa at pH 7.2. Parasites in thick smears were counted against 200 white blood cells (WBC) and the counts recorded for *P. falciparum* asexual forms and gametocytes, *P. malariae* and *P. vivax*. A smear was declared negative if a count against 200 WBCs revealed no parasite. An assumption of mean total WBC count of 8000 per µl of blood for the study population was made.

4.2.3.3 Quality Checks

Approximately 1 in 10 slides were randomly selected for repeat reading by the laboratory technician. The results of these readings were recorded on a quality control form and entered on to a database. Over a 2 week period in January 1995, 100 consecutive study women seen at study clinics had 2 Hemocue® readings done to check its accuracy and consistency. The data were also recorded and entered on to a database.

4.2.4 Emergency Medical and Obstetric Care for Study Women

The Research Team provided emergency obstetrical and medical care for all study women when the need arose. The project covered the cost of medical bills in such situations. Referrals were mainly for severe anaemia (2 cases), pregnancy-induced hypertension (2 cases), obstructed labour (4 cases), rabies (1 case) and malaria in pregnancy (5 cases). The Field Study Director was responsible for the management of the referrals at the Maternity Ward of the Navrongo Hospital. He conducted ward rounds at the Maternity Ward each morning before setting off for the field and reviewed any new cases after return from the

field. This role was complementary to that of the two Medical Officers who run the 140 bed district hospital.

4.2.5 Neonatal Weight Monitoring

At the start of fieldwork, all midwives were trained to weigh newborns within 5-7 days after delivery and record length, chest and head circumference. Midwives complained soon after starting to weigh newborns that they could not cope with the repeated travelling out of station to weigh newborns in their mothers' compounds due to their workload in the health centres' maternity wards. Most study participants were giving birth at home. Consequently Field Supervisors were quickly trained over a 3-day period to take up this role. They could not be trained on the Dubowitz method of gestational age assessment due to its highly technical nature. This could therefore be done only for deliveries at health facilities, which were relatively few. Newborns were weighed with an electronic scale which was calibrated at the start of each day's work. Neonatal anthropometric measurements (length, head circumference and chest circumference) were done with a locally purchased inelastic tape measure. All relevant data was recorded on a delivery form.

In order not to miss too many deliveries within the first 7 days, a list of pregnant women with gestation between 34 and 40 weeks as estimated by history at enrolment or palpation at clinic was generated and distributed amongst fieldworkers and supervisors. These women were visited at least once a week so that their deliveries could be reported to the Field Supervisor soon after the event. This work was done independently and had no relationship with the Navrongo Demographic Surveillance System (NDSS).

4.3 Examination of Non-Pregnant Adult Women

From February to March 1995, 241 non-pregnant adult females living in the compounds of study women were examined to provide a comparison with their pregnant relatives. The Laboratory Technician accompanied each of 4 Field Supervisors one day a week on their supervisory rounds and examined non-pregnant women in compounds where study participants lived. They had their blood taken for malaria microscopy, haemoglobin determination and also blood spots for chloroquine assay. The following measurements were also taken; height, weight and mid-arm circumference. They were also asked about whether they slept under a net.

4.4 Management of Field Data

4.4.1 Field Office Procedures

Data collection forms were designed by the Field Study Director and edited by a Social Scientist at NHRC to conform to the NHRC format of data collection tools. This was done after they had been approved by NHRC's Technical Committee. These forms were pretested during the training of fieldworkers and midwives and relevant modifications made.

The Field Office was responsible for duplication of forms for fieldwork. Memos were sent to the Data Manager indicating the quantities and types of forms required and when. Often, timeliness became a problem and on a few occasions the Field Study Director had to go outside NHRC to get the job done. Duplicated forms were stapled and batched at the Field Office where they were issued to the Field Supervisors and Research Team by the Field Co-ordinator. He kept records of all issues. This was monitored regularly. Field Supervisors issued forms to Fieldworkers on a weekly basis. In general, data collection in

the field and quality checks at the Field Office followed NHRC procedures (see **section 4.1.1**). This ensured proper record keeping, accountability and culpability in the event of any lapses. All these activities were carried out independently by the Research Team and staff of the Field Office.

4.4.2 Data Management at the NHRC Computer Centre

Screen design for data entry was done by one of the Data Managers at NHRC using FOXPRO 2.5 for DOS (version 2.5, 1993, Fox Software Inc., Ohio, USA) with built in logical checks and skips. Each form had a separate screen. Forms received at the Computer Centre were entered independently by the two Data Entry Clerks. At the end of each week, a verification programme was run on both entries and any inconsistencies checked and corrected. When any inconsistencies could not be resolved at the Computer Centre, the form was logged out and returned to the Field Office where it was logged in a Computer Centre Query log-in register. The Field Office resolved the inconsistency or referred the problem to the Field Supervisor to check for the specific problem. Once a form was logged in, field staff were not allowed to handle it again. After the accuracy of the data had been ascertained, the relevant corrections were made and the information passed on to the Computer Centre. When all queries had been resolved after verification, data for the week were backed up on the NHRC back-up facility and also on the Toshiba notebook PC of the Field Study Director. Due to several unforeseen problems, it was not possible to use the Computer Centre to monitor the progress of fieldwork. For example, with menstrual history and findings from clinic visit, it was possible to generate a list of women at a given gestation. This had to be done manually until the Field Study Director developed the skills to carry them out by computer.

4.5 Statistical Methods - Unit of Analysis

Statistical analysis was carried out using STATA (release 4.0, Stata Corporation, Texas, USA). Analysis was done on an intention-to-treat (ITT) basis. The cluster was the unit of intervention and analysis. Univariate analysis was done both at individual and cluster levels to check on the baseline factors in both groups. This was followed by stratified analysis at the individual and cluster levels to obtain a feel for the direction of effect of intervention. Parity was grouped into 3 categories, namely primigravidae, secundigravidae and multigravidae (3 or more pregnancies) during pregnancy or primiparae, secundiparae or multiparae (3 or more births) after delivery. Univariate and stratified analysis provided the basis for which covariates were selected for adjustment. The preliminary analysis also allowed the investigator to stay in closer touch with the data.

Two data sets were used in the analysis: i) first clinic visits only and ii) a combination of first and second clinic visits restricted to one record per woman with at least 26 weeks gestation. Cluster-level and individual level baseline risk factors were adjusted using a two-stage procedure (Gail et al., 1992). First, the residuals were obtained by fitting logistic regression models under the null hypothesis. Combined estimates of these residuals were used in the second stage to make inferences on the effect of treatment. Test-based confidence limits for the odds ratio were calculated using the t-statistic (Rothman, 1986). A detailed discussion of analysis strategies for community randomised trials is given by Donner and Klar (1993; 1994).

Chapter 5

Results

5.1 Sample Size

5.1.1 Sample Size Achieved in Fieldwork and Power Estimates: Parasitaemia and Anaemia

The target sample size for all endpoints in the study was not achieved due to time and logistical constraints. Table 5.1.1a summarises the number of primigravidae and secundigravidae identified through compound-to-compound interviews by fieldworkers. There were 1005 primigravidae and secundigravidae, with a breakdown as follows: primigravidae - treated net group (288), no net group (268) and secundigravidae - treated net group (232) and no net group (217). Slightly more women were recruited and interviewed in the treated bednet group.

Table 5.1.1a: Primigravidae And Secundigravidae Identified by Trial Arm

Parity	Treated Net	No Net	Total
1	288 (51.8)	268 (48.2)	556
2	232 (51.7)	217 (48.3)	449
Total	520 (51.7)	485 (48.3)	1005

(Row percentage in brackets)

Table 5.1.1b shows those subsequently enrolled into the study (i.e. seen at least once at a study clinic) for whom data on parasitaemia and haemoglobin levels (anaemia) is available. The total number of primigravidae and secundigravidae enrolled was compared to the original sample size estimates in relation to the endpoints of the study. With respect to parasitaemia and haemoglobin levels (anaemia), the final sample was 372 for the treated bednet group compared to 364 for the control group. Twenty-seven percent (269)

of primigravidae and secundigravidae interviewed were non-clinic attenders. The final sample size obtained gave an estimated power of 80 percent at the 5 percent significance level to detect a reduction in parasitaemia or anaemia in the no net group from 40 percent to 30 percent in the treated net group (i.e. 33 percent). The original sample size was based on a 40 percent reduction in anaemia or parasitaemia from 50 percent in control arm to 30 percent in intervention arm, with 90 percent power and at 5 percent level of significance. Although, sample size estimation was based on primigravidae and secundigravidae, it was the expressed wish of NHRC that all pregnant women in the study area be seen at least once at a study clinic. This was essential to maintaining continued community rapport and goodwill required for the work of the research station. Hence a total of 1961 pregnant women (all parities) were seen at least once in a study clinic. Haemoglobin values were available on 1956 of them. [5 haemoglobin results were missing]. Parasite count data was available on 1938 of them. [23 slides could not be traced and were declared missing].

Table 5.1.1b: Primigravidae and Secundigravidae enrolled by Trial Arm

Parity	Treated Net	No Net	Total
1	204 (50.3)	202 (49.7)	406
2	168 (50.9)	162 (49.1)	330
Total	372 (50.5)	364 (49.5)	736

(Row percentage in brackets)

5.1.2 Sample Size Achieved in Fieldwork and Power Estimates: Birth weight

The number of singleton births for all parities with recorded weight was 799. For primigravidae and secundigravidae, 160 birth weights were recorded for the treated net group compared to 169 for the no net group. The number of newborns weighed has been summarised below in Table 5.1.2.

Table 5.1.2: Birth weights Recorded by Parity and Trial Arm

Parity	Treated Net	No Net	Total
1	90 (48.4)	96 (51.6)	186
2	70 (49.0)	73 (51.0)	143
3	253 (53.8)	217 (46.2)	470
All	413 (51.7)	386 (48.3)	799

(Row percentage in brackets)

This gave an estimated power of 80 percent (compared to original 90 percent) at the 5 percent significance level to detect a reduction from a proportion of low birth weight in the no net group of 40 percent to 25 percent in the treated net group. Sample size determination based on primigravidae and secundigravidae only. Power estimates were obtained using STATCALC in EPI-INFO (version 6.0, CDC, Atlanta)

5.2 Baseline Characteristics of Study Women

5.2.1 Socio-economic Characteristics

The socio-economic characteristics of the study women enrolled in the trial are summarised in Table 5.2.1. The level of education in these women was very low. In the treated bednet group, 75 percent of them had no education compared to 78 percent in the no net group. However, this was lower than 90 percent found in the findings of the NHRC baseline studies for the main bednet trial. Occupation amongst study women was classified as farmer/housewife, trader or others. There were more traders in the treated net group compared to the no net group. This finding was significant but possibly due to chance. Pregnant women were randomly allocated to study arms based on cluster randomisation in main trial in order to ensure comparability in baseline characteristics.

The other factors analysed included religion, marital status, previous antenatal visits at enrolment, parity and gestation at enrolment. There was no difference in religion and marital status between groups. Traditional African religion was the dominant form, whilst

marriage was almost universal. A little over 50 percent of study women had not attended any antenatal clinic prior to enrolling in the study. One-fifth of the women in both the intervention and control groups were primigravidae. Most women were seen late at the antenatal clinic; 2 percent in the first trimester, 38 percent in the second trimester and 60 percent in the third trimester. There were 96 clusters in total; 48 treated bednet clusters and 48 no net clusters. 1033 women of all parities were enrolled in the treated net clusters giving an average of 22 women per cluster (range: 7-45) compared to 928 women in the no net clusters with an average of 19 women per cluster (range: 6-56). The total for primigravidae and secundigravidae enrolled was 736, giving an average of 8 per cluster.

5.2.2 Anthropometric Characteristics

The anthropometric characteristics of study women by cluster level is shown in Table 5.2.2. The mean age was 27 years for both the treated and the no net groups. The mean height was 160 centimetres in both treatment groups. The mean weight, mid-upper arm circumference and body mass index for both groups were similar.

5.2.3 Bednet Use, Compliance and Sleeping Behaviour

In the main bednet trial, nearly 32,000 bednets were distributed in July 1993. Table 5.2.3a provides information on net compliance and impregnation. Four-fifths of the total nets distributed were re-impregnated in January 1994, July 1994 and January 1995. For the period July to December 1994, a bednet compliance survey of 680 compounds revealed 3272 bednets, making an average of 5 nets per compound. Three-quarters of respondents reported using their bednets regularly and a tenth had washed them at least once prior to being interviewed. From January to June 1995, 946 compounds were surveyed with 4203 bednets being observed. This gave an average of 4 nets per compound. Half of the respondents reported using their nets whilst less than 4 percent had washed them at least

once. The reasons for poor compliance for the period were "warm weather" and "no mosquitoes".

Table 5.2.1 Socio-economic Characteristics of Study Women in Kassena-Nankana District, Ghana

Factor	Treated Bednet Group (N=1033)	No Net Group (N=928)
Education		
None	772 (74.7)	720 (77.6)
Primary	183 (17.7)	133 (14.3)
Secondary	68 (6.6)	65 (7.0)
Tertiary	10 (1.0)	10 (1.1)
Occupation		
Farmer/Housewife	787 (76.2)	767 (82.7)
Trader	235 (22.7)	151 (16.2)
Other	11 (1.1)	10 (1.1)
Religion		
Traditional	710 (68.7)	612 (65.9)
Christian	282 (27.3)	282 (28.9)
Muslim	38 (3.7)	46 (5.0)
Others	3 (0.3)	2 (0.2)
Marital Status		
Married	997 (96.5)	891 (96.0)
Single	20 (1.9)	22 (2.4)
Widowed	14 (1.4)	13 (1.4)
Divorced	2 (0.2)	2 (0.2)
Previous Antenatal Visits at Enrolment		
None	574 (55.6)	485 (52.2)
1	208 (20.1)	196 (21.1)
2	134 (13.0)	142 (15.3)
3	61 (5.9)	56 (6.0)
4	26 (2.5)	26 (2.8)
5 or more	30 (2.9)	23 (2.5)
Parity		
0	204 (19.7)	202 (21.8)
1	168 (16.3)	162 (17.5)
2	178 (17.2)	145 (15.6)
3	186 (18.0)	133 (14.3)
4	125 (12.1)	110 (11.8)
5 or more	172 (16.7)	176 (19.0)
Gestation at Enrolment		
1st Trimester	20 (1.9)	18 (1.9)
2nd Trimester	388 (37.6)	350 (37.7)
3rd Trimester	625 (60.5)	560 (60.4)
Number of Clusters	48	48
Average Number of Pregnant Women per Cluster	22 (7. 45)	19 (6. 56)

(Column percentages in brackets; range in brackets in last row)

Table 5.2.2 : Anthropometric Characteristics of Study Women at First Clinic Visit in Kassena-Nankana District, Ghana
[Cluster Level Analysis]

Variable	Treated Bednet Group			No Net Group		
	N	Mean	95% CI	N	Mean	95% CI
Age (years)	48	27.2	26.6, 27.8	48	27.0	26.4, 27.6
Height (cm)	48	159.9	159.4,160.4	48	159.7	159.2,160.2
Weight (kg)	48	55.3	54.8, 55.8	48	55.1	54.5, 55.6
MUAC[1] (cm)	48	25.4	25.2, 25.6	48	25.5	25.3, 25.6
BMI[2](kg/m^2)	48	21.6	21.4, 21.8	48	21.6	21.3, 21.8

[1] MUAC - Mid Upper Arm Circumference (cm), [2] BMI - Body Mass index

Table 5.2.3a: Net Compliance and Impregnation Results - Main Field Trial

	July-Dec 1994	Jan-June 1995
Compliance		
Use	72.4%	49.7%
Wash	11.5%	3.9%
No. of Nets	3272	4203
No. of Compounds	680	946
Reimpregnation		
No. Reimpregnated	25060 (82.7%)	24418 (78.6%)
Total	30292	31071

Table 5.2.3b shows the information on access to net, those who reported sleeping under a net the night before interview and reasons for non-use of nets in treated clusters. Access to net was defined as having a net (i.e. pregnant woman was given a net during distribution) or sharing a net with another person (i.e. although the person did not have a net, she slept under one). In the treated clusters, three-fifths of 204 primigravidae had access to nets. Four-fifths of secundigravidae and over 80 percent of multigravidae had

access to nets. Overall, nearly four-fifths of pregnant women had access to nets. The difference in access to nets by parity was highly significant.

Seventy percent of pregnant women in the treated net clusters with access to nets responded that they slept under nets the night before interview. Hence the effective net use by parity was; primigravidae - 41 percent (83/204), secundigravidae - 56 percent (94/168) and multigravidae - 67 percent (411/611). This situation reflected the original target group of treated bednets; children under 5 and their mothers or female guardians. Discussions on the possibility of providing pregnant women in the treated net clusters, without nets, with insecticide-impregnated nets were unsuccessful because both WHO/TDR and the trial team at NHRC, Navrongo were unable to accommodate such a change to the implementation of the main trial due to possible charge of "interference" with conduct of study. The main reasons for non-use of nets in the treated net clusters was warm weather and absence of mosquito nuisance biting. The extent of net use by parity was not significantly different. Reasons for non-use of nets by parity were similar. Net usage in no net clusters was insignificant (primigravidae - 5 percent, secundigravidae - 5.3 percent, multigravidae - 8.3 percent)

Tables 5.2.3c i-iii show the sleeping behaviour of pregnant women in the study area; when they usually went to bed, whether they got up at night to urinate, and their wake-up time in the morning.

Table 5.2.3b: Access to Net, Use and Reasons for Non-Use in Pregnant Women in Treated Net Clusters

	Access to Net[1]			Slept Under Net Last Night			Reasons for Non-Use			
Parity	Yes	No	Total	Yes	No	Total	Warm Weather	No Mosquitoes	Other	Total
Primigravidae	120(58.8)	84 (41.2)	204	83 (69.2)	37 (30.8)	120	17 (48.6)	10 (28.6)	8 (22.8)	35
Secundigravidae	132(78.6)	36 (21.4)	168	94 (71.2)	38 (28.8)	132	22 (59.5)	11 (29.7)	4 (10.8)	37
Multigravidae	567(85.8)	94 (14.2)	661	411(72.5)	156(27.5)	567	80 (52.3)	42 (27.4)	31 (20.3)	153
Total	819(79.3)	214(20.7)	1033	588(71.8)	231(28.2)	819	127 (52.9)	66 (28.0)	46 (19.1)	225

[1] Access to Net based on those who OWN or SHARE net in treated net group

Just under half of all pregnant women went to bed between 8.00 pm and 9.00 pm in the treated and the no net groups, whilst nearly one-third went to bed between 9.00 pm and 10.00 pm. However, the differences between the different parities in relation to sleeping behaviour were not significant. Pregnant women, in general, did not go to bed late in the study area.

Most pregnant women in the study area got up at night to urinate outside their rooms. Urinary frequency is common in late pregnancy and women may need to go out to urinate more frequently than usual at that time. Such unavoidable behaviour may reduce the effectiveness of bednet use especially if times of urinating overlap with peaking biting hours of local malaria vectors. The sites used, in order of importance were kraal, bath house or outside the compound. Very few pregnant women used chamber pots. Few pregnant women rose from bed before 5.00 am, with the majority rising between 5.00 am and 6.00 am. This was similar in both groups.

5.2.4 Non-Pregnant Women

Tables 5.2.4a and 5.2.4b show the results on anthropometric and malariometric indices in non-pregnant women in Kassena-Nankana district. The mean age of women examined was 25 and 28 years respectively in the treated and the no net groups. The difference was significant ($p<0.002$), although probably due to chance. The mean height, weight, mid-upper arm circumference (MUAC) and body mass index (BMI) were similar in both groups. A comparison of malariometric indices in non-pregnant and pregnant women is presented in **section 5.4**.

Table 5.2.3c: Sleeping Behaviour in Pregnant Women in Kassena-Nankana District, Ghana

(i) Estimated Time of When Pregnant Women Go to Bed

	Primigravidae		Secundigravidae		Multigravidae	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net
Estimated Bed-Time						
6.00 pm - 7.59 pm	30 (14.7)	29 (14.4)	18 (10.7)	30 (18.5)	82 (12.4)	86 (15.3)
8.00 pm - 8.59 pm	94 (46.1)	91 (45.3)	70 (41.7)	70 (43.2)	299 (45.4)	253 (44.9)
9.00 pm - 9.59 pm	58 (28.4)	65 (32.3)	54 (32.1)	51 (31.5)	212 (32.2)	164 (29.1)
10.00 pm-12 midnight	22 (10.8)	16 (8.0)	26 (15.5)	11 (6.8)	66 (10.0)	61 (10.8)
Total	204	201	168	162	659	564

(Column percentage in brackets) * 3 missing values

(ii) Distribution of Places Where Pregnant Women Urinate at Night When They Wake up from Sleep

	Primigravidae		Secundigravidae		Multigravidae	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net
Outside Compound	42 (20.6)	36 (17.8)	26 (15.5)	24 (14.8)	119(18.0)	88 (15.6)
In Kraal	112 (54.9)	115 (56.9)	112(66.7)	91 (56.2)	411(62.2)	354 (62.8)
At Bath House	46 (22.5)	48 (23.8)	27 (16.1)	43 (26.5)	122(18.5)	111 (19.7)
In Chamber Pot	0 (0.0)	2 (1.0)	1 (0.6)	0 (0.0)	1 (0.2)	2 (0.4)
Do not Wake Up	4 (2.0)	1 (0.5)	2 (1.2)	4 (2.5)	8 (1.2)	9 (1.6)
Total	204	202	168	162	661	564

(iii) When Pregnant Women Wake up from Bed Finally

Study Arm	Primigravidae		Secundigravidae		Multigravidae	
	Treated	No Net	Treated	No Net	Treated	No Net
Before 1st Cockcrow (4-5am)	4 (2.0)	8 (4.0)	4 (2.4)	6 (3.7)	52 (7.9)	38 (6.7)
Dawn (5-6am)	133(65.2)	132(65.3)	111(66.1)	107(66.0)	444(67.2)	386(68.4)
After Sunrise (6-7am)	67(32.8)	62(30.7)	53(31.5)	49(30.3)	165(25.0)	140(24.8)
Total	204	202	168	162	661	564

Table 5.2.4a: Anthropometric Characteristics of Non-Pregnant Women in Kassena-Nankana District, Ghana
[Individual data]

Variable	Treated Bednet Group			No Net Group		
	N	Mean	95% CI	N	Mean	95% CI
Age (years)	106	24.6	23.2, 26.1	133	28.0	26.5, 29.6
Height (cm)	107	159.3	158.0,160.6	134	159.1	158.1,160.2
Weight (kg)	107	50.6	49.1, 52.1	134	51.9	50.5, 53.3
MUAC[1](cm)	107	25.3	24.9, 25.7	134	25.4	25.0, 25.8
BMI[2](kg/m^2)	107	19.9	19.4, 20.4	134	20.5	20.0, 20.9

Based on individual observations: [1] MUAC - Mid Upper Arm Circumference [2] BMI - Body Mass index

Table 5.2.4b: Malariometric Indices and Mean Haemoglobin in Non-Pregnant Women in Kassena-Nankana District, Ghana

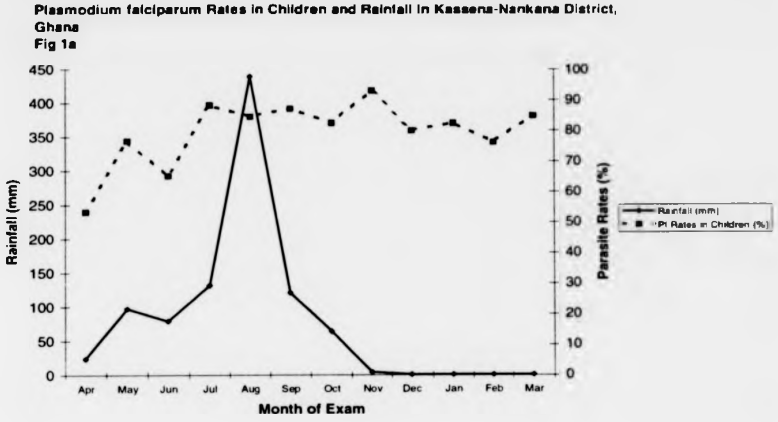
Study Arm	Treated Net Group (N =107)	No Net Group (N= 134)
Malaria Parasitaemia		
Proportion of tests positive	26/107	40/134
Percent positive tests (percent)	24.3	29.9
Mean Parasite Density		
Parasites/µl	61	67
95% CI	51 - 73	57 - 80
Mean Haemoglobin (g/l)	113.4	115.8
95% CI	109.4 - 117.4	113.1 - 118.6
% Below 100 g/l	21.5	14.9
% Below 70 g/l	4.7	1.5

The *P. falciparum* parasite rate was 24 percent in the treated net group compared to 30 percent in the no net group. The geometric mean parasite density was 61 parasites/µl in the treated net group compared to 67 parasites/µl in the no net group. The mean haemoglobin was 113.4 g/l in the treated net group compared to 115.8 g/l in the no net group. A fifth of women in the treated net group were anaemic (below 100 g/l as defined by MOH-Ghana) with less than 5 percent having severe anaemia (less than 70 g/l) compared to one-seventh with anaemia and less than 2 percent with severe anaemia in the no net group.

5.3 Malaria in Children in Kassena-Nankana District

Data on malaria in children in the study area, based on the 1992 pre-trial data, are presented to illustrate the relationship between malaria and climatic factors (Binka et al., 1994). Figure 1 shows the *P. falciparum* rates in children and climate data (monthly total rainfall (mm), minimum and maximum monthly mean temperatures (^{0} C)) in the study area.

Figure 1 - *Plasmodium falciparum* Rates in Children and Climate Data in Kassena-Nankana District, Ghana (Binka et al., 1994. Based on 1992 pre-trial data)



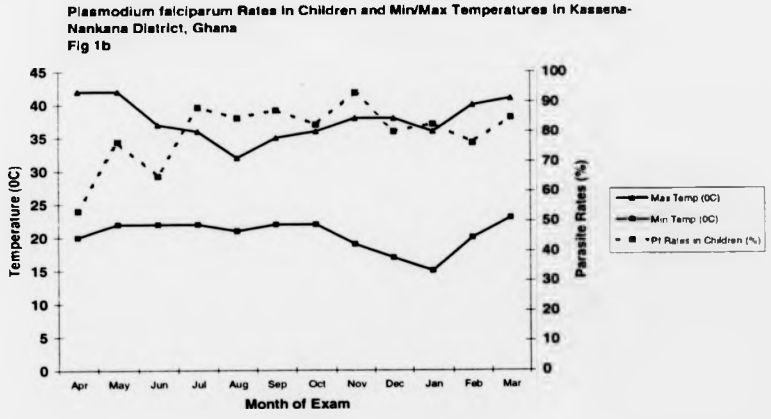


Figure 1a shows *Plasmodium falciparum* rates in children and monthly total rainfall (mm) and figure 1b shows *Plasmodium falciparum* rates in children and monthly mean minimum/maximum temperatures in the study area. The rainy season was from April to November, with December to March being the dry season with no rainfall. Parasite rates in children started to rise with the onset of the rains and reached over 80 percent in July and remained at that level till March. The maximum temperatures dipped during the months of heavy rainfall - July , August and September, with temperature hovering around 40^0 C. Minimum temperatures were around 20^0C, the coldest months being November to February.

5.4 Bednets and *Plasmodium falciparum* Parasitaemia in Pregnancy

Sections 5.4, 5.5, 5.6 and **5.7** present results on the impact of insecticide-treated bednet use on *P. falciparum* parasitaemia and parasite rates, haemoglobin levels, parasitaemia and haemoglobin by gestation (third trimester) and birth weights respectively.

Table 5.4a shows malariometric indices in pregnancy by parity and study group at the individual level. For primigravidae, just over 70 percent had parasitaemia in the treated net compared to three-quarters in the no net group. For secundigravidae, 58.7 percent had parasitaemia in the treated net compared to a little over half in the no net group. Parasite rates for multigravidae were 46.3 percent and 42.3 percent in the treated and the no net groups respectively. Despite a general decline in parasite rates with increasing parity, differences between the treated and the no net groups for a given parity were not significant.

The geometric mean parasite density (GMPD) for primigravidae was higher in the treated than the no net group. For secundigravidae, GMPD was lower in the intervention compared to the control group and for multigravidae it was similar in both groups (Table

5.4a). The results were not statistically significant. Probable malaria illness was defined as axillary temperature above 37.5^{0}C and 2000 or more parasites/µl. For primigravidae, prevalence was 0.5 percent in both groups. No probable malaria illness was observed in higher parities. Reducing the parasitaemia cut-off, increased the prevalence marginally. The results provided no evidence of protective effect of treated bednet use against *P. falciparum* malaria infection.

Table 5.4a: Malariometric Indices in Pregnancy in Kassena-Nankana District, Ghana

	Primigravidae		Secundigravidae		Multigravidae	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net
Malaria parasitaemia						
No. positive/No. tested	143/201	150/201	98/167	86/161	302/653	235/555
Percent positive tests (%)	71.1	74.6	58.7	53.4	46.3	42.3
Mean parasite density[1] (parasites/µl)	1159	1075	297	397	189	165
95% CI	719-561	819-412	219-403	273-578	162-219	140-196
Probable malaria illness						
No. positive/No. tested[2]	1/201	1/201	0/167	0/161	0/653	0/555
Percent positive diagnosis (%)	0.5	0.5	0	0	0	0
No. positive/No. tested[3]	5/201	3/201	0/167	1/161	7/653	9/555
Percent positive diagnosis (%)	2.5	1.5	0	0.6	1.1	1.6

[1] Geometric mean parasite density in positive slides [2] Temperature ≥ 37.5^{0}C and ≥ 2000 parasites/µl
[3] Temperature ≥ 37.5^{0}C and ≥1 parasite/µl

Cluster level analysis for *P. falciparum* parasite rates and parasitaemia, by period of clinic visit (season) and parity, is shown in Table 5.4b. The results are shown for both data sets (first clinic visits and combined data for first and second clinic visits). GMPD in primigravidae varied from 912 parasites/µl to 1566 parasites/µl. They were marginally lower in the no net group. Parasite rates varied from 54.2 percent to 78.9 percent and were marginally lower in the treated net group. In addition, parasite rates were higher in the wet season compared to the dry season. However, the differences between the treated

primigravidae. The treated net group had lower GMPD and parasite rates compared to the no net group. However, in the dry season among first clinic visits, parasite rates were higher in the treated net group. For multigravidae, GMPD was higher in the treated net compared to the no net group. Parasite rates were higher in the treated net compared to the no net group in the wet season. In the dry season, it was lower in the treated net compared to the no net group. For the combined data set, the parasite rates were similar in the treated net and the no net groups in the wet and dry seasons, although the wet season rate was more than double that in the dry season.

Cluster means of log of parasite density were analysed by ANOVA to test for the effect of parity and period of clinic visit (season). Based on F-test, F for parity was 77.23 (df: 2, 353; $p < 0.0001$), season 1.17 (df: 1, 354; p: 0.28) and bednet 0.77 (df: 1, 354; p: 0.38). ANOVA results suggest significantly higher parasite density in low parity women but little or no effect of season and bednet use on parasite density. Testing of effect of insecticide-treated bednets on parasitaemia was done in two stages. First, the residuals were obtained by fitting logistic regression models under the null hypothesis. Combined estimates of these residuals were used in the second stage to make inferences on the effect of treatment.

The odds ratio (OR) for developing *P. falciparum* parasitaemia in the treated net group compared with the no net group for first clinic visit was: parasitaemia (>0/µl): 1.13 (95% CI: 0.54, 2.38; p=0.21); parasitaemia (>1999/µl): 0.98 (95% CI: 0.85, 1.12; p=0.89). The OR for developing *P. falciparum* parasitaemia for the combined data was: parasitaemia (>0/µl): 0.89 (95% CI: 0.73, 1.08; p=0.56); parasitaemia (>1999/µl): 1.11 (95% CI: 0.93, 1.33; p=0.55). The risk estimates provided no evidence of protective effect of insecticide-treated net use on *P. falciparum* malaria infection.

Table 5.4b: Cluster Analysis - *P. falciparum* Parasite Rates and Density by Parity and Month of Clinic Visits in Kassena-Nankana District, Ghana

		1st Clinic				1st & 2nd Clinics[1]			
	Month of Clinic Visit	Jul-Nov		Dec - Mar		Jul-Nov		Dec - Apr	
	Study Arm	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net
PARITY [Treated Net Clusters = 48 No Net Clusters = 48]	Parasite Level								
Primigravidae	GMPD[2]	1053	1029	1108	1566	1220	1018	1657	912
	95% CI	729-1521	691-1531	584-2100	846-2899	722-2063	659-1572	888-3090	512-1627
	Parasite Rate (%)	74.3	76.2	67.8	72.2	74.3	78.9	54.2	63.8
Secundigravidae	GMPD	306	419	270	687	360	441	198	347
	95% CI	205-458	243-723	134-544	359-1313	222-584	241-809	99-395	206-584
	Parasite Rate (%)	59.7	61.4	54.3	43.4	58.8	63.0	44.6	47.0
Multigravidae	GMPD	192	165	217	150	231	166	184	185
	95% CI	160-230	134-203	121-390	96-233	172-311	125-219	108-312	116-294
	Parasite Rate (%)	52.8	47.5	18.6	29.1	51.7	54.3	24.6	23.4

[1] Analysis restricted to one record per woman after 26 weeks gestation, including all second clinic visits

[2] Geometric Mean Parasite Density (GMPD) based on positive slides

The data on estimated time of conception was analysed at the individual and cluster levels with respect to endpoints on *P. falciparum* parasitaemia recorded at first clinic visit. The results are shown in Tables 5.4c and 5.4d. At the individual level, the GMPD was similar when conception took place in both wet and dry seasons in the treated and no net groups, except for secundigravidae; when conception took place in the wet season, the GMPD for the treated net group was less than half that in the no net group. The 95 percent confidence intervals for each parity overlapped in both groups for the 2 periods of conception. The parasite rates were similar in the treated and no net groups by parity and period of conception (season), except for secundigravidae; when conception took place in the dry season, the parasite rate in the treated net group was higher compared to the no net group. These differences were not significant. From the cluster analysis, the results were similar between the treated and no net groups by parity and season of conception. However, parasite rates in secundigravidae and multigravidae were marginally higher when conception took place in the dry season.

Table 5.4c: *P. falciparum* Parasite Rates and Parasite Density by Parity and Estimated Month of Conception in Kassena-Nankana District, Ghana - Individual Analysis

	Est. Month of Conception	May - Nov		Dec - Apr	
PARITY	Study Arm Parasite Levels	Treated Net	No Net	Treated Net	No Net
Primigravidae	GMPD	1181	1011	1135	1122
	95% CI	782 -1783	676 - 1511	735 - 1753	768 - 1639
	Parasite Rate (%)	70.6	75.0	71.6	74.3
Secundigravidae	GMPD	296	603	295	273
	95% CI	193 - 454	365 - 998	191 - 455	158 - 471
	Parasite Rate (%)	52.0	53.3	64.4	53.5
Multigravidae	GMPD	188	157	186	168
	95% CI	147 - 240	116 - 212	153 - 226	136 - 206
	Parasite Rate (%)	43.8	40.0	48.1	43.8

Table 5.4d: Cluster Analysis - *P. falciparum* Parasite Rates and Parasite Density by Parity and Estimated Month of Conception in Kassena-Nankana District, Ghana

	Est. Month of Conception	May - Nov		Dec - Apr	
PARITY	Study Arm Parasite Levels	Treated Net	No Net	Treated Net	No Net
Primigravidae	GMPD	1106	1144	1103	1092
	95% CI	740 - 1653	776 - 1687	736 - 1656	726 - 1644
	Parasite Rate (%)	74.3	76.1	67.7	76.2
Secundigravidae	GMPD	289	654	276	320
	95% CI	204 - 410	441 - 969	187 - 408	190 - 538
	Parasite Rate (%)	48.6	50.5	66.7	57.2
Multigravidae	GMPD	176	162	203	159
	95% CI	135 - 228	120 - 219	150 - 276	126 - 201
	Parasite Rate (%)	46.6	39.5	47.0	44.1

Further to the results presented in **section 5.2.4**, parasite rates between pregnant and non-pregnant women were compared at the individual level. The results are shown in Table 5.4e. Parasite rates in pregnant women (when all parities were considered as a single group) were double that of non-pregnant women in both the treated and the no net groups, with age contributing little, if any, to the differences. However, parasite rates in primigravidae were nearly two and a half times the levels in non-pregnant women before adjusting for age. The parasite rates reduced to twice the level in non-pregnant women after adjusting for age. This finding suggests an age effect with primigravidae.

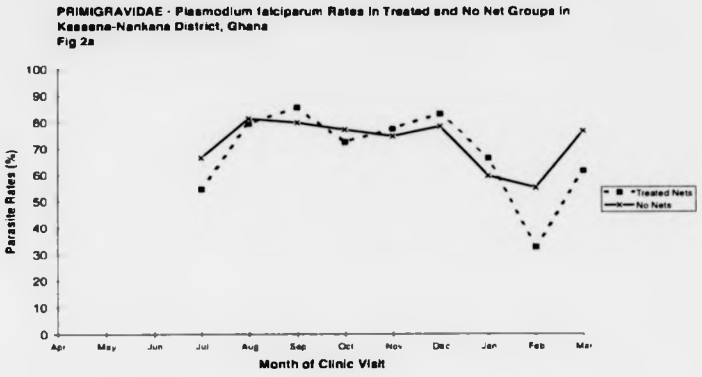
Table 5.4e: ***Plasmodium falciparum*** **Parasite Rates in Pregnant and Non-Pregnant Women in Kassena-Nankana District, Ghana**

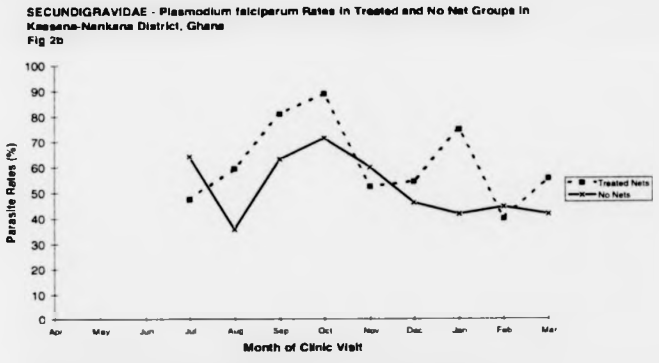
Study Arm	Treated Net (%)	No Net (%)
Pregnant Women (all)	53.2	51.4
Non-Pregnant Women	24.5	29.3
Pregnant Women (all)[1]	53.5	51.2
Non-Pregnant Women	23.9	27.7
Primigravidae	71.1	74.6
Non-Pregnant Women	24.5	29.3
Primigravidae[2]	64.3	63.0
Non-Pregnant Women	27.0	32.9

[1,2] Adjusted for age

Figure 2 shows the *P. falciparum* rates in the treated and no net groups by parity and month of clinic visit in the study area for first clinic visits. Figures 2a, 2b and 2c show the results for primigravidae, secundigravidae and multigravidae respectively. The parasite rates in pregnant women were highest in primigravidae, declining with increasing parity. The increase in parasite rates was associated with the onset of the rainy season, reaching a peak in August for primigravidae and levelling off till December before a decline was observed. Overall parasite rates were high in pregnancy. However, the drop in parasite rates from December to March was more pronounced in primigravidae in the treated net group.

Figure 2 - Plasmodium falciparum Rates in Treated and No Net Groups by Parity and Month of Clinic Visit in Kassena-Nankana District, Ghana





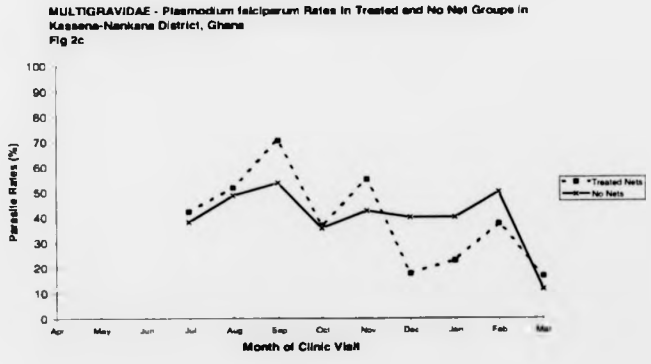


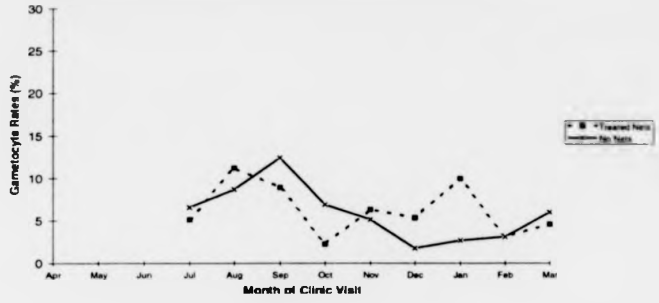
Figure 3 shows *P. falciparum* gametocyte and *P. malariae* rates in the treated and no net groups by parity and month of clinic visit in the study area. Figures 3a, 3b, 3c show the gametocyte rates for all parities, and *P. malariae* rates for primigravidae and secundigravidae respectively. In the treated and no net groups, the rates rose with the onset of the rains and peaked in September during the period of maximal rainfall, declining with the advance of the dry season. *P. malariae* rates were lower overall and for both primigravidae and secundigravidae individually in the treated compared to the no net group.

5.5 Bednets and Haemoglobin Levels in Pregnancy

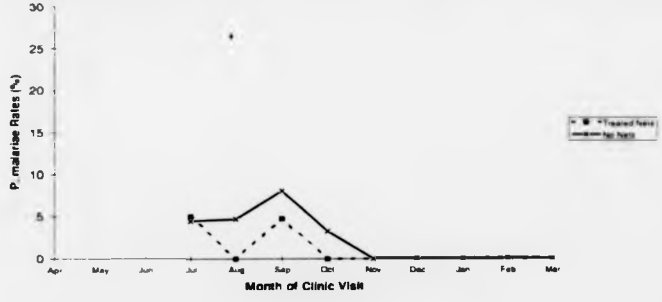
This section presents results on the impact of insecticide-treated bednets on haemoglobin levels (anaemia and severe anaemia) in pregnancy for both data sets at individual and cluster levels. The results are presented as mean haemoglobin, percentage with anaemia (<100 g/l) and percentage with severe anaemia (<70 g/l). Table 5.5a shows the results on haemoglobin levels and levels of anaemia (at first visit) in pregnancy according to parity and month of visit at individual level. Haemoglobin levels of pregnant women in the treated net and the no net clusters were similar at first clinic visit. The mean haemoglobin for primigravidae was 85.9 g/l for the treated group compared to 86.4 g/l for the no net group for the period July to November 1994 and 88.8 g/l for the treated net group compared to 88.3 g/l for the no net group for the period December 1994 to March 1995. The results on secundigravidae and multigravidae were comparable in both the treated net and the no net groups for both seasons. Mean haemoglobin levels increased slightly with parity and were marginally higher in the dry season (December to March). However, these were not significant. Mean haemoglobin at all parities in the two groups and in both seasons were below the MOH-Ghana cut-off for anaemia (<100 g/l).

Figure 3 - *Plasmodium falciparum* Gametocyte and *Plasmodium malariae* Rates in Treated and No Net Groups by Parity and Month of Clinic Visit in Kassena-Nankana District, Ghana

ALL PARITIES - Plasmodium falciparum Gametocyte Rates in Treated and No Net Groups in Kassena-Nankana District, Ghana
Fig 3a



PRIMIGRAVIDAE - Plasmodium malariae Rates in Treated and No Net Groups in Kassena-Nankana District, Ghana
Fig 3b



SECUNDIGRAVIDAE - Plasmodium malariae Rates in Treated and No Net Groups in Kassena-Nankana District, Ghana
Fig 3c

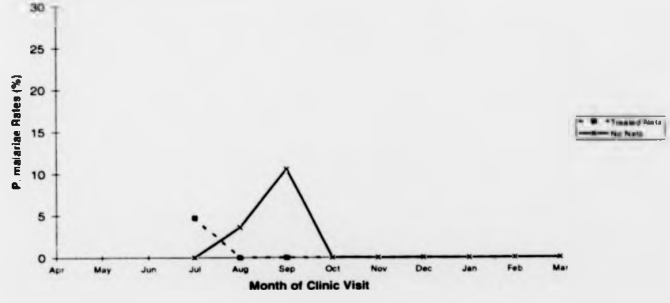


Table 5.5a: Haemoglobin Levels and Levels of Anaemia among Pregnant Women By Parity and Month of 1st Visit to Study Clinic in Kassena-Nankana District, Ghana

	Primigravidae				Secundigravidae				Multigravidae			
Month of 1st Clinic Visit	Jul-Nov		Dec-Mar		Jul-Nov		Dec-Mar		Jul-Nov		Dec-Mar	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net
Mean Haemoglobin (g/l)	85.9	86.4	88.8	88.3	89.5	92.0	96.4	95.9	92.0	91.6	98.3	96.5
Range	46,137	31,123	49,123	65,118	50,124	59,123	55,121	63,114	40,134	40,142	42,140	26,129
95% CIs	83- 88	84- 89	83- 94	84-92	87-92	90- 96	92-101	92-100	91- 93	90- 93	95-102	93-100
Haemoglobin below 100 g/l												
Proportion below	136/162	132/160	30/42	36/41	106/134	77/116	21/34	26/46	384/562	337/473	49/97	47/89
Percentage below (%)	84.0	82.5	71.4	87.8	79.1	66.4	61.8	56.5	68.3	71.2	50.5	52.8
Haemoglobin below 70 g/l												
Proportion below	22/162	21/160	5/42	2/41	9/134	5/116	1/34	2/46	41/562	36/473	3/97	8/89
Percentage below (%)	13.6	13.1	11.9	4.9	6.7	4.3	2.9	4.4	7.3	7.6	3.1	9.0

Amongst primigravidae , four-fifths of those in the treated net and the no net clusters were anaemic in the wet season. In the dry season, a little over 70 percent in the intervention group and nearly 90 percent in the control group were anaemic. The proportion with anaemia in the treated net group decreased from the wet to dry season but increased over the same period in the no net group. This may suggest a possible beneficial effect of bednets to primigravidae in the dry season. For primigravidae with severe anaemia, the proportions in the two groups were similar in the wet season. In the treated net group, they remained at the same level from the wet to dry season (13.6 percent vs. 11.9 percent) but decreased in the no net group (13.1 percent vs. 4.9 percent). This suggests that insecticide-treated bednet use had no impact on severe anaemia amongst primigravidae.

For secundigravidae and multigravidae, the proportion with anaemia was consistently higher in the wet compared to the dry season, with little difference between the treated net and the no net groups. For severe anaemia, the proportion in the treated net group decreased from the wet to dry season but remained at the same level in the no net group suggesting a possible beneficial effect of insecticide-treated bednet use. This evidence, although weak, suggests that primigravidae may be protected from anaemia, but not severe anaemia, whilst secundigravidae and multigravidae may be protected from severe anaemia but not anaemia through the use of insecticide-treated bednets. Given the inconsistency of the results, this may also be due to chance. Following on from the individual analysis, cluster level analysis was done by parity, month of clinic visit and study group, on haemoglobin levels for the two data sets. The results are shown in Table 5.5b. For primigravidae, mean haemoglobin varied from 85.0 g/l to 88.4 g/l for first visit and 84.0 g/l to 90.5 g/l for the combined data. Seasonal variation was minimal with little difference between the treated and the no net groups. There was a lower proportion with anaemia in the treated net group when comparing the dry with wet season. However the proportions in the no net group remained the same in both seasons. The proportion with severe anaemia was similar in both groups in the wet season for the two data sets.

Table 5.5b: Cluster Analysis - Haemoglobin by Parity and Month of Clinic Visits in Kassena-Nankana District, Ghana

		1st Clinic				1st & 2nd Clinic[1]			
	Month of Clinic Visit	Jul-Nov		Dec - Mar		Jul-Nov		Dec - Apr	
[Treat Net Clusters=48 No Net Clusters = 48]	Study Arm	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net
PARITY	Haemoglobin Levels								
Primigravidae	Mean HB	85.0	85.3	86.4	88.4	84.0	85.4	90.5	88.7
	Range	68,102	56,102	49,112	70,108	46,108	59,108	72,112	70,105
	95% CI	82 - 88	82 - 89	80 - 93	85 - 92	80 - 88	82 - 89	87 - 95	86 - 92
	% Below 100 g/l	86.4	84.6	77.0	88.9	88.0	85.0	72.7	85.7
	% Below 70 g /l	13.0	17.0	14.9	3.4	16.2	18.9	3.4	4.4
Secundigravidae	Mean HB	91.1	91.4	96.1	96.5	88.7	90.4	92.7	95.9
	Range	70,120	74,115	55,116	70,114	62,108	74,115	64,115	75,125
	95% CI	88 - 94	89 - 94	91 - 102	92 - 101	86 - 92	87 - 94	88 - 97	92 - 100
	% Below 100 g/l	78.1	72.0	59.4	55.1	84.4	73.9	69.1	67.5
	% Below 70 g/l	4.9	3.0	4.3	3.0	6.8	2.0	11.8	3.4
Multigravidae	Mean HB	92.4	92.2	97.9	95.7	91.3	91.6	97.7	93.9
	Range	80,107	82,107	42,126	72, 127	70, 106	78,116	64,124	66,127
	95% CI	91 - 94	91 - 94	93 - 102	92 - 100	89 - 94	89 - 94	95 - 101	90 - 98
	% Below 100 g/l	67.1	69.0	53.1	59.6	71.0	74.4	59.7	63.4
	% Below 70 g/l	7.1	7.7	4.2	7.8	9.2	7.6	4.6	6.5

[1] Analysis restricted to one record per woman after 26 weeks gestation, including all second clinic visits

Severe anaemia was much higher in the treated net group in the dry season for first visit but this difference disappeared with the combined data. For secundigravidae, mean haemoglobin varied from 88.7 g/l to 96.5 g/l and was similar in both treatment groups for first visits, with higher dry season values. In the combined data, mean haemoglobin was higher in the no net group. The proportion of secundigravidae with anaemia was higher in the no net group in both data sets with higher proportions in the wet season suggesting modest benefit with bednet use in secundigravidae.

For multigravidae, mean haemoglobin was higher in the treated net group compared to controls. The proportion with anaemia and severe anaemia was similar in both groups in the wet season but higher in the no net group in the dry season suggesting some protective effect of bednet use in the dry season.

Cluster mean haemoglobin for both data sets were analysed by ANOVA to test the effect of parity and season in relation to intervention group. For first visits, F for parity was 25.73 (df: 2, 448; p <0.0001), season 16.58 (df: 1, 449; p: 0001) and bednet 0.00 (df: 1, 499; p: 0.97). For combined data, F for parity was 15.54 (df: 2, 479; p <0.0001), season 22.97 (df: 1, 480; p < 0001) and bednet 0.01 (df: 1, 480; p: 0.93). Parity and seasonality had strong effects on mean haemoglobin as described above whilst bednets had none.

The odds ratio (OR) for developing anaemia or severe anaemia in the treated net clusters compared to the no net clusters for first clinic visit or combined data was as follows: first clinic visits; anaemia (Hb < 100 g/l) - 0.97 (95% CI: 0.86, 1.10; p=0.81), severe anaemia (Hb < 70 g/l) - 0.91 (95% CI: 0.57, 1.43; p=0.58) and for combined data; anaemia - 0.88 (95% CI: 0.70, 1.09; p=0.47), severe anaemia - 0.80 (95% CI: 0.55, 1.16; p=0.62). The testing of residuals was also not significant; Student's t = -0.74 with 94 df, ($p > 0.46$).

Table 5.5c shows the results on haemoglobin levels and levels of anaemia by parity, week of gestation and study group at the individual level. For primigravidae, mean haemoglobin

were similar in the treated and no net groups for the gestational periods; 14-26 weeks and 27-40 weeks. Four-fifths of primigravidae were anaemic in the treated net group and nearly 90 percent in the no net group for the 14-26 weeks gestational period. For 27-40 weeks gestational period, four-fifths in both groups were anaemic. For secundigravidae and multigravidae, the proportion with anaemia increased with increasing gestation in both the treated and no net clusters, being higher in the treated net group. The proportion with severe anaemia increased with increasing gestation for both secundigravidae and multigravidae in the treated net clusters but decreased or stayed the same level in the no net clusters.

Further data analysis was done to review the relationship between the period of conception and haemoglobin levels at first clinic visit at both individual and cluster levels. The results are shown in Tables 5.5d and 5.5e for individual and cluster analysis respectively. At the individual level, the mean haemoglobin levels in the treated and no net groups by period of conception and parity were similar, except for secundigravidae; mean haemoglobin in the treated net group was significantly lower ($p < 0.0008$). The 95 percent confidence intervals overlap for both treated and no net groups by parity and period of conception. Nearly 80 percent of primigravidae in both groups were anaemic. Severe anaemia occurred less frequently in the no net group when conception took place in the wet season and similar in both groups when conception took place in the dry season. The proportion with anaemia in secundigravidae in the treated net group was higher in both periods of conception. Severe anaemia was more prevalent in the no net group when conception took place in the wet season but less frequent in the dry season. With multigravidae, the proportion with anaemia was similar in both groups when conception took place in the wet season and marginally lower in the treated net group when conception took place in the dry season. Severe anaemia was less frequent in the treated net group when conception took place in the wet season. The prevalence was similar in both groups when conception took place in the dry season.

Table 5.5c: Haemoglobin Levels and Levels of Anaemia By Parity and Week of Gestation in Kassena-Nankana District, Ghana

	Primigravidae				Secundigravidae				Multigravidae			
Week of Gestation	14-26 weeks		27-40 weeks		14-26 weeks		27-40 weeks		14-26 weeks		27-40 weeks	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net
Mean Haemoglobin (g/l)	87.3	85.5	86.0	87.8	93.8	94.1	89.0	92.6	94.9	94.2	91.8	91.3
Range	49.120	31.123	46.137	47.118	54.124	59.123	50.121	63.116	42.140	41.133	40.138	26.142
95% CI	84 - 91	82 - 89	83 - 89	85 - 91	91 - 97	91 - 98	86 - 92	90 - 95	93 - 97	92 - 96	90 - 93	90 - 93
Haemoglobin below 100 g/l												
Proportion below	65/82	77/88	101/122	91/113	49/68	38/64	78/100	65/98	155/256	131/215	278/403	253/347
Percentage below (%)	79.3	87.5	82.8	80.5	72.1	59.4	78.0	66.3	60.5	60.9	69.0	72.9
Haemoglobin below 70 g/l												
Proportion below	10/82	9/88	17/122	14/113	2/68	4/64	8/100	3/98	8/256	16/215	36/403	28/347
Percentage below (%)	12.2	10.2	13.9	12.4	2.9	6.3	8.0	3.1	3.1	7.4	8.9	8.1

In the same parity group and treatment arm, mean haemoglobin levels were significantly higher when conception took place in the wet season. The results from the cluster analysis showed that mean haemoglobin levels in the treated and no net groups were similar by parity and period of conception. The prevalence of anaemia was similar in the treated and no net groups when conception took place in the dry season. In the same treatment arm, the mean haemoglobin levels were higher when conception took place in the wet season for each parity. Nearly a fifth of primigravidae in both groups had severe anaemia when conception took place in the dry season.

Figure 4 shows proportion of study women with haemoglobin below 100 g/l in the treated and no net groups by parity and month of clinic visit for first clinic visits. Figures 4a, 4b and 4c show the information for primigravidae, secundigravidae and multigravidae respectively. The proportion of primigravidae with anaemia (haemoglobin below 100 g/l) stayed above 80 percent in the treated and no net groups from July to November but declined slightly in the drier months in the treated net group. In higher parities, anaemia peaked with the maximum rainfall and declined rapidly with the advance of the dry season, being steeper in the treated bednet group. However, the proportions increased again after January.

Table 5.5d: Haemoglobin Levels and Levels of Anaemia among Pregnant Women By Parity and Estimated Month of Conception in Kassena-Nankana District, Ghana - Individual Analysis

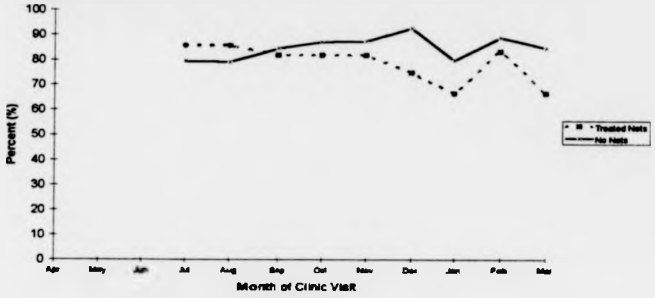
	Primigravidae				Secundigravidae				Multigravidae			
Estimated Month of Conception	May-Nov		Dec-Apr		May-Nov		Dec-Apr		May-Nov		Dec-Apr	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net
Mean Haemoglobin (g/l)	89.3	89.6	84.2	84.6	93.9	91.0	88.4	95.8	95.0	95.4	91.5	90.5
95% CIs	86 - 92	87 - 92	81 - 87	82 - 88	91 - 97	93 - 99	86 - 91	88 - 94	93 - 97	93 - 98	90 - 93	89 - 92
Haemoglobin below 100 g/l												
Proportion below	70/92	73/88	96/112	95/113	52/77	40/75	75/91	63/87	172/282	129/219	261/377	255/343
Percentage below (%)	76.1	83.0	85.7	84.1	67.5	53.3	82.4	72.4	61.0	58.9	69.2	74.3
Haemoglobin below 70 g/l												
Proportion below	6/92	3/88	21/112	20/113	3/77	4/75	7/91	3/87	11/282	15/219	33/377	29/343
Percentage below (%)	6.5	3.4	18.8	17.7	3.9	5.3	7.7	3.5	3.9	6.9	8.8	8.5

Table 5.5e: Cluster Analysis - Haemoglobin Levels and Levels of Anaemia among Pregnant Women By Parity and Estimated Month of Conception in Kassena-Nankana District, Ghana

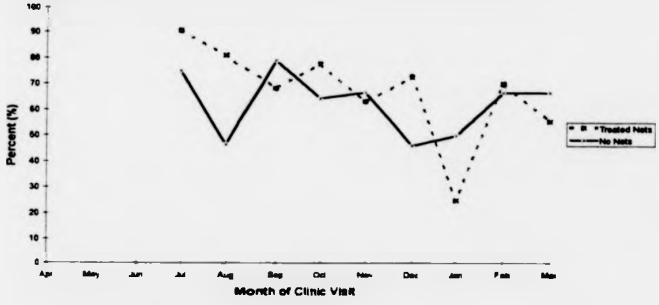
	Primigravidae				Secundigravidae				Multigravidae			
Estimated Month of Conception	May-Nov		Dec-Apr		May-Nov		Dec-Apr		May-Nov		Dec-Apr	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net
Clusters per arm = 48												
Mean Haemoglobin (g/l)	88.7	89.5	82.5	83.2	92.5	95.3	89.2	90.0	95.4	95.1	91.7	91.8
95% CIs	86 - 92	87 - 92	79 - 86	80 - 87	89 - 96	92 - 99	86 - 92	88 - 92	93 - 97	93 - 97	89 - 94	90 - 94
Haemoglobin below 100 g/l												
Percentage below (%)	77.2	81.3	90.9	87.2	70.5	59.3	79.5	78.2	59.8	62.5	69.2	71.1
Haemoglobin below 70 g/l												
Percentage below (%)	6.0	3.8	18.3	22.3	7.3	4.1	6.8	2.4	3.4	6.7	8.4	7.4

Figure 4 - Proportion with Haemoglobin below 100 g/l in Treated and No Net Groups by Parity and Month of Clinic Visit in Kassena-Nankana District, Ghana

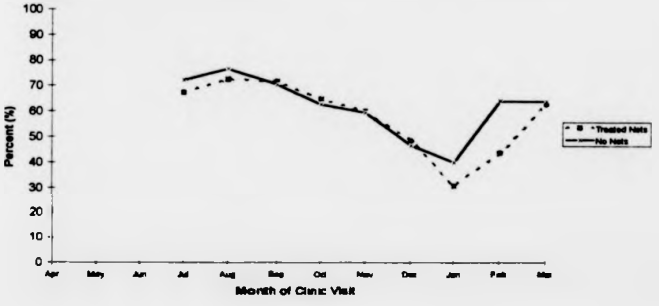
PRIMIGRAVIDAE - Proportion with Haemoglobin below 100 g/l in Treated and No Net Groups in Kassena-Nankana District, Ghana
Fig 4a



SECUNDIGRAVIDAE - Proportion with Haemoglobin below 100 g/l in Treated and No Net Groups in Kassena-Nankana District, Ghana
Fig 4b



MULTIGRAVIDAE - Proportion with Haemoglobin below 100 g/l in Treated and No Net Groups in Kassena-Nankana District, Ghana
Fig 4c



5.6 Possible Delayed Effect of Bednets on Malaria and Anaemia in Pregnancy

In order to explore the possibility of a delayed protective effect of bednet use on malaria and anaemia in pregnancy, the combined data set was analysed further by gestational period. Table 5.6a summarises the results on haemoglobin levels by gestational age-groups and parity at individual level. The mean haemoglobin and 95 percent confidence intervals for primigravidae were similar in the treated and no net groups at different gestational periods. The proportions with anaemia were similar in the two groups till 36 weeks gestation, after which the proportion with anaemia was higher in the treated net group. Anaemia was more common in both groups in early third trimester compared to late third trimester. Severe anaemia was more common before 30 weeks gestation and higher in the no net group. Anaemia decreased with increasing gestation and parity. Evidence suggests weak beneficial effect of bednet use against severe anaemia in primigravidae in early third trimester.

For secundigravidae, the mean haemoglobin with 95 percent confidence interval was similar in the treated and no net groups. However, the proportion with anaemia and severe anaemia was higher in the treated net group. For multigravidae, the mean haemoglobin with 95 percent confidence interval varied by gestational age or intervention group. The proportion with anaemia and severe anaemia was consistently higher in the treated net group from the 26th week through to the end of pregnancy. There was weak beneficial effect on anaemia for all multigravidae in the third trimester; on severe anaemia, this effect was found in the late third trimester only.

Table 5.6a: Haemoglobin Levels and Levels of Anaemia By Parity and Gestation (26-42 weeks) in Kassena-Nankana District, Ghana (Combined 1st & 2nd Visits) [one record per woman]

	Gestation (in weeks)	26- 29		30 - 36		37-42	
PARITY	Study Arm Haemoglobin Levels	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net
Primigravidae	Mean HB	82.0	80.0	89.0	87.0	90.0	93.0
	Range	47,110	31,113	46,137	47,124	57,123	67,118
	95% CI	78 - 86	73 - 87	86 - 92	85 - 89	82 - 99	86 - 100
	% Below 100g/l	90.2	93.1	80.2	80.2	75.0	64.7
	% Below 70g/l	19.5	37.9	9.2	9.2	6.3	5.9
Secundigravidae	Mean HB	87	92	91	92	89	102
	Range	54,127	75,106	56,125	61,123	50,121	74,125
	95% CI	80 - 94	88 - 96	89 - 94	90 - 95	80 - 98	94 - 110
	% Below 100g/l	85.7	68.2	76.4	71.4	72.2	53.3
	% Below 70g/l	14.3	0	7.3	4.8	5.6	0
Multigravidae	Mean HB	90	93	94	91	95	92
	Range	47,128	52,134	40,134	28,127	62,148	38,142
	95% CI	87 - 93	90 - 96	93 - 96	89 - 93	91 - 99	86 - 99
	% Below 100g/l	71.7	73.8	65.0	71.1	65.7	66.7
	% Below 70g/l	11.7	8.2	5.7	7.0	6.0	14.3

HB - Haemoglobin; CI - Confidence Interval

Table 5.6b shows haemoglobin levels and levels of anaemia by parity, gestation and study group at the cluster level. Mean haemoglobin increased with increasing parity and gestation. Anaemia and severe anaemia decreased with increasing parity and gestation. Cluster mean haemoglobin were analysed by ANOVA to test for effect of parity and gestation. F for parity was 13.62 (df: 2, 538; p <0.0001), gestation (third trimester) 4.52 (df: 2, 538; p: 0.011) and bednet 0.58 (df: 1, 539; p: 0.45). ANOVA results suggested a strong influence of parity and gestation on mean haemoglobin while bednets had no effect.

Table 5.6c shows the findings on *P. falciparum* parasite rates and density by parity and gestation at individual level. GMPD declined with increasing gestation but remained higher in the treated net group among primigravidae. In secundigravidae and multigravidae, it remained lower in the treated net group. Parasite rates were highest before 30 weeks and declined with increasing gestation, being similar in both groups. Parasitaemia and parasite density decreased with increasing gestation and parity.

Table 5.6d shows *P. falciparum* parasite rates and density by parity, gestation and study group at the cluster level. GMPD remained higher in the treated net groups in primigravidae and multigravidae, but lower in secundigravidae. Parasite rates declined with increasing gestation in primigravidae and secundigravidae but remained constant in multigravidae.

The cluster means of the log of parasite density were analysed by ANOVA to test for effect of parity and gestation. F for parity was 59.26 (df: 2, 418; p <0.0001), gestation 1.19 (df: 2, 418; p: 0.305) and bednet 1.53 (df: 1, 419; p: 0.216). ANOVA results suggested strong influence of parity on parasitaemia. Bednets and gestation had limited effects on parasitaemia.

Table 5.6b: Cluster Analysis - Haemoglobin Levels and Levels of Anaemia by Parity and Gestation in Kassena-Nankana District, Ghana (26-42 weeks) (Combined 1st & 2nd Visits) [one record per woman]

	Gestation (in weeks)	26- 29		30 - 36		37-42	
PARITY [Treat Net Clusters=48 No Net Clusters = 48]	Study Arm / Haemoglobin Levels	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net
Primigravidae	Mean HB	81.7	80.7	88.2	87.3	90.8	93.0
	Range	47, 103	47, 113	61, 108	68, 121	57, 123	76, 118
	95% CI	77 - 87	74 - 88	85 - 92	84 - 91	82 - 100	86 - 100
	% Below 100g/l	88.0	90.9	77.9	84.8	73.3	64.3
	% Below 70g/l	19.0	36.4	11.7	11.4	6.7	3.6
Secundigravidae	Mean HB	86.6	93.1	91.6	91.2	85.9	102.6
	Range	66, 108	75, 104	63, 115	74, 113	50, 121	82, 125
	95% CI	80 - 93	89 - 98	88 - 95	88 - 94	76 - 96	95 - 111
	% Below 100g/l	88.5	66.7	74.8	75.3	78.6	50.0
	% Below 70g/l	14.6	0	8.4	3.3	7.1	0
Multigravidae	Mean HB	90.4	94.2	95.0	91.4	94.1	90.7
	Range	61, 112	75, 134	74.3, 120	75, 113	62, 124	51, 128
	95% CI	88 - 93	90 - 98	93 - 97	89 - 94	89 - 99	83 - 99
	% Below 100g/l	74.2	74.7	63.3	72.0	66.6	73.5
	% Below 70g/l	11.7	5.2	6.2	6.9	8.1	13.4

Table 5.6c: *P. falciparum* Parasite Rates and Parasite Density by Parity and Gestation in Kassena-Nankana District, Ghana (26-42 weeks) (Combined 1st & 2nd Visits) [one record per woman]

	Gestation (in weeks)	26- 29		30 - 36		37-42	
PARITY	Study Arm	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net
	Parasite Levels						
Primigravidae	GMPD	1759	854	1208	1101	711	572
	95% CI	1011 - 3060	324 - 2249	807 - 1809	785 - 1545	188 - 2690	212 - 1539
	Parasite Rate (%)	84.6	67.9	60.0	70.2	62.5	52.9
Secundigravidae	GMPD	428	607	331	408	275	107
	95% CI	103 - 1780	196 - 1879	211 - 520	253 - 660	89 - 853	46 - 250
	Parasite Rate (%)	52.4	63.6	48.6	50.5	55.6	46.7
Multigravidae	GMPD	177	167	209	181	208	200
	95% CI	123 - 255	116 - 238	165 - 266	141 - 233	123 - 351	108 - 370
	Parasite Rate (%)	51.7	41.7	39.1	40.2	42.4	54.8

GMPD - Geometric Mean Parasite Density

Table 5.6d: Cluster Analysis - *P. falciparum* Parasite Rates and Parasite Density by Parity and Gestation in Kassena-Nankana District, Ghana (26-42 weeks) (Combined 1st & 2nd Visits) [one record per woman]

[Treat Net Clusters=48 No Net Clusters = 48]	Gestation (in weeks)	26- 29		30 - 36		37-42	
	Study Arm	Treated Net	No Net	Treated Net	No Net	Treated Net	No Net
PARITY	Parasite Levels						
Primigravidae	GMPD	1708	851	1496	963	577	572
	95% CI	800 - 3647	326 - 2220	889 - 2516	635 - 1460	141 - 2370	212 - 1539
	Parasite Rate (%)	82.3	75	61.9	77.0	60.0	57.1
Secundigravidae	GMPD	428	665	268	460	322	107
	95% CI	103 - 1780	180 - 2457	167 - 429	258 - 823	75 - 1375	46 - 250
	Parasite Rate (%)	58.3	61.1	49.8	49.6	57.1	46.1
Multigravidae	GMPD	169	142	242	175	217	214
	95% CI	116 - 246	96 - 210	166 - 429	134 - 228	116 - 407	105 - 435
	Parasite Rate (%)	54.4	44.6	39.8	44.6	50.5	54.7

5.7 Bednets and Pregnancy Outcome

5.7.1 Delivery Outcome

An initial attempt to develop a computer-based system for pregnancy outcome surveillance linked to the Navrongo Demographic Surveillance System was unsuccessful. The principal reason was that the system had not hitherto been used outside the main trial and there was concern about lack of data security which had not been worked through. Consequently, a manual system of active surveillance was developed using pregnancy registers. This assisted fieldworkers and field supervisors to visit study women at 34 weeks and beyond at least once a week to monitor pregnancy outcome. Initial results were encouraging.

However, financial constraints resulted in staff reductions in September and November 1994, thus reducing the effectiveness of the manual surveillance system. By December 1995, pregnancy outcome surveillance had become a passive system. We estimated that by the end of the study period, approximately 2400 (85 percent) out of 2812 pregnant women who had been interviewed had delivered. The results on delivery outcome should be seen in this context. The pregnancy outcomes for 847 women were reported with the following breakdown: 799 live singleton births, 15 live twin deliveries, 15 stillbirths and 18 abortions. Overall the surveillance system yielded 35 percent of likely events compared to 70 percent during the period of active surveillance, i.e. between July and December 1994. Pregnancy outcomes in the treated and the no net clusters were followed up using the same surveillance system. Despite the underreporting of events, no bias is expected since an equal number of events were reported in both the treated and the no net clusters. In spite of the low coverage of events on delivery outcome as a result of passive surveillance, the sample size achieved for primigravidae and secundigravidae was adequate (see **section 5.1.2**). This notwithstanding, a higher coverage would have been preferable to give the study more power.

Data on delivery outcome is shown in Table 5.7.1a. For primiparae and secundiparae, the number of live singleton births were similar in the treated and no net groups, with fewer births amongst secundiparae. For multiparae, there were more births in the treated net group. Fourteen sets of live twins were born to multiparae, equally divided among the treated and the no net groups, and additionally one pair of twins was born to a secundiparae in a treated net cluster. Eighteen abortions were reported; primigravidae - 2: one in each group, secundigravidae - 4: treated net group - 3, no net group - 1 and multigravidae - 12; treated net group - 3, no net group - 9.

The reported perinatal and neonatal deaths are shown in Table 5.7.1b. The study was not designed to assess perinatal and neonatal mortality, however the issues were explored due to the availability of data. For perinatal deaths, the proportions in the treated and the no net groups were similar in primiparae and multiparae but with secundiparae, the proportion in the treated net group was more than double that in the no net group. Total perinatal deaths by intervention group was similar (total - 53: treated clusters - 27, no net clusters - 26). Numbers in each category were small. For total neonatal deaths, the proportions were lower for primiparae and multiparae and higher in secundiparae in the treated net group. Total neonatal deaths was lower in the treated bednet group (total - 63: treated clusters - 28, no net clusters - 35). There was no evidence of protective effect of bednet use against perinatal mortality ($z=0.71$, $p=0.48$: Wilcoxon ranksum test) or neonatal deaths ($z=0.94$, $p=0.35$: Wilcoxon ranksum test).

Table 5.7.1a: Delivery Outcome in Kassena-Nankana District, Ghana

	Primigravidae		Secundigravidae		Multigravidae	
Study Arm Outcome	Treated	No Net	Treated	No Net	Treated	No Net
Live -singleton	90(94.7)	96(97.0)	70(94.6)	73(97.4)	253(96.9)	217(95.2)
Stillbirths	4 (4.2)	2 (2.0)	1 (1.4)	1 (1.3)	5 (1.9)	2 (0.9)
Abortions	1 (1.1)	1 (1.0)	3 (4.0)	1 (1.3)	3 (1.2)	9 (3.9)
Total Abortions/Births	95	99	74	75	261	228
Live-twins	0	0	2	0	14	14

* (Column percentage in brackets)

Table 5.7.1b: Perinatal and Neonatal Deaths in Kassena-Nankana District, Ghana

	Primigravidae		Secundigravidae		Multigravidae	
Study Arm Deaths	Treated	No Net	Treated	No Net	Treated	No Net
Stillbirths	4	2	1	1	5	2
Early Neonatal	5	8	4	1	8	12
Total Perinatal	9	10	5	2	13	14
% of Total Births[1]	9.6 (9/94)	10.2(10/98)	7.0 (5/71)	2.7 (2/74)	5.0 (13/258)	6.4 (14/219)
Late Neonatal	2	3	2	3	7	8
Total Neonatal	7	11	6	4	15	20
% of Live Births[1]	7.8 (7/90)	11.5(11/96)	8.6 (6/70)	5.5 (4/73)	5.9 (15/253)	9.2 (20/217)

[1] Singleton Births Only

5.7.2 Birth weights

Weights of newborns ("birth weights") were recorded within 7 days of delivery based on experience from the Gambia indicating newborn weight within 7 days of birth as a good proxy for birth weight. Birth weight adjustment factors, based on data from the Gambia

(kindly provided by Umberto D'Alessandro), were used to take account of the fact that it was not possible to weigh all babies on the day of birth, but "birth weights" were recorded within 7 days of birth. These adjustment factors were: Day 1 - 99 percent, Day 2 - 98 percent, Day 3 - 96 percent, Day 4 - 97 percent, Day 5 - 99 percent and Day 0, 6 and 7 after delivery - 100 percent of birth weight. Analysis of data on birth weights is based on both unadjusted and adjusted birth weights at both individual and cluster levels.

The results on birth weights are shown in Table 5.7.2a. The proportion of low birth weight was higher in the wet season than in the dry season for all parities and regardless of which cut-off point was used. Birth weights increased consistently with increasing parity. There was no evidence of any effect of the treated nets on birth weights. Newborn weights were recorded for 799 singleton live births; primiparae - 186, secundiparae - 143 and multiparae - 470. For primiparae, mean birth weight increased from the wet to dry season, being more marked in the treated net clusters. Mean birth weight in the treated net group was lower in the wet season and higher in the dry season compared to the no net group. For secundiparae, mean birth weight was similar in both groups in the wet season (2.52 kg vs. 2.53 kg) with a slight increase in the dry season, although to a lesser extent in the treated net group (2.69 kg vs. 2.78 kg). For multiparae, mean birth weight was higher in the treated net clusters in both wet (2.69 kg vs. 2.54 kg) and dry (2.92 kg vs. 2.87 kg) seasons. There was no difference in the cluster-level mean birth weight (for all parities) in both treated and no net clusters (treated: 2.61 kg, no net: 2.55 kg; $t = 0.79$, $p = 0.4$, $df = 94$).

Table 5.7.2a: Birth weights by Parity and Month of Birth in Kassena-Nankana District, Ghana (Individual Level - Unadjusted)

	Primiparae				Secundiparae				Multiparae			
Month of Birth	Jul-Nov		Dec-Apr		Jul-Nov		Dec-Apr		Jul-Nov		Dec-Apr	
Study Arm	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net	Treated	No Net
Mean Birth weight (kg)	2.16	2.31	2.53	2.42	2.52	2.53	2.69	2.78	2.69	2.54	2.92	2.87
Range	0.87,3.13	1.05,390	1.24,3.45	1.08,3.00	1.01,4 62	0.84,3.60	2.01,3.50	1.60,3 90	1.15,4.07	1.08,4.27	1.25,4.27	1.91,4.05
95% CI	2.04-2.27	2.16-2.46	2.33-2.73	2.25-2.59	2.31-2.73	2.36-2.70	2.50-2.88	2.52-3.05	2.61-2.77	2.44-2.64	2.79-3.06	2.77-2.98
Birth weight below 2.5kg												
Proportion below	47/59	38/65	13/31	14/31	20/54	21/52	3/16	5/21	55/193	62/158	11/60	8/59
Percentage below (%)	79.7	58.5	41.9	45.2	37.0	40.4	18.8	23.8	28.5	39.2	18.3	13.6
Birth weight below 2.0kg												
Proportion below	14/59	18/65	5/31	5/31	11/54	6/52	0/16	2/21	23/193	30/158	2/60	1/59
Percentage below (%)	23.7	27.7	16.1	16.1	20.4	11.5	0	9.5	11.9	19.0	3.3	1.7

Low birth weight (LBW) was classified as birth weight less than 2.50 kg (Lechtig, 1977; Chiswick, 1986). For primiparae, in the wet season, four-fifths of newborns in the treated net group and three-fifths in the no net group were LBWs. In the dry season, this decreased to less than half in both groups, but to a greater extent in the treated net group (41.9 percent vs. 45.2 percent). Two-fifths of secundiparae had LBW babies in the wet season in both groups. In the dry season, the proportion decreased to about a fifth in the treated net clusters and about a quarter in the no net clusters (18.8 percent vs. 23.8 percent). For the multiparae, in the wet season less than a third had LBW babies in the treated net clusters and two-fifths had LBW babies in the no net clusters. This decreased in the no net group in the dry season but remained unchanged in the treated net group (18.3 percent vs. 13.6 percent). The proportion of LBW in primiparae was nearly double that in secundiparae. The proportion in the latter was only slightly higher than that of multiparae.

For further analysis of low birth weight, a different cut-off of 2.0 kg was used. This cut-off point has been used in Ghana in previous work on birth weights in Agogo Presbyterian Hospital (van der Mei, 1994). Some investigators have argued for country-specific birth weight standards instead of that proposed by WHO (Rooth, 1980; Munjanja & Masona, 1990) since current cut-off point classify otherwise healthy infants as LBWs. For primiparae, in the wet season the proportion of LBWs was less than a quarter in the treated net group and above a quarter in the no net group. In the dry season, one-sixth of newborns were LBWs in both groups. For secundiparae, in the wet season a fifth had LBWs in the treated net group compared with a tenth in the no net group. In the dry season, the proportion of LBWs in the treated net group was reduced to none but remained unchanged in the no net group. For multiparae, in the wet season a tenth had LBWs in the treated net group compared with a fifth in the no net group. This declined to less than 5 percent in both groups in the dry season, more marked in the no net group.

Following from individual level analysis, cluster level analysis was done on birth weight by parity and period of birth, both adjusted and unadjusted as shown in Table 5.7.2b. Adjustment increased birth weight by between 20 to 30 grams. The mean birth weights, regardless of adjustment, increased with parity and from the wet to dry season. In primiparae, mean birth weight was lower, both adjusted and unadjusted, in the wet season in the treated net group compared to the no net group. In the dry season, mean birth weight was higher in the treated net group. For secundiparae, mean birth weight was higher in the treated net group in both wet and dry seasons, for both adjusted and unadjusted birth weights. For multiparae, mean birth weight was higher in the treated net group in the wet season but lower in the dry season, irrespective of adjustment.

At both individual and cluster levels, the proportion of LBWs declined with increasing parity and from the wet to dry seasons. For primiparae, the proportion of LBWs was higher in the treated net group in both wet and dry seasons. For secundiparae, the proportion of LBWs was higher in the treated net group in both seasons. However, the proportion of LBWs in multiparae was lower in the treated net group in the wet season and higher in the dry season.

Mean birth weights (unadjusted) were analysed by ANOVA to test for effect of parity and period of birth (season) at cluster levels. F for parity was 31.14 (df: 2, 361; $p < 0.0001$), period of birth (season) 18.16 (df: 1, 361; $p < 0.0001$) and bednet 0.73 (df: 1, 361; $p = 0.39$). ANOVA results provided evidence of increased birth weight with increasing parity and from wet season (July to November) to dry season (December to April). Bednets had little or no effect on mean birth weights.

Residuals were obtained by fitting logistic regression models under the null hypothesis. Combined estimates of these residuals were used in the second stage to make inferences on the effect of treatment.

Table 5.7.2b: Cluster Analysis - Birth weight by Parity and Month of Birth in Kassena-Nankana District, Ghana (Adjusted and Unadjusted)

PARITY [Treated Clusters = 48 No Net Clusters = 48]	Month of Birth / Study Arm / Birth weight Level	Adjusted[1] Jul-Nov Treated Net	Adjusted[1] Jul-Nov No Net	Adjusted[1] Dec - Apr Treated Net	Adjusted[1] Dec - Apr No Net	Unadjusted Jul-Nov Treated Net	Unadjusted Jul-Nov No Net	Unadjusted Dec - Apr Treated Net	Unadjusted Dec - Apr No Net
Primiparae	Mean Birth weight (kg)	2.19	2.35	2.49	2.39	2.17	2.33	2.46	2.36
	95% CI	2.05-2.33	2.15-2.54	2.26-2.72	2.21-2.57	2.03-2.31	2.13-2.53	2.23-2.70	2.19-2.54
	No. of Clusters (48)								
	% less than 2.50 kg	68.0	50.8	47.2	42.4	69.7	53.8	47.2	47.7
	% less than 2.00 kg	20.2	23.0	18.1	11.6	21.5	23.0	18.1	16.8
Secundiparae	Mean Birth weight (kg)	2.62	2.48	2.93	2.88	2.59	2.46	2.91	2.86
	95% CI	2.47-2.76	2.31-2.64	2.80-3.05	2.72-3.04	2.44-2.73	2.29-2.62	2.78-3.04	2.70-3.02
	No. of Clusters (48)								
	% less than 2.50 kg	33.4	38.9	11.1	16.1	34.2	41.1	11.1	16.6
	% less than 2.00 kg	14.5	19.0	0	3.6	14.5	19.0	0	3.6
Multiparae	Mean Birth weight (kg)	2.87	2.71	2.81	2.95	2.84	2.69	2.78	2.93
	95% CI	2.69-3.04	2.55-2.88	2.50-3.13	2.73-3.18	2.67-3.01	2.52-2.85	2.47-3.10	2.70-3.15
	No. of Clusters (48)								
	% less than 2.50 kg	19.0	27.6	25.0	8.9	19.0	27.6	25.0	8.9
	% less than 2.00 kg	10.9	11.6	9.4	1.1	10.9	11.6	9.4	1.1

[1] Adjusted for number of days after delivery

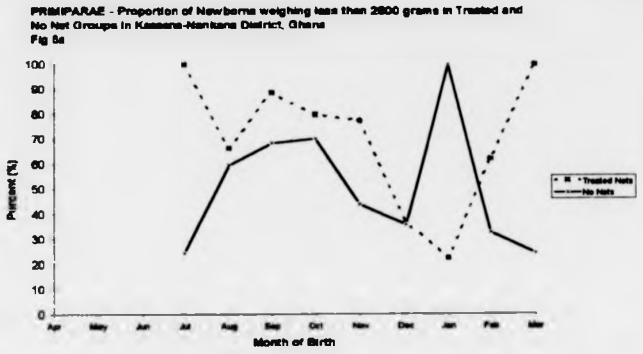
This was not significant (t = 0.40, df = 94, p > 0.69). The OR for being LBW in a treated net cluster was as follows: birth weight (adjusted) - LBW <2500 g; 0.87 (95% CI: 0.63, 1.19; p=0.25), LBW <2000 g; 0.80 (95% CI: 0.48, 1.32; p=0.26) and birth weight (unadjusted) - LBW < 2500 g; 0.88 (95% CI: 0.61, 1.24; p=0.36), LBW < 2000 g; 0.76 (95% CI: 0.39, 1.50; 0.27). Based on the risk estimates, there was no evidence of protective effect of bednet use against LBW.

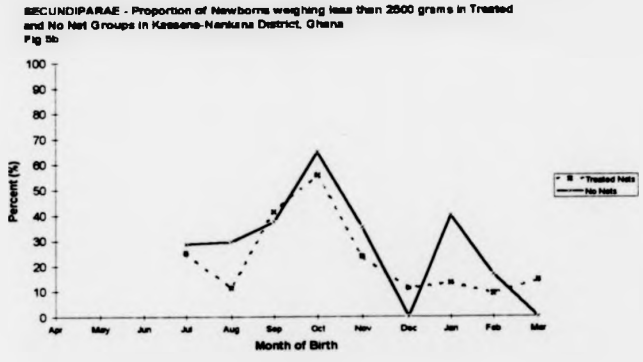
Figure 5 shows proportion of newborns weighing less than 2500 grams (LBW) in the treated and no net groups by parity and month of birth in the study area. Figures 5a, 5b, 5c show the information for primiparae, secundiparae and multiparae respectively. The proportions of LBW babies rose with the onset of the rains and peaked at the time of maximum rainfall and subsequently declined till December but rose again afterwards. However, the proportion of LBW babies in primigravidae in the treated was higher than in the no net group. Their distribution in the no net group had 2 peaks in October and January compared to the treated bednet group with peaks in July, September and March.

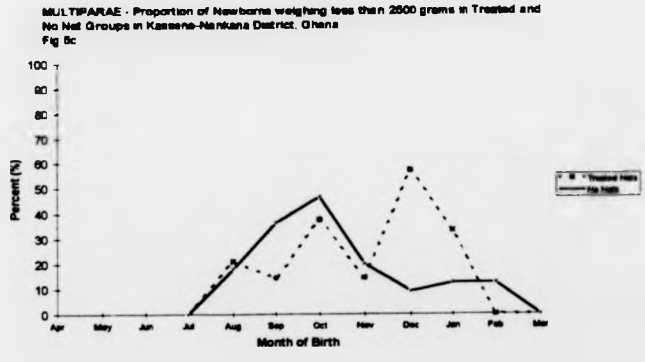
5.8 Summary of Estimates of Effect of Insecticide-treated Bednets in Pregnancy

Tables 5.8.1a and 5.8.1b summarise the estimates of effect of insecticide-treated bednet use in pregnancy based on results presented in **sections 5.4** to **5.7**. Table 5.8.1a presents the odds ratios based on intention-to-treat analysis for all endpoints whilst Table 5.8.1b presents odds ratios for endpoints for first clinic visits and unadjusted birth weights based on individual protection analysis at cluster level. Individual protection analysis was restricted to women who responded they had slept under a net the night before interview in a net cluster and those in no net clusters who did not use a net.

Figure 5 - Proportion of Newborns weighing less than 2500 grams in Treated and No Net Groups by Parity and Month of Birth in Kassena-Nankana District, Ghana







During pregnancy, two data sets were used based on first clinic visit and combined first and second clinic visits restricted to one record per woman with at least 26 weeks gestation. For data on birth weights, estimation of effects of bednet use was based on adjusted and unadjusted birth weights. Adjusted birth weights took account of the interval between day of delivery and recording of newborns' weight. The endpoints considered were anaemia, parasitaemia and low birth weight. Each endpoint had two cut-off points due to their different clinical significance or impact of severity.

Table 5.8.1a: **ESTIMATES OF EFFECT OF INSECTICIDE-TREATED BEDNETS IN PREGNANCY IN KASSENA-NANKANA DISTRICT, GHANA. ODDS RATIOS WITH 95% CONFIDENCE INTERVAL (Nets vs. No Nets)**
(Based on Intention-To-Treat [ITT] Analysis)

PERIOD	ENDPOINT		ODDS RATIO [Nets vs. No Nets]	95% CI	P - Value
First Clinic Visit	Anaemia	(<100 g/l)	0.97	0.86, 1.10	0.81
	Severe Anaemia	(<70g/l)	0.91	0.57, 1.43	0.58
	Parasitaemia	(>0/µl)	1.13	0.54, 2.38	0.21
	Parasitaemia	(>1999/µl)	0.98	0.85, 1.12	0.89
Combined Data [1st & 2nd Visits]	Anaemia	(<100 g/l)	0.88	0.70, 1.09	0.47
	Severe Anaemia	(<70g/l)	0.80	0.55, 1.16	0.62
	Parasitaemia	(>0/µl)	0.89	0.73, 1.08	0.56
	Parasitaemia	(>1999/µl)	1.11	0.93, 1.33	0.55
Birth Weight (Adjusted)[2]	LBW[1]	(<2500g)	0.87	0.63, 1.19	0.25
	LBW	(<2000g)	0.80	0.48, 1.32	0.26
Birth Weight (Unadjusted)	LBW	(<2500g)	0.88	0.61, 1.24	0.36
	LBW	(<2000g)	0.76	0.39, 1.50	0.27

[1] LBW - Low birth weight
[2] Birth weight adjusted according to interval between birth and recording of weight (in days)

Table 5.8.1b: **ODDS RATIOS WITH 95% CONFIDENCE INTERVAL**
(Based on Individual Protection [IP] Analysis)
[NET USE in NET CLUSTERS vs. NO NET USE in NO NET CLUSTERS]
(Net Clusters - 48; No Net Clusters - 48)

PERIOD	ENDPOINT	ODDS RATIO [Nets vs. No Nets]	95% CI	P - Value
First Clinic Visit	Anaemia (<100 g/l)	0.90	0.58, 1.40	0.50
	Severe Anaemia (<70g/l)	0.83	0.38, 1.82	0.50
	Parasitaemia (>0/µl)	1.14	0.57, 2.25	0.52
	Parasitaemia (>1999/µ/)	0.86	0.40, 1.87	0.35
Birth Weight	LBW[1] (<2500g)	0.82	0.66, 1.01	0.29
[Unadjusted]	LBW (<2000g)	0.65	0.42, 1.02	0.11

[1] LBW - Low birth weight

For anaemia, the cut-off point of 100 g/l represented the standard for MOH-Ghana. Many women go through pregnancy with mean haemoglobin levels below this without harm. However, the cut-off point of 70g/l represented severe anaemia which may lead to death from congestive heart failure or death from minor bleeding episodes in pregnancy or during delivery. For parasitaemia, the cut-off points were selected to detect any effect on low or high parasite densities since most pregnant women had low parasite density. Further, the degree of malaria-related anaemia is not dependent on parasite load, although in children higher parasite load is associated with severe morbidity and mortality. For low birth weight, the two cut-off points were selected based on the standard WHO classification for low birth weight and a lower cut-off taking into consideration the pervasive poverty and nutrition adversity in the study area.

Overall, the odds ratios (ORs) based on intention-to-treat were consistent for anaemia (both mild and severe) in both first visit and combined visits data sets and low birth weight (WHO and local standard) for both adjusted and unadjusted. The confidence intervals for anaemia in first visit and combined data sets overlapped (range: 0.55-1.43). Although, the results were not significant (p-value - range: 0.47-0.80), a modest protective effect of bednet use could not be excluded. Similarly, the confidence intervals for low birth weight overlapped (range: 0.39-1.50). A modest protective effect of bednet

use on low birth weight was also plausible despite insignificant results. The results for parasitaemia were not consistent, although given the range of values for the confidence interval and the p-values, a weak protective effect could not be excluded.

The ORs based on individual protection analysis were similar to that based on ITT. Although the results were not significant, the direction of the evidence was consistent with possible beneficial effects of insecticide-treated bednet use in pregnancy with respect to anaemia, high parasitaemia and low birth weight.

5.9 Attitudes of Pregnant Women to Antenatal Care and Bednets

Focus group discussions (FGDs) were organised in September 1994 during study clinics at Sirugu, Kandiga and Paga. The FGDs were conducted by a female fieldworker who was fluent in both Kassem and Nankam using a guide developed by a social scientist at NHRC. Her first two interviews were supervised by the social scientist. At each clinic, two FGDs were done; one for a group of 5 primigravidae and secundigravidae and the other for multigravidae. Each session was recorded on a voice-activated cassette recorder and later transcribed by the interviewer and a field supervisor fluent in both Kassem and Nankani.

All FGD participants at the ANC clinics in Sirigu, Kandiga and Paga were highly appreciative of study and routine antenatal clinics. The reasons for clinic attendance were: to have safe deliveries and healthy babies, early detection and treatment of health problems in pregnancy, treatment for illness and ensure good care by midwives during supervised delivery. The clinic attenders were asked about reasons for non-attendance. The reasons given were; lack of money - husbands sometimes refuse to provide money for ANC, taboos about antenatal clinic attendance due to traditional beliefs, negative staff attitudes (some mothers claimed midwives shouted at them), refusal of some traditional

birth attendants to refer pregnant women due to default in payment of token fees in previous delivery, some women do not appreciate value of ANC and laziness. There were no differences between responses according to parity or clinic site.

FGD discussants were asked to comment on bednet usage. Those without nets complained bitterly and felt cheated. Those with nets felt it was very nice to sleep under them since they were free from mosquito bites. However, sleeping under nets was unbearably hot during the warm season and as a result many of them did not use their nets. They also did not use their nets when they felt there were no mosquitoes. The advice from the NHRC not to wash nets for at least 6 months could not be adhered to because young children often defecated or urinated on them and the nets had to be washed. Majority of discussants expressed preparedness to purchase their own nets if prices were low and affordable. There was strong support for some form of subsidy to enable every family afford bednets.

5.10 Quality Control in Malaria Microscopy

A 10 percent random sample of blood slides (253) was re-examined by the laboratory technician as a quality check. The films were re-examined blindly, i.e. the technician did not know which slides were selected for quality checks. Quality checks were restricted to asexual *P. falciparum* count since it was the primary area of focus of this study. The k (kappa) statistic for asexual *P. falciparum* count was 0.6 (Landis & Koch, 1977). The level of agreement was 78.3 percent. McNemar's χ^2 test for the concordant pairs was 0.02, with a p-value of 0.89. There was no significant difference between the results of the first blood film examination for asexual *P. falciparum* count and the quality checks. Careful attention was paid to quality of laboratory tests both in the field and in the laboratory through regular supervision and spot checks by the author. The results of the quality control were comparable to those in a previous study on malaria in children in the study area (Binka et al., 1994).

5.11 Use of Chloroquine in Pregnancy

In order to assess the proportion of pregnant women with evidence of recent intake of chloroquine, ELISA assays were performed on dried blood spots on filter paper. The cut-off for a positive ELISA test was below 60 ng/µl. Analysis was done at individual level only due to small number of positive tests. A total of 1961 women were seen at first clinic visits and test results were available for 1247 of them (64 percent). Results on the ELISA assays are shown in Table 5.11. The mean chloroquine levels in blood are for positive results only. In primigravidae, mean chloroquine levels were higher, but not significantly different, in the treated net group during the July to November and December to March periods. The percentage with positive ELISA tests were similar in the treated and no net groups in both periods, but marginally higher in the dry season.

Work on Chloroquine

ELISA based on previous work by Dr. Eggelte (Brabin et al., 1990; Eggelte, 1990; Witte et al., 1990).

Table 5.11: Recent Intake of Chloroquine in Pregnancy by Parity and Month of First Clinic Visit in Kassena-Nankana District, Ghana - Individual data

	Month of First Visit	Jul - Nov		Dec - Mar	
PARITY	Study Arm Chloroquine Levels	Treated Net	No Net	Treated Net	No Net
Primigravidae	Mean (ng/µl)	251	125	113	80
	Proportion +ve	4/74	3/74	5/63	5/63
	Percent +ve (%)	5.4	5.5	7.9	7.9
Secundigravidae	Mean (ng/µl)	121	96	80	162
	Proportion +ve	3/65	9/61	2/49	2/42
	Percent +ve (%)	4.6	14.8	4.1	4.8
Multigravidae	Mean (ng/µl)	442	94	315	335
	Proportion +ve	17/222	12/166	8/200	8/168
	Percent +ve (%)	7.7	7.2	4.0	4.8

In secundigravidae and multigravidae, mean chloroquine levels were higher in the treated net group in the wet season and in the no net group in the dry season. In secundigravidae,

the percentage with positive ELISA tests was significantly lower in the treated net group in the wet season ($\chi^2 = 3.8$, $p = 0.05$), but similar in the dry season. In multigravidae, the percentage with positive tests was similar in both wet and dry seasons, being marginally higher in the wet season. These results confirm the lack of chloroquine chemoprophylaxis during pregnancy and preferential use of traditional herbal treatment for presumptive malaria. Only a minority of pregnant women in the study area, regardless of study arm or period of clinic visit, used chloroquine during pregnancy (range: 4.0 - 14.8 percent).

Chapter 6

Discussion

6.1 Conducting A Supplementary Trial on Malaria Control in Pregnancy

6.1.1 Overview of Trial Results

The study was conducted in the context of a large-scale trial designed to assess the impact of insecticide-treated bednets on child mortality in northern Ghana, in a setting which was characterised by almost no net use, high child mortality, low literacy levels, constrained women's autonomy and pervasive poverty, even by West African standards (Binka et al., 1995a; Nazzar et al., 1995; Binka et al., 1994; Ross et al., 1994; Ghana VAST Study Team, 1993; Ghana VAST - 3rd Dosing Report, 1990). Results from the supplementary trial showed no significant protective effect of insecticide-treated bednets on *P. falciparum* parasitaemia, on malaria-related anaemia in pregnancy or on low birth weight in Kassena-Nankana district, Ghana. However, effective net use was found to be low, especially in primigravidae. The primary objective of the main bednet trial was to assess the impact of insecticide-treated bednets on child mortality (Binka et al., 1996). Consequently, the target group for net distribution was children and their mothers. Women without children, whether married or not, were not given top priority.

This study was a supplementary trial in the main bednet trial in Navrongo, Ghana. An assumption underlying its design was that all persons resident in the treated net clusters had nets. The fact that some women in the treated net clusters had not been provided bednets became apparent to the author after the start of this study, nearly 12 months after the commencement of the main trial. This was a departure from the protocol of the main trial and was due to a shortfall in the quantity of nets expected. The author suggested that

the pregnant women who had not received nets in the treated net clusters be catered for. However, the main trial team was not able to accommodate the suggestion due to "fears of contamination of the study". The trial design and protocol had been agreed upon as part of a multi-country trial. Changes to trial implementation therefore required agreement of other collaborators outside Ghana. The provision of nets at this stage was not deemed necessary or desirable, particularly as it was considered inappropriate scientific practice. The opinion of the main trial team was that the constraints in this supplementary study would be considered in the discussions of its findings. Use of insecticide-treated bednets in the main trial was lower than expected at 70 percent in the rainy season and 50 percent in the dry season when mosquito biting was perceived as low. The lower than expected compliance may be attributed to the lack of general community education to encourage daily net use during the trial. Given that nets, insecticides and net impregnation/re-impregnation were provided free, strategies for improving net use and compliance need to be considered prior to and during routine bednet programme implementation. Issues related to cost-recovery in bednet programmes are discussed further in **section 6.3.2.2** on financing net programmes.

Reduced effectiveness of bednets resulting from poor compliance has been reported in previous bednet trials (Rozendaal, 1989; Curtis, 1992). Net usage was observed to decline during the hot dry seasons in Papua New Guinea (Cattani et al., 1986). Community perception of low risk of malaria during periods of low nuisance biting may also potentially influence net usage as observed in Bagamoyo district, Tanzania (Winch et al., 1994). Net programmes therefore need to carefully consider factors influencing poor net compliance at the planning stages so that effective communication strategies can be designed to address them. These should emphasise both malaria prevention and control and other benefits of nets, like privacy or decoration (MacCormack & Snow, 1986; Aikins et al., 1994).

Although the main trial offered a rare opportunity to assess the impact of insecticide-treated bednets on malaria and malaria-related anaemia in pregnancy, the supplementary study investigated the impact of insecticide-treated bednets which were provided primarily to reduce child mortality, on malaria and malaria-related anaemia in pregnancy. Possibly, a higher effective net use could have offered some protection, although this is speculative. The study was an effectiveness trial rather than an efficacy one, i.e. it simulated the real-life situation of a routine net programme.

Study women woke up in the night to urinate outside their rooms. This coincided with the peak daily biting period of the local malaria vectors (Binka, 1993, unpublished). Few compounds had in-house toilet facilities and the use of chamber pots, a practice more common in southern rural Ghana, was rare. Moreover, the nature of rural life is such that women are expected to stay up till late as a result of their domestic and farm responsibilities. However, in this study nearly 90 percent of pregnant women went to bed before 10.00 pm. This did not vary significantly by parity or treatment groups. Therefore, going to bed late and getting sufficient infective bites to negate the benefits of insecticide-treated bednets is an unlikely explanation for the observed lack of effect. Further research is required to assess the impact of insecticide-treated bednet use by pregnant women, in combination with use of chamber pots and community education to promote net compliance and proper use, preferably in a programme setting that targets young women regardless of marital or child status. Preliminary results from the Burkina Faso insecticide-impregnated curtains trial suggest a 30 percent reduction in all-cause childhood mortality (Lamizana et al., 1995, unpublished; WHO, 1996b, unpublished). In areas with potential low net use, especially those with "hot seasons" sometime in the year and perennial malaria transmission, the alternative use of insecticide-treated curtains may be worth exploring.

The results of this study, especially in relation to the effect of parity and seasonality on *P. falciparum* infection, haemoglobin levels and distribution of birth weights, were

consistent. This provided strong evidence that the data collected during the fieldwork was of high quality. Consequently the results on the effect of insecticide-treated nets in pregnancy in the study area reflected the true situation and could not be attributed to weaknesses in data collection or poor quality data.

6.1.2 Constraints in Fieldwork

Supplementary trials are a useful approach in answering research questions in the context of other trials designed with different objectives and endpoints. They offer savings in terms of shared personnel, time and costs associated with a study designed to answer different questions. However, their major disadvantage may lie in "non-complaining" acceptance of ground rules of the main trial, i.e the study design and study protocol have to be taken as given. These may create serious difficulties for the supplementary study, if these rules are inflexible and more importantly, as was the case here, the two research teams involved operate almost independently. Preferably, supplementary trials should be considered and developed at the planning stage of the main trial so that the different requirements of the studies (of which there may be several) can be harmonised, and ground rules agreed upon before commencement of fieldwork. This may avoid some of the pitfalls encountered in this study. Supplementary trials, conceived after commencement of fieldwork, should preferably be done at the invitation of the donor or research team involved so that a more favourable and enabling climate for teamwork and better co-ordination can be created.

Despite the constraints, the opportunity to conduct this study was a rare one which could not be missed since insecticide-treated bednets appeared to offer a community-based and sustainable approach to malaria control in pregnancy. Although the results of this study provided no evidence of significant beneficial effects of bednet use in pregnancy, they provided insight into areas worth exploring in further research, including evaluating the

impact of high effective bednet use in pregnancy, possibly in combination with existing or new strategies for malaria control in pregnancy.

The main trial was conducted by scientists at the Navrongo Health Research Centre (NHRC), one of the 3 national health research stations of the Ministry of Health (MOH), Ghana. The Kassena-Nankana District Health Management Team (DHMT) or sub-district health teams were not involved in the operational aspects of the trial; net distribution, impregnation/re-impregnation, monitoring compliance and net use etc. Consequently, the DHMT missed a vital learning opportunity on the operational issues related to the establishment and sustainability of insecticide-treated net programmes in rural settings, as part of the Primary Health Care (PHC) system. This was particularly important in a situation where the DHMT was implicitly expected to take over the running of the net programme after the completion of the trial. Some remedial actions have been taken to facilitate the DHMT's take-over of the net programme; including the recent appointment of one of the senior researchers at NHRC as the District Director of Health Services. The DHMT, in collaboration with the Social Sciences Unit of NHRC, is undertaking operational research on different strategies for net re-impregnation and cost recovery. The strategies being explored are:

- net impregnation using an outreach team that goes round compound to compound dipping nets (mobile/outreach house-to-house strategy),
- net impregnation by a trained community member (community-based house-to-house strategy),
- net impregnation on market days (flexible fixed point strategy),
- net impregnation at health facilities (permanent fixed point strategy).

The cost per net dipped is 800 cedis (US$0.50). The "dipping teams" retain 20 percent of any income generated as incentive. The DHMT is also exploring mechanisms for procuring more supplies of insecticide as current stocks ran out.

The supplementary study worked closely with all midwives in the district from the start of fieldwork. All midwives from outside Navrongo and a selected few from the Navrongo Hospital were trained to assist with the running of study clinics and monitoring of birth weights. Two full-time midwives from Navrongo Hospital were seconded to the research team. Although gestational age assessment using the Dubowitz method (Dubowitz et al. 1970) was planned, this was abandoned since nearly 80 percent of all deliveries took place at home and it was impossible for midwives to combine their routine work with monitoring birth weights in the community. Field Supervisors trained to take over this role performed creditably.

6.1.3 Operational Issues related to Main Trial

A qualitative exploratory study on bednet acceptability preceded the main trial. It was designed to investigate issues related to acceptability, cultural taboos on net use, side effects of insecticides and willingness to pay for nets in an area without a tradition of bednet use. The study identified approaches to improving net acceptability and use, including community education on net use (Gyapong et al., 1992, unpublished; Gyapong et al., 1996). However, very little was done after the start of the main trial to maintain a high level of bednet use through sustained community education on daily net use or other strategies. Given the operational nature of the trial and the implications for its findings, this was a serious oversight. Repeated compliance surveys, after the start of the trial, indicated relatively low compliance in net use despite high acceptability. The extent to which potential hostility of "no net" communities to research staff contributed to the lack of organised effort at public education on net use remains unclear. Confidence in the research team was reduced in "no net" communities when the date for completion of the main trial was postponed twice to allow for adequate sample size in terms of the endpoint.

In spite of the free provision of nets and insecticides to the study population, effective net use/compliance was lower than expected in both dry and wet seasons. This raises

fundamental questions about the likely impact of bednet programmes based on "user fees" or "ability to pay". Future bednet programmes for malaria control need to carefully address the issue of "cost recovery" and its implications for disease control objectives, knowing that low net coverage and use may be of no public health value. The main bednet trial was a success in spite of the difficulties encountered. Providing insecticide-treated nets to communities and re-impregnating them in rural northern Ghana was a major logistical and organisational undertaking. Frustrations and anger in "no net" communities was always close to "boiling point" but the research team displayed remarkable tact and negotiating skills to reassure them till the end of the study when they were provided with insecticide-treated bednets. The 17 percent reduction in all-cause child mortality in the intervention group was equally impressive, given the high child mortality in the study area (Binka et al., 1995b; Binka et al., 1996).

6.2 Findings from the Trial on Malaria Control in Pregnancy using Insecticide-treated Bednets

6.2.1 Effect on Malaria in Pregnancy

Insecticide-treated bednets had no significant impact on *P. falciparum* parasitaemia in pregnancy. Parasite rates were higher in the wet season and in the lower parities. However, the treated and no net clusters did not show any important differences in malariometric indices. Probably, this was due in part to lower than expected net usage among study participants, especially in primigravidae. Effective net usage by parity was: primigravidae - 41 percent, secundigravidae - 56 percent and multigravidae - 67 percent. Alternatively, this could be due to pregnant women waking up at night to urinate outside their compounds and hence getting sufficient infective bites. Consequently, any partial protection might be nullified. Entomological work done as part of the main trial showed annual infective bites varying from 100 to 1000 (Armah et al., 1996, in press). Although, higher entomological inoculation rates suggest higher malaria transmission, no direct

relationship between entomological inoculation rate and burden of disease has been established (Snow et al., 1994; Mbogo et al., 1995; Trape & Rogier, 1996). Further research is required to clarify the relationship between the burden of disease and intensity of transmission in different ecological settings.

Research from Thailand on insecticide-treated bednets showed no impact on *P. falciparum* parasitaemia and parasite density in pregnancy (Dolan et al., 1993). In the Gambia, a recent evaluation of the impact of a national impregnated bednet programme on pregnancy outcome in primigravidae showed reduced parasite prevalence in net users in the rainy season but not in the dry season (D'Alessandro et al., 1996, in press). Results from a bednet trial in Bo, Sierra Leone also showed reduced *P. falciparum* rates in all parities (David et al., 1996, in preparation). Malaria in Thailand is perennial but mesoendemic, transmission in the Gambia is seasonal and hyperendemic, whilst in Sierra Leone malaria is perennial and hyperendemic. In all three ecological settings, transmission is less intense than in northern Ghana. In the Gambia and Ghana, net use in primigravidae was less than 50 percent. This evidence suggests that treated nets may work better in areas with less intense transmission (Rosendaal, 1989; Curtis, 1992).

Malaria in pregnancy, especially in primigravidae, in Kassena-Nankana district remains an important public health problem. Although parasite densities were relatively low, parasite rates were very high, especially in primigravidae in both the treated and the no net groups. No placenta smears were done to assess the extent of placental malaria. Nevertheless, placental malaria is most likely to be a serious problem. Parasite rates in pregnancy reported by Brabin (1991), in a recent review of different countries in Sub-Saharan Africa, were much lower than that observed in the study area in both wet and dry seasons. The parasite rates in pregnant women in this study were higher than in Mangochi district in Malawi although seasonal variations in parasite densities by parity were similar (Steketee et al., 1993). Similar data from the Gambia and northern Nigeria indicated a

lower parasite rate and density compared to the study area (Bray and Anderson, 1979; Isah et al., 1985; Fleming et al., 1986).

6.2.2 Effect on *P. falciparum*-related Anaemia in Pregnancy

Insecticide-treated bednets had no discernible impact on malaria-related anaemia in pregnancy. However, there was some indication of higher mean haemoglobin levels in treated net clusters, although this did not achieve statistical significance. The proportion of pregnant women with anaemia (haemoglobin less than 100g/l) was higher in the wet compared to the dry season, varied proportionately with *P. falciparum* parasite rates and reduced with increasing parity. The study did not investigate other causes of anaemia in pregnancy in the study area, apart from malaria. In a similar ecological setting in northern Nigeria, anaemia in pregnancy was due to malaria, nutritional deficiency (iron and folate mainly), or haemoglobinopathies (Isah et al., 1985). Iron deficiency anaemia may also be due to hookworm infestation (Royston, 1982). Although no specific studies have quantified the extent of the problem in the study area, *P. falciparum*-related anaemia is presumed to be a major contributor to anaemia in pregnancy, especially in primigravidae and secundigravidae. The proportion of pregnant women with anaemia in the study area was far above the average of 40 percent reported for West Africa (WHO, 1992a; WHO, 1993d).

Prevalence of parasitaemia and anaemia were strongly associated. Both peaked during the rainy season in the study. The rainy season is also a recognised period of intense farming activity, general food shortage and increased incidence of disease (Roberts et al., 1982). Maximal weight loss in adults, which may be associated with anaemia, also occurs during the preharvest rainy season (Adams, 1995). Most pregnant women attended antenatal clinics in the third trimester, when it may be late to correct anaemia through supplementation. Current literature on malaria in pregnancy in Sub-Saharan Africa suggests that the peak prevalence of *P. falciparum* parasitaemia occurs at 9-16 weeks of

gestation (Brabin, 1983). However, in the study area parasite rates remained high throughout pregnancy declining only modestly in the late third trimester. *P. falciparum* parasitaemia is a major contributor to anaemia in pregnancy in endemic areas (Gilles et al., 1969; Kortmann, 1972; McGregor, 1984; Fleming et al., 1984). Anaemia in pregnancy is also associated with severe morbidity in pregnancy and the postpartum period in the mother. The risk of premature delivery is increased with anaemia (Scholl et al., 1992), which in turn leads to low birth weight. *P. falciparum*-related anaemia is also associated with anaemia in the newborn (Brabin et al., 1990b; Brabin, 1992) and increased mortality in infants (Dolan et al., 1993). Anaemia in infants may play a major, yet to be quantified, role in perinatal and infant mortality in the study area. In the long-term, anaemia in the infant produce alterations in brain function that may result in poor mother-child interactions and impaired learning ability later (Viteri, 1994). Longitudinal studies are required to assess the long-term impact of *P. falciparum*-related anaemia in pregnancy on child survival and development.

Insecticide-treated bednet use in Thailand, the Gambia and Sierra Leone had an impact on haemoglobin levels in pregnancy; reduction in anaemia prevalence in Thailand, reduction in prevalence of severe anaemia in the Gambia and increase in PCV in Sierra Leone. The definition of anaemia in Thailand was based on hematocrit less than 30 percent whilst in the Gambia the definition of severe anaemia was based on haemoglobin less than 80 g/l. In Sierra Leone, the PCV increase in the treated net group ranged from 2.6 percent in primigravidae to 4.0 percent in multigravidae. The extent to which higher effective net use may protect against anaemia in pregnancy in northern Ghana remains to be explored. Anaemia is a recognised major contributor to maternal mortality in the study area (Dollimore et al., 1992, unpublished) and elsewhere (Mati et al., 1971; Kampikaho & Irwig, 1991) and is also a leading cause of child mortality nationally and in the study area (MOH Annual Report, 1994; Kassena-Nankana DHMT Annual Reports, 1992).

6.2.3 Effect on Low Birth weight

There was no significant impact of insecticide-treated bednets on low birth weight in the study. Similar findings were observed in both Thailand and the Gambia in relation to birth weight (Dolan et al., 1993; D'Alessandro et al., 1996, in press). However, in the Gambia, mean birth weight in the rainy season was 130g higher in villages with treated bednets compared to control villages. The differences disappeared when babies classified as premature were excluded. Furthermore, during the dry season, the mean birth weight in control villages was 135g higher. The evidence that treated bednets protected against prematurity was significant.

The causes of low birth weight are multifactorial (Kramer, 1987), including malaria, low prepregnant weight, low caloric intake or weight gain, short stature and general morbidity. Low birth weight is strongly associated with poor immunity and susceptibility to infections, which depress immunity and aggravate existing malnutrition (Chandra, 1988). Newborns with low birth weight are at increased risk of death in infancy (McCormick , 1985). In malaria endemic communities, malaria accounts for a sizeable proportion of low birth weights (Brabin, 1991) and has been shown to account for 25-50 percent of the attributable risk of low birth weight in primiparae. The lack of appreciation of malaria as a major contributor to low birth weight in Sub-Saharan Africa in some studies (Newby & Lovel, 1995) has recently been criticised (Brabin et al., 1996). In terms of infant health and development, the low birth weight infant is disadvantaged in the developing world where the risk of malnutrition, infection and death are markedly increased (Viteri, 1994).

Low birth weight is an important public health problem in northern Ghana and far in excess of the 14 percent average estimated for Africa (Puffer and Serrano, 1987). It correctly reflects the low socio-economic development of the study area, including inadequate and weak health infrastructure. Low birth weight significantly contributes to the high infant mortality in the study area of which 55 percent occurs in the neonatal

period (Binka et al., 1995a). In addition, in Kassena-Nankana district, various dietary restrictions are practised in pregnancy to ensure a "small baby" and easy delivery. Such practices may make an important contribution to negating any beneficial effects of nets, especially in relation to increasing anaemia and low birth weight. Some of the restrictions include not eating eggs, beans and groundnuts (Dollimore et al., 1992, unpublished). Similar dietary restrictions in pregnancy are common practice in other parts of West Africa. Midwives trained to assess gestational age in newborns in the community could not cope with the extra workload and this was abandoned. Hence the proportion of low birth weights due to premature delivery or intrauterine growth retardation could not be determined.

There was strong seasonal variation in mean birth weights which were lower in the rainy season. Increase in mean birth weight was associated with the dry season and more pronounced in the treated net groups in secundiparae and multiparae, although the differences did not achieve significance. Garner and colleagues (1992) have suggested that over-enthusiastic promotion of interventions to increase birth weight may put mothers at risk of difficult deliveries. However, in a chemoprophylaxis in pregnancy trial in the Gambia, this was not observed (Greenwood, et al., 1994).

A system of passive surveillance was used to collect data on abortions, stillbirths and neonatal deaths. There was no difference between the treated and no net groups. This may be due to the underreporting of events although there was no evidence of bias by treatment group. Greenwood and colleagues (1992) estimated that chemoprophylaxis in pregnancy reduced infant deaths by 18 percent in primiparae and 4 percent in multiparae, with an even higher impact on neonatal deaths in primiparae. In areas where health care delivery based on PHC is functional, the use of lay-reporting of pregnancy outcomes and perinatal, neonatal, infant and childhood deaths for surveillance purposes should be explored using culturally sensitive approaches.

6.3 Implications of Research Findings

6.3.1 Possible Reasons for Lack of Effect

As indicated earlier, the lack of public education on insecticide-treated bednets for malaria control and reduction of nuisance biting may have significantly contributed to the lower than expected compliance in net use in pregnant women who had access to the nets. Malaria, as a disease entity is well-understood by trained health workers as a single disease entity with different manifestations (Makemba et al., 1996; Winch et al., 1996). However, the most rural communities have a different understanding of malaria (Agyepong, 1992; Mwenesi et al., 1995; Winch et al., 1996). Cerebral malaria and malaria-related anaemia are often attributed to different causes apart from malaria. Findings of the detailed ethnographic studies that preceded the main bednet trial should have been incorporated into a well-designed public education programme to increase net use (Gyapong et al., 1996). In future, bednet programmes designed primarily for child survival should take into account community perceptions of malaria and anaemia in pregnancy and perceived effectiveness of treated nets in relation to seasonal factors. Such information should be used to design health promotion activities to increase net use at the individual and household levels. In addition, ethnographic studies should be built into programmes to monitor changing perceptions on net use in order to sustain compliance and ensure successful programme implementation.

During net distribution in the treatment clusters, the primary targets were young children and their mothers. Young non-pregnant women or pregnant women without children were therefore not targeted. The adolescent females later became the primigravidae in the supplementary study. Consequently there was a higher proportion of secundigravidae and multigravidae with access to nets compared to primigravidae.

The lack of effect may also be related to entomological indices, as stated earlier in **section 6.2.1**. In the study area, malaria transmission intensity has been estimated at 100-1000 infective bites per person per year [average - 300/person/year] (Armah et al., 1996, in press) compared to 1-10 infective bites per person per year in the Gambia (Thomson et al., 1994) and 10 infective bites per person per year in coastal Kenya [range: 0-60] (Mbogo et al., 1995). During the evaluation of the impact of the national impregnated bednets programme (NIBP) on child mortality in the Gambia (D'Alessandro et al., 1995), it was observed that bednets had no impact in an area with the highest pre-intervention entomological inoculation rate due to very high sporozoite rates in *A. gambiae* combined with low biting rates. Further inquiry revealed low net usage in children compared to the average of 60 percent for the other areas. Bockarie and colleagues (1996) have recently suggested that in areas where *Anopheles* mosquitoes have a late-biting cycle and a low parous rate, exposure to mosquitoes infected with *P. falciparum* during the pre-bedtime period (18:00 to 22:00) is very low and could explain why bednets protect children better in areas of seasonal transmission, where nulliparous females tend to predominate, than in areas of perennial transmission, where parous females are more numerous. The relationship between entomological inoculation rates and reduction in childhood mortality in the different bednet trials is yet to be clarified. The reduction in childhood mortality was 17 percent (Binka et al., 1996) in the study area compared to 25-63 percent in the Gambia (Alonso et al., 1991; D'Alessandro et al., 1995) and 33 percent in coastal Kenya (Nevill et al., 1996).

Another possible explanation for the low compliance may be related to variations in temperature, especially during the hot season when it is unbearably warm indoors and nuisance biting is perceived to be low. In such circumstances, sleeping under nets is not a preferred option. During such periods, most individuals sleep outdoors. Public education could have been planned to motivate community members to mount and sleep in their nets outdoors. A method for hanging nets outdoors had been demonstrated in the pre-trial ethnographic studies. In fact, community members had developed a variety of ingenious

ways for mounting their nets on floors and outdoors. The recent findings from Burkina Faso indicate that insecticide-treated curtains are effective for malaria control and may offer an alternative approach to overcoming the problems of poor compliance related to warm weather and perceived low nuisance biting, provided community members sleep indoors.

6.3.2 Issues in Setting Up Net Programmes

6.3.2.1 Implementation Capacity at Local Level

Despite the lack of evidence for significant beneficial effects of insecticide-treated bednets in pregnancy, net programmes are likely to be established to reduce childhood mortality and morbidity in Sub-Saharan Africa. Consideration of implementation capacity at the local level is important in order to further explore issues on enhancing of the effectiveness of bednets for malaria control in pregnancy. The main trial was implemented with strong and technically competent leadership and with substantial external funding. Future routine net programmes are unlikely to have the same advantages. A recent publication of IDRC (International Development Research Centre) has recognised that donors, researchers and programme managers often fail to recognise the distinction between efficacy and effectiveness (Lengeler et al., 1996). Consequently, the ease with which research findings can be translated into programmes is grossly overestimated. A joint TDR/IDRC initiative has been developed to promote operational research on insecticide-treated netting as a part of the overall process of establishing sustainable control programmes (Lengeler et al., 1996). The initiative is aimed at introducing research results on insecticide-treated netting into programme settings in a more systematic manner.

The decentralised PHC system in Ghana, with the district level as the focus for implementation, offers a great opportunity for introducing insecticide-treated bednet

programmes as part of integrated malaria control. Although DHMTs do not have the level of expertise, competence and external funding available to the main trial, there exists sufficient capacity to establish decentralised insecticide-treated bednet programmes. To succeed, health districts will require direction and re-orientation at the onset and continuing technical support and regular supervision. Based on available evidence, bednet programmes are most likely to be implemented with the objective of improving child survival. Young women, especially those aged between 15 and 30 years, should be targeted since they form the bulk of current and future primigravidae. "Saturation coverage" would be particularly desirable in areas where "benefits", such as bednets, accrue to older members of the community first and to children and young women last. The extent to which public education may minimise "seizure of nets" from children and young women by other members of the family, especially adult males needs to be explored.

Makemba and colleagues (1995) have described the experience of setting up a community-based bednet programme in Bagamoyo district, Tanzania. It was planned and implemented as a partnership between the health sector and the local community based on partial cost recovery. The key actors were the village bednet committees under the supervision of the District Medical Officer. The key issues raised were the selection criteria for membership of the committees, financial accountability and transparency, supervision and feedback by district level health staff, affordability and sustainability of a net programme and the fact that children were the last to gain access to a net. Trust as financial accountability between programme managers and community leaders was a key issue in ensuring programme success. Although successful, continuing attention to the key issues raised was required in order to maintain progress. This programme offers important lessons for bednet programmes in the planning stages. However, experiences need to be adapted to culture-specific contexts.

6.3.2.2 Financing Net Programmes

Nets, insecticide and dipping services were provided free of charge to the treatment clusters in the main trial. The control clusters also benefited at the end of the main trial period. In spite of the free provision, compliance was lower than expected in the treated clusters. As discussed earlier, the unanswered challenge remains whether future routine net programmes in the study area, or elsewhere in Ghana, based on partial cost recovery can maintain sufficiently high levels of bednet use to have a significant public health impact.

Experience from the Gambia with partial cost-recovery for net-impregnation and re-impregnation was negative (D'Alessandro et al., 1995). In 1993 when villages were asked to pay 5.00 Dalasi (US$0.50) per bednet treated, coverage dropped sharply with a reversal to pre-intervention child mortality rates in these villages. Further research on innovative approaches to financing the programme was being accorded top priority. The inability of the NIBP in the Gambia to institute partial cost-recovery has been criticised as being due to lack of partnership between the programme and the public (Shiff et al., 1995), and a failure to promote active public participation in the programme based on local perceptions and priorities about malaria and its control. The criticisms were based on the experiences of the Bagamoyo Bednet Project in Tanzania which recovered part of the cost of the programme from contributions from community members.

Current health sector reforms in Ghana, including introduction of user fees and principles of cost recovery, make the possibility of a publicly-funded insecticide-treated bednet programme remote. However, future net programmes based on direct fees at point of service use (whether purchase of nets or dipping with insecticides) are unlikely to have a significant public health impact, especially in communities with seasonal income. Further research is required to explore financing options and mechanisms for net programmes. Attention should be paid to systems of pre-payment managed at the community level,

flexible payment schemes and establishment of community solidarity funds for health, including net programmes for child survival.

6.3.3 Improving Maternal and Neonatal Health - the Contribution of Malaria Control

Malaria and anaemia in pregnancy and low birth weight are important public health problems in Kassena-Nankana district. Although several recommendations exist for combating these problems, local operational research should be an integral part of any interventions or package of services designed to address them. Issues worth exploring include community perceptions of malaria, anaemia and low birth weight and their impact on the health of mothers and newborns, health care seeking behaviour and factors that hinder or facilitate positive health-seeking behaviour, community perceptions of interventions and feasibility of implementation, and organisation of mother-friendly services in rural communities.

Weekly chloroquine chemoprophylaxis is MOH policy for malaria control in pregnancy. However, no formal evaluation of this has been done to date. Routine antenatal clinics in Kassena-Nankana district did not provide chloroquine chemoprophylaxis in pregnancy during the period of the study. Drugs were available only through the revolving drug fund or "cash and carry" system on a strictly cash basis. Since user fees were a potent deterrent to the utilisation of antenatal services, midwives only treated presumptive malaria cases. The research team was therefore requested not to provide chemoprophylaxis to pregnant women, after much heated discussion, since its continuity could not be guaranteed at the end of the study period. Consequently, the opportunity to discuss strategies to ensure adequate implementation of the MOH policy on free weekly chloroquine chemoprophylaxis was missed as a result of the decision to maintain the status quo to the detriment of all pregnant women, especially primigravidae. Results from the chloroquine ELISA assays also confirmed the low usage of chloroquine by the study participants,

providing confirmatory evidence of non-implementation of MOH policy on weekly chloroquine prophylaxis for all pregnant women.

The effectiveness of weekly chloroquine chemoprophylaxis is reduced by poor compliance (MacCormack & Lwihula, 1983). Factors resulting in poor compliance include irregular drug supply, lack of consistent patient education, bitter taste of drug (sometimes associated falsely with abortifacient effects) and refusal to take drugs when well. In an area of Papua New Guinea where chloroquine resistance was above 30 percent (85 percent of cases being at RI level), pregnant women were followed while attending mobile antenatal clinics and receiving chloroquine chemoprophylaxis (300 mg base weekly). Despite drug resistance, a missed clinic attendance resulted in a 2-fold increase in incidence of *P. falciparum* infection for all parities, indicating that chloroquine was having some effect (Brabin et al., 1990a). Recent evidence from the Cameroon also suggests that, in spite of moderate resistance, supervised weekly chloroquine prophylaxis was highly effective in increasing birth weights in primiparae (Cot et al., 1995). The effectiveness of chloroquine chemoprophylaxis in pregnancy will vary depending on the degree of chloroquine resistance and local socio-cultural factors.

Experience from Sub-Saharan Africa indicates that, despite the increasing number of pregnant women attending antenatal clinics, services have not been re-organised towards providing them with optimal care. In Malawi and Kisumu district of western Kenya, approximately 90 percent of pregnant women perceived malaria to be a threat to the successful outcome of their pregnancies (Schultz et al., 1995). However, in Malawi where, antenatal care includes weekly chloroquine prophylaxis, over 25 percent reported that they did not receive any chloroquine. In Kenya, antimalarial drugs were not routinely provided during antenatal visits resulting in 96 percent of women not receiving chloroquine.

Recent research findings from Malawi (Schultz et al., 1994) and Kenya (Parise et al., 1995) have shown the effectiveness of a 2-dose sulphadoxine-pyrimethamine (SP) fixed combination given in the second and third trimester, and monthly SP given after 20 weeks gestation for malaria control in pregnancy. Use of SP combinations is associated with rare side-effects which may be life-threatening (Phillips-Howard et al., 1989; Phillips-Howard & Bjorkman, 1990). Any antenatal programmes planning to use these regimens need to carefully monitor their side effects. They should not be given to pregnant women with a history of allergy and after 32 weeks gestation due to a theoretical risk of kernicterus in the newborn. In addition, adequate training and procedures should be in place to ensure the prompt recognition and referral of any life-threatening conditions to the appropriate level of care.

Re-organisation of maternal health services, including antenatal care, to provide effective and optimal care, especially malaria and anaemia control, in rural Ghana deserves priority attention. A recent report by WHO/UNICEF (WHO, 1996c) revising maternal mortality ratios upwards for different regions of the world, with the highest mortality and morbidity in Sub-Saharan Africa reinforces the urgent need for reform. Revised package of services for better maternal health should be based on culturally acceptable and effective strategies. These should incorporate operational research assessing programme performance and effectiveness. The impact of high insecticide-treated bednet use in pregnancy, backed by intensive public education on daily net use, in combination with supervised chemoprophylaxis in routine programme settings may be assessed as part of this package of services for better maternal health.

Community-based supervised chemoprophylaxis in pregnancy is a feasible and practical option in rural Africa. In the Gambia, TBAs demonstrated good competence in providing supervised prophylaxis for malaria and anaemia control in pregnancy (Greenwood et al., 1989; Greenwood et al., 1990; Menendez et al., 1994). However, they need regular

supplies, regular updates, technical support and supportive supervision to remain successful.

During the study, field supervisors were trained (lay persons with no specific training in health or midwifery) to weigh newborns in the community. This demonstrated the feasibility of training and equipping lay persons in the community to weigh and record the birth weight of all newborns. In recent years in Ghana, donor-funding has supported the nation-wide retraining of all traditional birth attendants (TBAs). This makes it easier to introduce community-based monitoring of birth weights by TBAs, with the relevant technical support and supervision from the sub-district and district health teams.

6.4 Improving Maternal and Neonatal Health in the wider context of Socio-economic Development in Ghana

The findings of this study raise a more fundamental issue of the need to address maternal and neonatal health problems in the wider socio-economic context of Ghana's development. Dollimore and colleagues (1993) identified the husband's educational level as a protective factor in maternal mortality in Kassena-Nankana district. In addition, membership of a women's group in a village was also protective. Women's groups engage in income-generating activities and can access external support more readily. These provide additional network support for women in times of adversity. Tripp (1981) also observed in Kassena-Nankana (Navrongo) district that mothers who had additional income from trading had the highest proportion of children above the median weight-for-age. Limited research done by the Health Research Unit of the Ministry of Health, Ghana also suggest that improving the income of women results in better health for themselves and their families and greater access to health services (HRU, 1990, unpublished). In the Eastern Region of Ghana, maternal socio-economic status was also positively associated with current weight-for-age and also birth weights of children aged 12 to 18 months (Brugha & Kevany, 1994).

The observation that most pregnant women got up at night to urinate outside their rooms adequately reflected a cultural setting with limited or no sanitary facilities, in-house or outside. Improvements in village sanitation, using low-cost appropriate technology, is urgently needed to improve maternal and child health. In-house sanitary facilities designed such that pregnant women do not get exposed to insect bites whilst urinating deserve priority attention. Such improvements need to be accompanied by public education and community mobilisation to facilitate gradual change of age-old habits inimical to health. Further, improvements in rural housing design using local raw materials, with a view to malaria control preferably using insecticide-treated curtains and other methods to reduce mosquito entry, will need investments in experimental housing to determine what is culturally acceptable and appropriate. Although the north of Ghana has enjoyed free education since independence, school enrolment is far lower than in the south of the country where fees are paid. Free education is not cost free, especially in an economically deprived society where child labour is a much valued economic resource. However, serious efforts need to be made to increase school enrolment, especially for female children, as part of an overall strategy to improve maternal and neonatal health for sustained socio-economic development in Ghana.

General socio-economic development for the north of Ghana, especially paying attention to improved access to education for development, improved housing, improved sanitation and better socio-economic opportunities will require additional investment of national resources. Current neoliberal economic policies in Ghana have increased inequality and poverty, particularly reducing access to health services for the very poor (Waddington & Enyimayew, 1990). Malaria and anaemia in pregnancy and low birth weight are significant public health problems deeply embedded in poverty and socio-economic inequality. Although public health interventions exist which can ameliorate some of the effects, their results will be sustainable only in the context of improved living standards for the rural poor.

Chapter 7

Conclusions and Summary

7.1 Conclusions

1 This study did not demonstrate a significant protective effect of insecticide-treated bednets on malaria, on *P. falciparum*-related anaemia in pregnancy, or on pregnancy outcome, especially low birth weight. This may be due to low effective net use. Thus it cannot be excluded that there is a true effect if nets are used properly and in combination with the use of chamber pots.

2 Insecticide-treated bednets are not recommended as a primary tool for malaria control in pregnancy in northern Ghana. However, in areas where programmes are being planned or implemented, consideration should be given to insecticide-treated bednets in combination with use of chamber pots in addition to existing or new strategies on malaria control in pregnancy. If such opportunities arise, research should be conducted to determine the impact of treated bednets and chamber pot use in pregnancy either alone or in combination with existing policies or new ones, using anaemia (haemoglobin level < 100g/l), placental malaria and low birth weight (birth weight < 2500 gms) as endpoints. Ongoing public education on treated bednets for malaria control should address issues related to net compliance and the need to stay indoors after dark. In newly-established treated bednet programmes, especially those with child survival objectives, careful consideration should be given to targeting all teenage and adolescent females on account of early age at marriage and the cultural practice of concealing first pregnancies until after "official inauguration" as found in northern Ghana.

3 Despite the constraints, this study provided new insights on further issues (see **section 7.2**) worth exploring in order to improve the effectiveness of insecticide-treated bednets for malaria control in pregnancy. Improvements in socio-economic conditions in Kassena-Nankana district will create a sustainable environment for better maternal health. Current health strategies for better maternal health, implemented in isolation from the wider issues of socio-economic development, may be less effective in an environment of pervasive poverty and nutritional adversity. Improvements in living standards should focus on education, income generation for women, improved sanitation and better housing based on culturally acceptable modification of existing local architecture.

4 Malaria and anaemia in pregnancy and low birth weight remain important public health problems waiting to be addressed. Maternal health services, including routine antenatal care, as presently organised, do not address these health problems sufficiently and need to be re-organised based on efficacious interventions. In rural communities, these services should be free, more courteous and mother-friendly, and provided at the "doorsteps" of pregnant woman. Relevant operational research should be built into the process of re-organisation and implementation of the services.

7.2 Issues for Further Research

The issues for future research have been categorised broadly into 5 areas: malaria, anaemia, pregnancy outcome, maternal health services and general issues. Research implementation will critically depend on the availability of funding. Ghana has sufficient research capacity to carry these out, although external collaboration will not be excluded.

The details are:

Malaria

* Epidemiology of malaria in pregnancy in rural Ghana.
* Impact and feasibility of supervised chemoprophylaxis in pregnancy in rural Ghana.
* Social science research on factors influencing net compliance to develop effective communication strategies for saturation net usage in rural Ghana.
* Financing mechanisms for planned bednet programmes for malaria control and its implications in rural Ghana.
* Impact of insecticide-treated bednets, in combination with use of chamber pots and community education, on malaria and anaemia in pregnancy and pregnancy outcome in rural Ghana.
* Impact of supervised chemoprophylaxis, in combination with insecticide-treated bednets, on malaria and anaemia in pregnancy and pregnancy outcome in rural Ghana.
* Relationship between the burden of disease and intensity of malaria transmission in different ecological settings in rural Ghana.

Anaemia

* Epidemiology of anaemia in pregnancy in rural Ghana.
* Contribution of *P. falciparum*-related anaemia to burden of anaemia in pregnancy.
* Long-term impact of *P. falciparum*-related anaemia in pregnancy on child survival and development.

Pregnancy Outcome

* Epidemiology of pregnancy outcome, including birth weights, in rural Ghana.

* Train rural midwives to routinely assess gestational age using the Dubowitz method (Dubowitz et al., 1970) or the Primhak method (Primhak & McGregor, 1989) to determine the proportion of low birth weights which are due to premature delivery or intrauterine growth retardation.

* Train rural midwives to routinely analyse data on pregnancy and pregnancy outcome and use findings for service evaluation.

* Lay-reporting on pregnancy outcome, including birth weights, and perinatal, neonatal, infant and childhood deaths in rural Ghana.

Maternal Health Services

* Impact of user fees, including illegal fees and bribes, on utilisation of maternal health services in rural Ghana.

* Community perceptions of malaria and anaemia in pregnancy and perceived effectiveness of intervention strategies.

* Impact of re-organised maternal health services on malaria and anaemia in pregnancy and pregnancy outcome in rural Ghana.

* Impact of economic and health sector reforms on malaria and anaemia in pregnancy and pregnancy outcome in rural Ghana.

General Issues

* Impact of improved rural housing on malaria in rural Ghana.

* Impact of improved village sanitation, using low-cost appropriate technology, on health of women and children in rural Ghana.

7.3 Summary

- In the context of a major TDR-initiated insecticide-treated bednet trial in northern Ghana, based on a cluster randomisation study design, a supplementary study was conducted to assess the impact of insecticide-treated bednets on malaria and malaria-related anaemia in pregnancy.

- The study area was divided into 96 clusters, a random sample of 48 were given insecticide-treated bednets at the start of the trial and the remainder had theirs at the end of the trial. The trial commenced in July 1993 preceded by 12 months baseline data collection and ended in June 1995. The supplementary study took place from April 1994 to April 1995, with data collection commencing from June 1994.

- The main objective of this study was to assess the effect of insecticide-treated bednets on malaria and malaria-related anaemia in pregnancy in Kassena-Nankana District.

- The major endpoints of the study were haemoglobin levels, *P. falciparum* parasite rates and density, and birth weight.

- Data management was done at the NHRC, Navrongo, Ghana using Foxpro 2.5 for DOS software. Data analysis was done using STATA 4.0 for Windows in LSHTM, London, UK. The outcomes were analysed according to intention to treat. Protection at the individual level was also explored.

- The final sample size obtained gave an estimated power of 80 percent at the 5 percent significance level to detect a reduction in parasitaemia or anaemia in the no net group from 40 percent to 30 percent in the treated net group.

- Odds ratios, with confidence limits, for the different endpoints were as follows:

First clinic visit: Anaemia	- 0.97 (0.86, 1.10)
Severe anaemia	- 0.91 (0.57, 1.43)
Low Parasitaemia	- 1.13 (0.54, 2.38)
High Parasitaemia	- 0.98 (0.85, 1.12)
Combined data: Anaemia	- 0.88 (0.70, 1.09)
Severe anaemia	- 0.80 (0.55, 1.16)
Low Parasitaemia	- 0.89 (0.73, 1.08)
High Parasitaemia	- 1.11 (0.93, 1.33)
Low birth weight: Adjusted (<2500g)	- 0.87 (0.63, 1.19)
Unadjusted	- 0.88 (0.61, 1.24)

Results from individual protection analysis were similar.

- This study did not provide sufficient evidence that insecticide-treated bednets are an effective primary tool for malaria control in pregnancy. Additional research is needed to assess the impact of high effective net usage on malaria, anaemia and pregnancy outcome. Where bednet programmes are being set up for child survival, female adolescents and young adults should be targeted more effectively.

- Operational research on supervised chemoprophylaxis in pregnancy requires urgent attention, preferably in combination with insecticide-treated bednets. Malaria and anaemia in pregnancy and low birth weight are significant public health problems in Kassena-Nankana District, Ghana. These health problems are deeply embedded in the poor socio-economic development of the study area. Improvements in health should be accompanied general improvements in living standards in order to sustain any health gains. The impact of economic and health sector reforms in Ghana on women and children, especially the rural poor, should be reviewed regularly in order to address their negative effects.

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APPENDICES

Appendix I

Assessing the Impact of Permethrin-impregnated Bednet on Childhood Mortality in Kassena-Nankana District, Ghana: Main Bednet Trial

A large-scale WHO/TDR-funded insecticide-treated bednet trial in the Kassena-Nankana district of Upper East Region, Ghana was set up to assess the effect on childhood mortality, was commenced in January 1992 and completed in June 1995. This appendix summarises the design of that trial. The operational base of the study was Navrongo Health Research Centre, Ministry of Health, Ghana. It was designed to evaluate the effect of the introduction of permethrin-impregnated bednets on all-cause mortality in children aged 6 months-4 years, based on a randomised cluster design.

The area was divided into 96 clusters which were geographically contiguous with an average of 120 compounds per cluster. The intervention clusters, comprising half of the total, were randomly chosen on the basis of open ballot by community leaders from the 96 clusters to ensure openness. This random selection was stratified by chiefdom such that each had approximately equal numbers of clusters with and without treated bednets. All the compounds within clusters randomised to intervention were given insecticide-treated bednets in July 1993. Those randomised to the control group were to receive nets at the end of the 2 year follow up period. The sample size for the trial was 18,500 children/year aged 6 months-4 years (Power - 90 percent, p - 5 percent, difference to be detected - 30 percent). The endpoint for the study was death. Verbal autopsy was used to ascertain the cause of death. The trial also included collection of cross-sectional morbidity data during the dry season and end of the rainy season, social surveys on attitudes to bednet use, economic studies on costs and detailed entomological studies.

Objectives

The objectives of the field trial were:

Main Objectives

1. To evaluate the impact of permethrin-impregnated bednets on all-cause mortality rate in the 6 months-4 year age group in the Kassena-Nankana district.
2. To investigate the community's attitudes to insecticide-impregnated bednets.
3. To calculate the cost per person protected and the cost per death prevented.

Secondary Objectives

1. To estimate the impact of malaria-specific and other cause-specific mortality rates in the 6 months-4 year age group.
2. To measure the effects of the impregnated bednets on longevity, human biting behaviour and sporozoite rates of the anopheles vector population.
3. To estimate the impact on malaria parasite rates, parasite density, haemoglobin levels and probable malaria illness.

Enumeration and mapping

All compounds and important landmarks were mapped onto a 1 in 5000 map to enable easy access to and identification of all compounds in the study area, by updating those used in the Ghana VAST studies. A census was carried out to update the basic demographic characteristics of all members of the compounds. The unique compound numbers which were assigned to each compound in the Ghana VAST studies were maintained, both on the walls of the compounds and within the demographic databases.

Community-based Impregnation of Bednets

Village-level meetings were held at which net hanging and net impregnation were demonstrated. Community members were allowed to seek clarification on issues they did not understand. Net distribution was done on the basis of a list of members of a

compound and subsequently impregnated with permethrin. Compound members were asked to provide water after which a fieldworker (from Navrongo Health Research Centre - NHRC) demonstrated the impregnation procedure and then invited those given nets to repeat it. 20 ml of permethrin (50 percent EC, ICI Public Health) was added to 500 ml of water in a plastic bowl, mixed thoroughly and the net soaked in it. The excess liquid was wrung out and the bednets laid on beds or sleeping mats to dry, away from any source of drinking water or direct sunlight. The maximum number of nets impregnated in a bowl at a time was five. All those involved in the net impregnation were supervised to wash their hands with soap (provided by the fieldworker) and water. The dose of permethrin on the netting was estimated at 500mg/m^2. All treated bednets were marked with indelible ink and counted to assess the number of bednets treated per compound and village. At another point, washable ink was used to mark the bednet to detect how often it was washed after impregnation.

Impregnation of bednets was repeated in January and July each year till the end of the field trial. In practice, not all compounds in the bednet clusters received adequate numbers of bednets due to unexpected shortfall. Hence, priority was given to young children and their mothers. The bednets were made of coloured 100 denier nylon, rectangular in shape, with length 180cm, width 190cm and height 150cm for large groups sleeping together and a small size (100cm x 180cm x 150cm) for smaller groups.

Collection of entomological data, including insecticide resistance

Data on entomological indices for the study area were collected for the duration of the field trial. The details of entomological work summarised below is based on proposed work and is as follows: Six sentinel sites were developed in the district; west, south and north-east. In each area, a sentinel site was located in a bednet and control clusters. Mosquito collection was carried out on a monthly basis from April 1992. The entomology teams visited each of the paired sites once a month for one week. Mosquitoes were sampled twice during that week using:

1. Human bait catches (HBC) - indoors from 7pm to 6am and outdoors from 7pm to 10pm and from 4am to 6am.
2. Pyrethrum Spray Catches (PSC) the window Exit Traps (WET) in four designated bedrooms.
3. CDC miniature light trap (LTC) catches set beside untreated bed nets in 4 other designated bedroom in the study area.

In addition, untreated bednets with holes in them were set up to catch mosquitoes for insecticide resistance tests based on standard WHO methodology.

Sporozoite species identification and sporozoite rate by ELISA

The adult female mosquitoes caught from CDC miniature light traps, were stored under silica gel and sent to the Noguchi Memorial Institute for Medical Research (NMIMR) for ELISA tests. These tests determined the presence of sporozoites and also identified the source of the blood meal. The thorax and abdomen of each mosquito was separated from the other body parts. The thorax was used for the sporozoite species identification. The species of plasmodium present, *P. falciparum*, *P. malariae* or *P. ovale* was determined by ELISA with monoclonal antibodies specific for those sporozoite species. The thorax was crushed in coating buffer and used as coating agent for the ELISA. All ELISA tests were done in triplicate with the median value taken as the true value. 12 wild male mosquitoes were used as negative controls on each plate. The cut-off point for judging a mosquito to be positive was mean + 3SD of negative controls.

Identification of mosquito blood meal.

The freeze-thawed and crushed abdomen of the dried female mosquitoes was used as coating antigen in an ELISA for the determination of the origin of the blood. Human blood meal origin was detected by the use of horse-peroxidase goat anti-human immunoglobulin antiserum. Those of other animal origins was identified by the substitution of the anti-human conjugate with conjugated sera directed against immunoglobulin of the cow. This was being done on a monthly basis.

Determination of key (vectorial transmission) rates.

From July 1992 to June 1993 (pre-intervention year), indoor and outdoor human bait catches and the pyrethrum spray catches combined with exit trap catches were used to calculate two independent estimates of man-biting rate. CDC miniature light trap catches were used to assess vector density.

Adult mosquito susceptibility to permethrin and DDT.

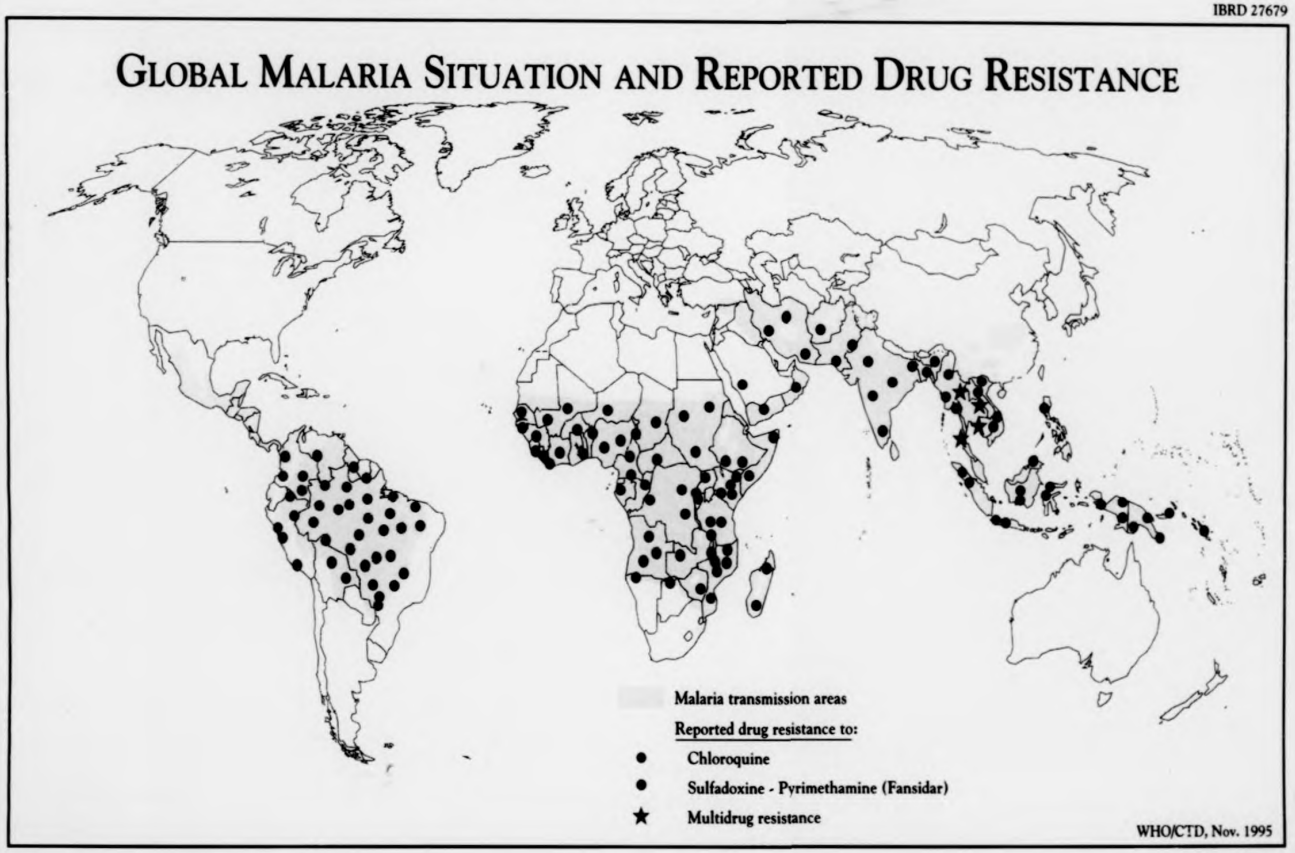
Standard WHO adult susceptibility tests was carried out every year with well-fed female mosquitoes caught using the bednets with holes made in them. If survivors were found, an attempt was made to rear the progeny and tests carried out to determine inherited resistance, if any.

Bioassay to test the persistence of permethrin residues on net using WHO bioassay cones.

Twenty-seven (27) permethrin-treated bednets were retrieved from the treated areas in weeks 2, 4, 8 and 12 after impregnation to evaluate the residual effect of permethrin. The retrieved nets were packaged, labelled and sent to NHRC for the bioassays. Retrieved bednets were replaced with newly impregnated ones. The assays were done on an improved version of the WHO cone. Briefly, a portion of the net to be assayed was drawn around a ball of fixed volume constructed from 2 very thin but sturdy metal rings and 20 blood fed mosquitoes caught by aspiration on the morning of the assay were introduced into the space created by the ball. After exposure for 3 minutes, they were retrieved into labelled holding cups and given 10 percent sugar solution and left undisturbed for 24 hours after which mortality was recorded. The average of 4 readings was taken as the true value. Controls were also set up with non-impregnated nets. Four assays were carried out on different parts of each net.

Appendix II - Global Malaria Situation and Reported Drug Resistance: 1993

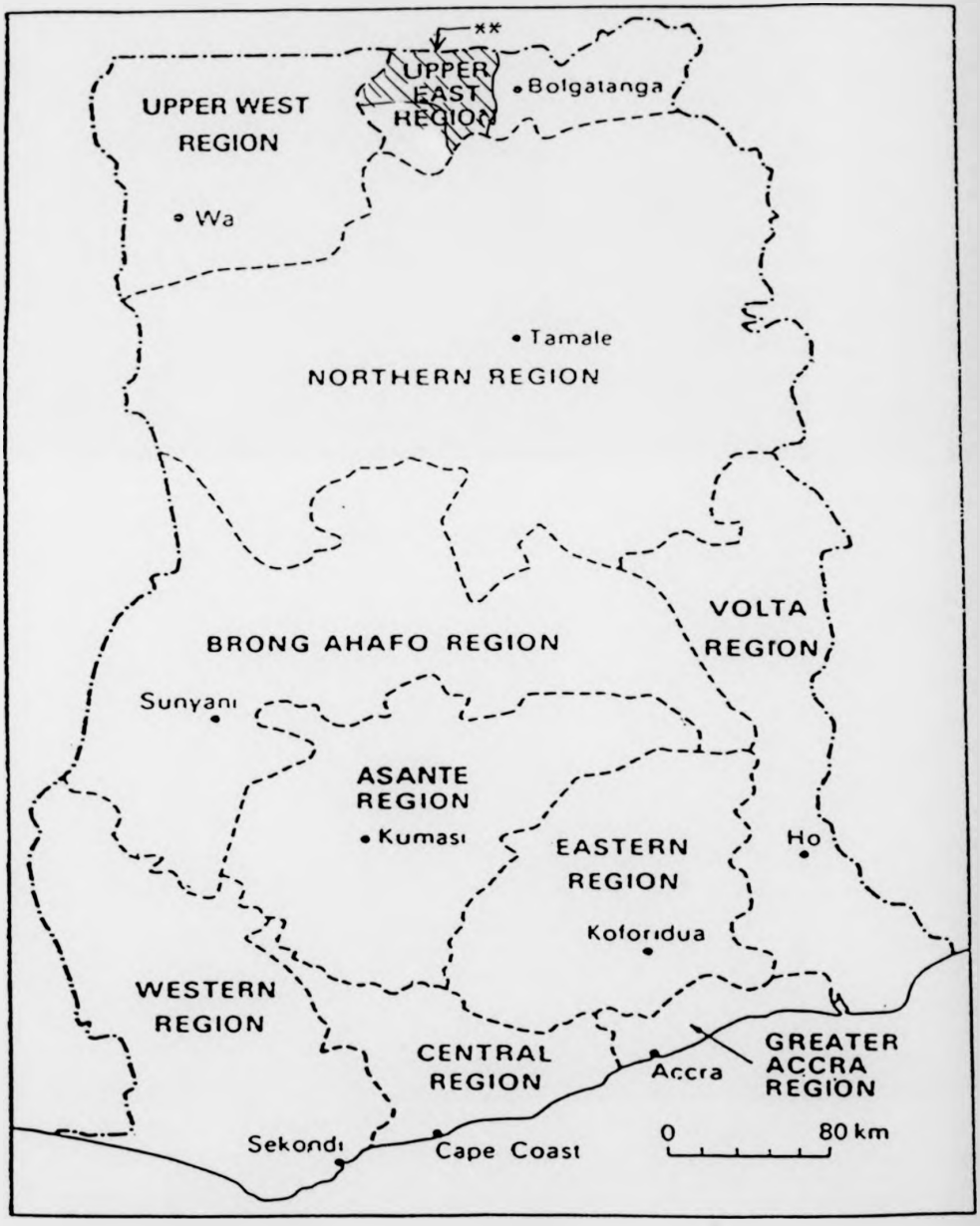
IBRD 27679



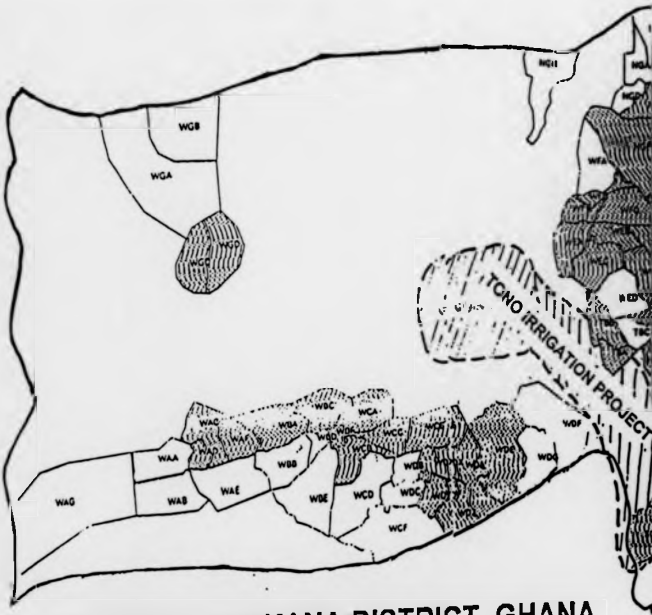
JANUARY 1996

GHANA

THE ADMINISTRATIVE REGIONS



** Kassena-Nankana District - study area

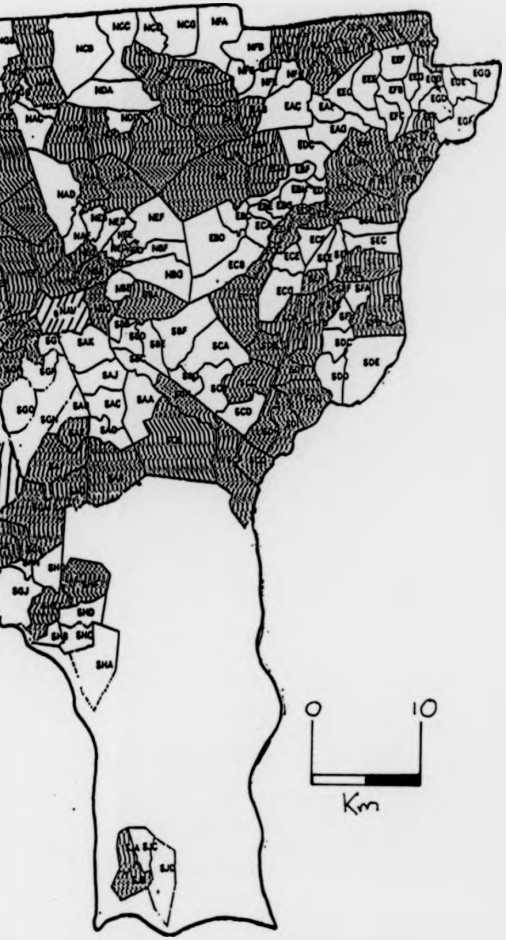


KASSENA-NANKANA DISTRICT, GHANA
Study Area for Main Bednet Trial

BedNet Distribution

NDSS Clusters
- NOT DEFINED (NAV)
- TREATED
- CONTROL

Appendix IV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Appendix V

Data Collection Tools Used in Field Study on Malaria Control in Pregnancy

Form No MIPF01

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
INTERVIEW OF PREGNANT WOMEN
FORM 01.

Time Started .....

A. Identification

Study Number (TO BE COMPLETED BY NB)	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of Interview	DINT
Fieldworker Code	FWCODE

1.0 Position of Visit | 1 ... Enrolment | 2 ... 36 WEEKS | PVISIT

(FOR 36 WEEKS VISIT, MARK NA FOR 1.1 TO 1.31.2)

1.1 Name of Husband.....

1.2. Name of Compound Head.....

1.3. Is there a TBA in this community? | 1.....Yes | 2 ..... No | 9 .... NK | COMMTBA

1.4. Name of TBA .....

(IF NO TBA, ENTER NA)

1.5 Are you pregnant now? | 1.... Yes | 2 ..... No | 9 ..... NK | PREGNOW

(IF YES, CONTINUE INTERVIEW. OTHERWISE STOP!)

1.6. Apart from current pregnancy, how many times have you been pregnant? NOPREG

NUMBER OF PREGNANCIES
(IF NONE, ENTER 00)

1.7 Take Pregnancy History

	Live Birth			
	Sex (M, F)	Gestation (in months)	Stillbirth (SB)	Abortion (AB)
Pregnancy Order				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

(Start From The Most Recent Birth of Woman)

1.8. How many months ago did you have your last menstrual period? LASTBLD

01	02	03	04	05	06	07	08	09	NK

(CIRCLE APPROPRIATE NUMBER OF MONTHS)

B. BACKGROUND INFORMATION

1.9. Have you ever been to school?

1 .... Yes	2 ... No

BSCH

1.10. Highest educational level attained by respondent

1. Primary	2. Middle/JSS	HEDU
3. Secondary/Tertiary	8. NA	

1.11. What is your religious denomination?

1 Traditional	2 Christianity	RELDENO
3 Islam	4 Others (specify)	

1.12. What is the main occupation you engage in?

1. Farmer/housewife	2. Trader	MAOCC
3. Other (specify)		

1.13. What is the marital status of respondents?

1 Married	2 Single	MARSTAT
3 Divorced	4 Widowed	

1.13.1 Are you the only wife of your husband?

1. Yes	2. No	WFSTAT
8. NA		

1.13.2 What is your rank among your husband's wives? [ ][ ] RANK

(IF ONLY WIFE, ENTER 88)

C. CURRENT PREGNANCY

1.14. Have you felt your baby move today? 1.... Yes | 2...No | 9.. NK FETMOVE

1.15. Are you well today? 1 .... Yes | 2 .. No | 9 .... NK MATWELL

(IF NO, REFER TO NEAREST HEALTH FACILITY)

1.16. What type of medication have you been using during this pregnancy?

1. Modern medicine	2. Traditional herbs	
3. Enemata	4. (1 and 2 or 1 and 3)	TYMED
5. None of above	8. NA	

1.17. What type of health worker has seen you during this pregnancy?

1. Midwife	2. Doctor	
3. Nurse	4. Medical Assistant	ANCARE
5. No one	6. Other (Specify)	
8. NA	9. NK	

1.18. How many times have you been seen by him/her? [ ][ ] ANCVISIT

(IF NONE, ENTER 88)

1.19. Number of Tetanus Toxoid injections ever received by pregnant woman

		TTNO

(CHECK YELLOW CARD FOR DETAILS)

(IF NONE, ENTER 88)

1.20. Have you had any complications in this pregnancy?

1.20.1Bleeding	1.Yes/spont	2...Yes/probed	3.....No	BLEED
1.20.2. Paleness	1.Yes/spont	2...Yes/probed	3.....No	PALE
1.20.3. Swollen feet	1.Yes/spont.	2...Yes/probed	3..... No	SWOFEET
1.20.4 Other (specify)	1.Yes/spont.	2...Yes/probed	3..... No	OTHERS

D. ILLNESS IN THE PAST ONE MONTH

1.21. Apart from today, have you been sick in the past one month? | 1 ..... Yes | 2 .. No | SICKMTH

(IF NO, MARK 1.22 TO 1.25 NA)

1.22. What type of sickness did you have? PROBLEM

ASK THE PREGNANT WOMAN TO DESCRIBE HER PROBLEM AND THEN PROBE FOR OTHER VARIABLES

1.22.1. Fever	1.Yes/spont	2.Yes/probed	3. No	FEVER
1.22.2. Headache	1.Yes/spont	2.Yes/probed	3. No	HEADACHE
1.22.3. Dizziness	1 Yes/spont	2. Yes/probed	3. No	DIZZINESS
1.22.4. Cough	1.Yes/spont	2.Yes/probed	3. No	COUGH
1.22.5. Frequent urinating	1.Yes/spont	2. Yes/probed	3. No	FURINAT
1.22.6. Get tired easily	1.Yes/spont	2. Yes/probed	3. No	TIRED
Breathlessness 1.22.7. At rest or exertion	1 Yes/spont	2. Yes/probed	3. No	EXERTION
Bleeding 1.22.8.1 per vagina	1.Yes/spont	2. Yes/probed	3. No	PERVAGINA
1.22.8.2 per rectum	1Yes/spont	2.Yes/probed	3. No	PER RECTUM
1.22.9. other (specify)	1 Yes/spont	2. Yes/probed	3. No	OTHER

1.23. Were you given any treatment? | 1.....Yes | 2 .... No | 8... NA | TREAT

1.24. Who treated you when you were sick?

1. Self	2.Relatives	
3 .TBA	4. Traditional healer.	WTREAT
5. Health worker .	6. Others (Specify)	
8. NA		

1.25. What treatment did you receive?

1. Modern medicine	2. Traditional herbs.	
3. Enemata	4 . (1and 2 or 1 and 3)	TREATRECD
5.None of above	8. NA	

E. USE OF BEDNET

1.26. Do you have a bednet ? | 1 ..... Yes | 2 .... No | OWNNET

1.27. If No, do you share a net with someone? | 1....Yes | 2.... No | 8 .. NA | SHARENET

(IF NO, MARK 1.28 & 1.29 NA)

1.28. Did you sleep under your net last night? | 1 ... Yes | 2 ..No | 8..NA | DSLEEP

1.29. If No, please give me any reasons for not sleeping under your net last night

1. Warm weather	2. No mosquitoes	WSLEEP
3. Others (specify)	8. NA	

1.30. What time did you go to bed last night? | | | | | BEDTIME

1.31. Did you get up last night to urinate? | 1 ... Yes | 2.... No | URINATE

1.32. Where do you usually urinate at night in the compound?

1. Outside compound	2. In kraal
3. Chamber pot	4. Bath house
5. Other (specify)	8. NA
9. NK	

WURINATE

1.33. At what time do you usually get up from bed in the morning?

1. Before 1st cockcrow (4-5 am)	2. Dawn (5-6 am)
3. After sun rise (6-7 am)	4. Other (specify)
8. NA	9. NK

TWAKE

Time ended .....

1.34. CERTIFIED CORRECT BY DATE...../...../...../ CCB

Form No MIPF02/Rev.1

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
CLINICAL EXAMINATION
FORM 02

Time started .....

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of Examination	DEXAM
Fieldworker Code	FWCODE

2.0 Clinical Exam [1 .... ENROLMENT] [2 ... 36 WEEKS] CLINVST

B. PHYSICAL EXAMINATION

2.1. Height (cm) [ ] . [ ] HGTCE

2.2. Weight (kg) [ ] . [ ] WGTCE

2.3. Mid-arm circumference (cm) [ ] . [ ] MACCE

2.4. Blood pressure [ ] / [ ] mm Hg BPCE

2.5. Axillary temp [ ] . [ ] ^{0}C AXTEMPCE

2.6. Pallor [1 ... Yes] [2 ..... No] PALLOR

2.7. Nipple [1.... Normal] [2 ..... Everted] [3 .... Other (specify)] NIPPLE

2.8. Abdominal girth (cm) at umbilicus [ ] . [ ] ABDGIRTH

2.9. Symphysio-fundal height (cm) [ ] . [ ] SYMHTCE

2.10. Presentation
[1 .... Cephalic] [2 .. Transverse] [3 ... Breech] [4 .... Other (specify)] LIE

2.11. Estimated gestation in weeks [ ] GESTCE

2.12. Spleen (cm) [ ] . [ ] SPLEENCE

2.13. Liver (cm) [ ] [ ] LIVERCE

2.14. Varicose vein	1 ... Yes | 2 ..... No	VVEINCE

2.15. Swollen feet

2.15.1 Left	1 .... Yes	2 .... No	LEFTCE
2.15.2. Right	1 ..... Yes	2 ..... No	RIGHTCE

C. LABORATORY

2.16. Have you had 'fever' in the past 7 days?
[INTOLEGERE/YERA LONNA PUA/PAA]

1 .... Yes | 2 ..... No | 9 . NK — FEVER7CE

2.17. HAEMOGLOBIN [ ][ ][ ] gm/l HBCE

2.18. TREATMENT GIVEN FOR MALARIA GIVEN 1 .... Yes | 2 .... No — FEVTRTCE

2.19. COLLECTION OF SPECIMEN

2.19.1. BLOOD	1 .. Yes	2 ... No	BLOOD
2.19.2. STOOL	1.. Yes	2 ... No	STOOL
2.19.3. URINE	1 ...Yes	2 .... No	URINE
2.19.4.OTHER (SPECIFY)	1... Yes	2 .... No	OTHER

2.20. Laboratory No. [ ][ ][ ][ ] LABNOCE

2.21. CERTIFIED CORRECT BY DATE...../...../...../ [ ][ ] CCB

Form No MIPF03

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
ANTENATAL CLINIC ATTENDANCE MONITORING
FORM 03

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of ANC VISIT	DANC
Fieldworker Code	FWCODE

3.0 Position of Visit [1...1ST] [2...2ND] [3..3RD] [4....4TH] [5..5TH] VSTANC

B. ANTENATAL CLINIC ATTENDANCE

3.1. Name of attending midwife ..... MWNAME

3.2. Estimated gestation [ ][ ] GESTANC

3.3. Name of clinic ..... CLINAME

3.4. Was she refered? [1 ..... Yes] [2 .... No] REFANC

C. ROUTINE DRUGS GIVEN

3.5.

Chloroquine...	No of tablets	TCHLOR
Pyrimethamine...	No of tablets	TPYRIM
Iron tablets	No of tablets	TIRON
Folic acid...	No of tablets	TFOL
Multivitamin ...	No of tablets	TMULT

3.6. CERTIFIED CORRECT BY DATE...../...../...../ [ ][ ] CCB

Form No. MIPF04/Rev.1

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
DELIVERY - FORM 04

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of VISIT	DDELVIS
Fieldworker Code	FWCODE

B. PLACE AND TIME OF DELIVERY

4.1. Place of Delivery

1. Home	2. Health Centre	PDELVIS
3. Hospital	4. Other (Specify)	
8. NA		

4.2. Date of delivery [ ][ ][ ][ ][ ][ ] DDELIV

4.3. Time of delivery [ ][ ][ ][ ] TDELIV

4.4. Attendant at delivery

1. Compound member	2. Trained TBA	ATDELIV
3. Untrained TBA	4. Midwife	
5. Doctor	6. Other (specify)	

(IF DELIVERY DONE BY MIDWIFE OR DOCTOR, PUT DOWN NA FOR 4.5)

4.5. Time of visit by midwife [ ][ ][ ][ ] TMWVIS

C. PHYSICAL EXAMINATION AT DELIVERY
MOTHER

4.6 Weight (kg) [ ][ ][ ] . [ ] WGTD

4.7. Mid-arm circumference (cm) [ ][ ] MACD

4.8. Blood pressure [ ][ ][ ] / [ ][ ][ ] mm Hg BPD

4.9. Axillary temp [ ][ ] . [ ] °C AXTEMPD

4.10. Pallor | 1 .... Yes | 2 ..... No | PALLORD

4.11. Nipple | 1.. Normal | 2 ... Everted | 3.... Other (Specify) | NIPPLED

4.12. Symphysio-fundal height (cm) | | | . | | SYMHTD

4.13 Spleen (cm) | | | . | | SPLEEND

4.14 Liver (cm) | | | . | | LIVERD

4.15. Varicose vein | 1 ..... Yes | 2 ..... No | VVEIND

4.16 Swollen feet

4.18.1. Left	1 .. Yes	2 .... No	LEFTD
4.18.2 Right	1 .. Yes	2 ... No	RIGHTD

D. DELIVERY FINDINGS
MATERNAL

4.17. Did you have any complication during delivery? COMPDEL

1. Postpartum haemorrhage	2. Fits
3. Fever	4. None
5. Other (Specify)	9. NK

4.18. Midwife should describe the condition of the mother at time visit CONMUM

1. Very good	2. Good
3. Average	4. Poor

NEWBORN

4.19. Is the baby alive today? | 1 .... Yes | 2 .... No | TALIVE

4.20. If NO, was baby born alive? | 1 ... Yes | 2 ..... No | 8 .... NA | BALIVE
(IF BABY DIED AFTER BIRTH, INFORM FIELD SUPERVISOR. MARK 4.21 TO 4.32 NA)

4.21. If NO, was baby a stillbirth? | 1..... Yes | 2 ... No | 8 ... NA | SBIRTH

4.22. If stillbirth, what was it? | 1 .... Fresh | 2 .. Macerated | 8. NA | SBWHAT
(IF STILLBIRTH, MARK 4.23 TO 4.32 NA)

4.23. Birth weight of newborn (gm) | | | | | BTHWGT

4.24 Birth length of newborn (cm) | | | . | | BTHLGT

4.25. Head circumference of newborn (cm) | | | . | | BTHEADC

4.26. Chest circumference (cm) | | | . | | BCHCIRC

4.27. Dubowitz score | | | DSCORE

4.28. Gestation | 1 ..... Term | 2 ... Preterm | NGEST

4.29 Date of birth | | | | | | | NDOB

4.30. Sex | | SEX

4.31. Name of child .....BNAME

E. LABORATORY

4.32. Have you had 'fever' in the past 7 days?
[INTOLEGERE/YERA LONNA PUA/PAA]

1 ... Yes	2 ... No	9 .. NK	FEVER7D

4.33. Haemoglobin [ ][ ][ ] gm/l HBD

4.34. Treatment given for malaria given | 1 .... Yes | 2 .... No | FEVTRTD

4.35. Collection of specimen

4.35.1. Blood	1 .. Yes	2 ... No	BLOODD
4.35.2. Stool	1 .. Yes	2 ... No	STOOLD
4.35.3. Urine	1 ...Yes	2 .... No	URINED
4.35.4. Other (Specify)	1... Yes	2 .... No	OTHERD

4.36. Laboratory No. [ ][ ][ ][ ] LABNOD

4.37. Certified correct by Date...../...../...../ [ ][ ] CCB

Form No. MIPF05

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
POST PARTUM FOLLOW UP FOR DAY 28
FORM 05

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of visit	DVSTPP
Fieldworker Code	FWCODE

B. PHYSICAL EXAMINATION - MOTHER

5.1. Weight (kg) [ ][ ][ ] . [ ] WGTPP

5.2. Mid-arm circumference (cm) [ ][ ] MACPP

5.3. Blood pressure [ ][ ][ ] / [ ][ ][ ] mm Hg BPPP

5.4. Axillary Temp [ ][ ] . [ ] ^{0}C AXTEMPPP

5.5. Pallor [1 ..... Yes] [2 ..... No] PALLORPP

5.6. Nipple [1 ... Normal] [2.... Everted] [3 .....Other(specify)] NIPPLEPP

5.7. Spleen (cm) [ ][ ] . [ ] SPLEENPP

5.8. Liver (cm) [ ][ ] . [ ] LIVERPP

5.9.. Varicose vein [1 ..... Yes] [2 ..... No] VVEINPP

5.10 Swollen feet

5.10.1Le ft	1 .... Yes	2 .... No	LEFTPP
5.10.2 Right	1 .... Yes	2 .... No	RIGHTPP

5.11. Lochia	1 .... Clear	2 .... Dark	3 ..... Blood stained	4 ...Other (specify)	LOCHIA

C. PHYSICAL EXAMINATION OF NEONATE

(CHECK IF BABY IS ALIVE OR DEAD, IF DEAD INFORM FIELD SUPERVISOR. MARK 5.12 TO 5.20 NA)

5.12. Weight of baby (gms) [ ][ ][ ][ ] BWGT

5.13. Axillary Temp [ ][ ] . [ ] ^{0}C NAXTEMPPP

5.14. Length of baby (cm) [ ][ ] . [ ] BLGTPP

5.15. Cord	1 .... Clean	2 .... Septic	3 ... Other (Specify)	CORDPP

D. QUESTIONS TO MOTHER

5.16. Does baby suckle well?	1..... Yes	2 ..... No	SUCKLE
5.17. Does baby sleep well?	1 .... Yes	2 .... No	WSLEEP
5.18. Does baby feel "hot"?	1 ..... Yes	2 ..... No	FHOT

5.19. Does mother want to discuss any other issues about child? ISSUES

.....

.....

.....

.....

.....

.....

5.20 Does mother complain of been sick? 1 .... Yes | 2 .... No MSICKPP

(IF YES, REFER TO THE NEAREST HEALTH FACILITY)

E. LABORATORY

5.21. Have you had 'fever' in the past 7 days?
[INTOLEGERE/YERA LONNA PUA/PAA]

1 .... Yes	2 ..... No	9 . NK	FEVER7PP

5.22. Haemoglobin [ ][ ][ ] gm/l HBPP

5.23. Treatment given for malaria given

1 .... Yes	2 .... No	FEVTRTPP

5.24. Collection of specimen

5.24.1. Blood	1 .. Yes	2 ... No	BLOODPP
5.24.2. Stool	1.. Yes	2 ... No	STOOLPP
5.24.3. Urine	1 ...Yes	2 .... No	URINEPP
5.24.4. Other (Specify)	1... Yes	2 .... No	OTHERPP

5.25. Laboratory No. [ ][ ][ ][ ] LABNOPP

5.26. CERTIFIED CORRECT BY DATE...../...../...../ [ ][ ] CCB

FORM NO. MIPF06

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
INTERVIEW FOR MISCARRIAGE
FORM 06

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of visit	DVSTMIS
Fieldworker Code	FWCODE

B. DETAILS OF MISCARRIAGE

6.1. Date of miscarriage [ ][ ][ ][ ][ ][ ] DMISS

6.2. Estimated gestation of pregnancy at miscarriage [ ][ ] GESTPREG

6.3. Did you have any complications during or after the miscarriage?

1 .... Yes	2 ..... No	8 ..... NA	MISCOMP

6.4. If Yes, what was the complication?

1. Bleeding	2. Sepsis	YCOMP
3. Other (Specify)	8. NA	

6.5. If you bled, for how many days did you bleed? [ ][ ] MISBLED
(IF DON'T KNOW, ENTER 99)

6.6. Did you have fever just before the miscarriage?

1 ..... Yes	2 ..... No	8 .... NA	9 ..... NK	MISFEV

6.7. Did you attend antenatal clinic before the miscarriage?

1 .... Yes	2 .... No	8 .... NA	MISANC

6.8. Ask woman to describe events leading to miscarriage? EVENTMIS

.....

.....

.....

.....

6.9. Certified correct by Date...../...../...../ [ ][ ] CCB

FORM NO. MIPF07

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
INTERVIEW FOR NEONATAL DEATHS
FORM 07

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth of Mother	YOB
Date of Interviews	DINTND
Field Supervisor Code	FSCODE

B. DETAILS OF NEONATAL DEATH

7.1 Date of Birth [ ][ ][ ][ ][ ][ ] NDOB

7.2. Date of Death [ ][ ][ ][ ][ ][ ] NDOD

7.3. Allow mother or interviewee to describe in own words events leading to neonatal death .
EVENTND

.....

.....

7.4. What illnesses did child have the before death?

7.4.1. 'Fever'	1 .. Yes/Spont	2 ..Yes/Probe	No. 3	NDFEVER
7.4.2. Inability to open mouth/stiffness	1 .. Yes/Spont	2. .. Yes/Probe	No. 3	NDMOUSTIF
7.4.3. Stiffness of neck	1 ... Yes/Spont	2 .. Yes/ Probe	No..3	NDSNECK
7.4.4. Yellowish discoloration of eyes	1 ... Yes/Spont	2 .. Yes/ Probe	No..3	NDYEYES
7.4.5. Septic cord	1 ... Yes/Spont	2 .. Yes/ Probe	No..3	NDSCORD
7.4.5. Vomiting/ frequent stools	1 ... Yes/Spont	2 .. Yes/ Probe	No..3	NDVSTOOL
7.4.6. Rash	1 ... Yes/Spont	2 .. Yes/ Probe	No..3	NDRASH
7.4.7. Other (specify)	1 ... Yes/Spont	2 .. Yes/ Probe	No..3	NDOTHER

7.5. CERTIFIED CORRECT BY DATE...../...../...../ [ ][ ] CCB

Form No. MIPF08

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
INTERVIEW FOR MATERNAL DEATH
FORM 08

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of interview	DINTMD
Field Supervisor Code	FSCODE

B DETAILS OF MATERNAL DEATH

8.1. Name of Respondent ..... RESNAME

8.2. Relation to Deceased

1. Husband	2. Mother	RELMDED
3. Sister	4. Brother	
5. Other (Specify)		

8.3. Date of death MDOD

8.4. Did woman die during pregnancy? 1 ... Yes | 2 .... No | 8. NA WPREG

8.5. In what week of gestation did she die? GESTMD

8.6. Did woman die during labour? 1 .... Yes | 2 ..... No | 8. .... NA LABMD

8.7. Did woman die after delivery? 1 .... Yes | 2 ..... No | 8. .... NA DELMD

8.8. How long after delivery?
Days DDAY
Weeks DWEEK
NA

8.9. Allow interviewee to narrate events leading to maternal death. EVENTMD

.....

.....

8.10. Presumed cause of maternal death from interviewee point view?

8.10.1. Failure to delivery	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	DELIVF
8.10.2. Bleeding during pregnancy	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	BLEEP
8.10.3. Bleeding during labour	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	BLEEL
8.10.4. Bleeding after delivery	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	BLEED
8.10.5. Retained placenta	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	RPLA
8.10.6. Fever	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	FEVERMD
8.10.7 Anaemia	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	ANAEMD
8.10.8. Fits	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	FITSMD
8.10.9. Other (specify)	1 ... Yes/Spont.	2 ... Yes/Probe	3 .. No	OTHERMD

8.11. CERTIFIED CORRECT BY DATE...../...../...../ CCB

Form No. MIPF09

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY.
LABORATORY (PREGNANT WOMAN)
FORM 09

IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date Specimen was taken	LABVST
Fieldworker Code	FWCODE

9.1. Laboratory no..... LABNO

9.2. Staff code SCODE1

LABORATORY WORK

9.3. Date DTEST

9.4 Haemoglobin g/l HBL

9.4.1 Urine sugar 1 .. Yes | 2... No | 8 .. NA SUGL

9.4.2 Urine protein 1 ... Yes | 2 .. No | 8 .. NA PROTL

9.5. P. FALCIPARUM (ASEXUAL FORM) FALCAC
[PARASITE COUNT PER 200 LEUKOCYTES]

9.6. P. FALCIPARUM (ASEXUAL FORM) FALCAOC
[PARASITE COUNT PER 2.500 PER 200 LEUKOCYTES]

1 .... Yes | 2 ..... No

9.7. P. FALCIPARUM (GAMETOCYTES)..... FALCGC

9.8. P. MALARIAE | | | | MALC

9.9. P. OVALE | | | OVALEC

9.10. P. VIVAX | | | VIVAXC

9.11. Certified correct by: DATE...../...../...../ | | | CCB

Form No. MIPF10

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY.
PREGNANT WOMAN REFERRAL FORM
FORM 10

A. IDENTIFICATION

Study Number	STUDNUM
Cluster Code	CLUSCOD
Compound Name & No.	COMPNUM
Name of Pregnant Woman	NAME
Year of Birth	YOB
Date of referral	DREF
Fieldworker Code	FWCODE

10.1 Type of Referral | 1. Routine | 2. Emergency | REFTYPE

10.2 Name of clinic ..... CLINAME

10.3 Health problem for which referral is being made

1. Bleeding in pregnancy	2. Feels tired easily (Anaemia)	
3. Swollen feet	4. Losing liquor	REFPROB
5. Fever	6. Other (Specify)	

[FILL THE FORM IN DUPLICATE, GIVE A COPY THE PREGNANT WOMAN AND THE OTHER TO YOUR SUPERVISOR]

Part II

[TO BE COMPLETED BY ATTENDING MIDWIFE. TO BE COLLECTED BY FIELD SUPERVISOR]

10.4 Seen by (Name of attending midwife) ..... RMWNAME

10.5 Health problem found at examination REFEXAM

.....

.....

10.6 Treatment given REFTRT

.....

.....

10.7 Date | | | | | | | DATETRT

Form No MIPF11

NAVRONGO HEALTH RESEARCH CENTRE
MALARIA IN PREGNANCY SURVEY
SPECIAL EXAMINATION OF NON-PREGNANT WOMEN AGED 15-45 YEARS
FORM 11

A. IDENTIFICATION

10.1 Name of Woman — NAME

10.2 Compound Name — COMPNAM

10.3 Cluster code CLUSCOD | 10.4 Compound Number COMPNUM | 10.5 Study Number STUDNUM (9 5 0)

10.6 Year of birth YOBW | 10.7 Date of examination DEXAMW | 10.8 Fieldworker code FWCODE

B. PHYSICAL EXAMINATION

10.9 Height (cm) . HGTW

10.10 Weight (kg) . WGTW

10.11 Mid-arm circumference (cm) . MACW

10.12 Axillary temp . ^{0}C AXTEMPW

C. FEVER?

10.13 Have you had 'fever' in the past 7 days?
[INTOLEGERE/YERA LONNA PUA/PAA]
1 .... Yes | 2 ..... No | 9 . NK — FEVER7W

10.14 Treatment given for malaria? 1 .... Yes | 2 .... No — FEVTRTW

10.14a Do you use a bed net? 1... Yes | 2.... No | 9.... DK — NETUSER

10.14b Did you sleep under a net last night? 1 . ... Yes | 2. .... No | 8. ... NA — NETSLP

D. LABORATORY

10.15 COLLECTION OF SPECIMEN

10.15.1 BLOOD	1 .. Yes	2 ... No	BLOOD
10.15.2 FILTER	1... Yes	2 .... No	FILTER

10.16 Laboratory No. (9 5 0) LABNOW

F. LABORATORY WORK

10.17 Staff code [ ][ ] SCODEW

10.18 Date [ ][ ][ ][ ][ ][ ] DTESTW

10.19 Haemoglobin [ ][ ][ ] g/l HBW

10.20 P. FALCIPARUM (ASEXUAL FORM) [ ][ ][ ][ ][ ] FALCACW

[PARASITE COUNT PER 200 LEUKOCYTES]

10.21 P. FALCIPARUM (ASEXUAL FORM) FALCAOCW

[PARASITE COUNT PER 2.500 PER 200 LEUKOCYTES]

1 .... Yes	2 ..... No

10.22 P. FALCIPARUM (GAMETOCYTES)..... [ ][ ][ ] FALCGCW

10.23 P. MALARIAE [ ][ ][ ] MALCW

10.24 P. OVALE [ ][ ] OVALECW

10.25 P. VIVAX [ ][ ] VIVAXCW

10.26 Certified correct by: DATE...../...../...../ [ ][ ] CCB

ORIGINAL IN COLOUR

Appendix VI
+ VII

Appendix VI

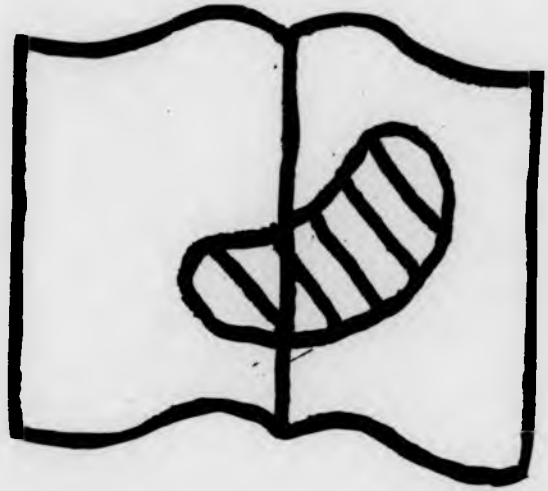
African mothers impregnating bednets with insecticide in a rural community

[Courtesy of Prof. Chris Curtis, London School of Hygiene & Tropical Medicine]

Appendix VII

An African mother and child standing by a mounted insecticide-treated bednet
[Courtesy of Prof. Chris Curtis, London School of Hygiene & Tropical Medicine]

BEST COPY
AVAILABLE



In sickness or in health: TDR's partners

2. The London School of Hygiene & Tropical Medicine

The London School of Hygiene & Tropical Medicine has been a strong partner of TDR from the beginning, and staff across the School continue to be heavily involved in TDR's steering committees and in TDR projects overseas. Much of the collaboration has involved the School's strengths in laboratory research, clinical medicine, public health, epidemiology and social and economics sciences.

The School was founded in 1899, and now has four academic departments, Public Health & Policy, Epidemiology & Population Sciences, Medical Parasitology, and Clinical Sciences, with a total of 305 academic staff, of whom approximately 50% work on the tropical side. The School's mission is to contribute to the improvement of health worldwide and this is reflected in research which addresses major issues of public health in the UK, Europe and the tropics.

The School collaborates with over 300 institutions worldwide, and raises $20 million annually through research grants and contracts. The School is keen for its overseas collaborations to result in institution building and capacity strengthening and it therefore maintains and develops long-term partnerships in research and training schemes such as those supported and encouraged by TDR.

Recent collaboration between the School and TDR is illustrated by the large-scale randomized, controlled trials of insecticide-treated nets (ITNs). Following collaborations by members of the Tropical Health Epidemiology Unit in field research in ITNs at the MRC Laboratories, The Gambia in the late 1980s, and preliminary discussions with TDR, a workshop was hosted by the School in 1991 to develop guidelines for the design of trials to assess the effect of the treated nets on child mortality. Draft project protocols were drawn up by six research groups and a further workshop was held in the School in 1992 to standardize the protocols as far as possible and finalize the designs. A coordinator, Dr Christian Lengeler, was appointed to the School for the four studies in Kenya, The Gambia, Ghana and Burkina Faso with financial support from ODA through TDR. The coordinator was initially responsible to the TDR Steering Committee on Applied Field Research in Malaria and later to the Task Force on Insecticide Impregnated Bednets and other Materials. The role of coordinator was crucial not only in assisting with the logistics of getting enough nets and insecticide to the trial sites in time for the initial distribution, but also in keeping the investigators in touch with other sites, implementing standard procedures where appropriate, and organising football matches! In addition, a statistical epidemiologist from the School was attached to each site, to assist with aspects relating to data collection and management, and data analysis. A key role was also played by economists from the Department of Public Health & Policy in planning and supervising studies of cost-effectiveness and cost-benefit, and by entomologists from the Department of Medical Parasitology in advising on technical aspects of the intervention and monitoring of the vector.

During the progress of the trials, a number of workshops for investigators were held in Africa, covering economic issues, entomology and operational issues, and a final workshop was held in London in May 1995 to discuss strategies and methods for analysis. Since clusters of villages were randomized to receive treated nets or no nets, the analysis of these trials has been based on the mortality rates in each cluster. The analysis of such community randomized trials presents interesting methodological problems which have been addressed by members of School staff, and which have wider application to trials of other interventions which are delivered to communities, such as improved treatment and diagnosis of sexually transmitted diseases (STD).

The School has a flourishing post-graduate teaching programme and offers Ph.D. training, 23 M.Sc. courses and a growing number of short courses. The M.Sc. programme is taught on a modular system which allows students great flexibility to choose units which reflect their training needs and interests. The student body form a truly international group, representing 89 countries in the current year. A further development to be promoted this summer is the opportunity for external participants to take individual units from the M.Sc. programme, as short courses. TDR has given training awards to many Ph.D. students over the years, and four Ph.D. are based on studies planned within the framework of the ITNs trials.

TDR has, on many occasions, encouraged the School to examine its research priorities and training portfolio. The close relationship between members of School staff and TDR continues to be fruitful and stimulating.

LSHTM

Gilly Maude with TDR-funded Ph.D. student Edmund Browne (far right) at a training session for fieldworkers in Navrongo, Ghana.

Appendix IX

Staff List: Malaria in Pregnancy Project, NHRC, Navrongo, Ghana April 1994-April 1995

Field Study Director
Dr. Edmund N. L. Browne

Field Coordinator
Mr. Charles Zandoh

Laboratory Technician
Mr. Emmanuel Foli

Research Midwives
Ms Patricia Kwopa
Ms Mary-Grace Akanlu

Field Supervisors

Mr. Leander Allou	- North Zone
Mr. Arthin Amenga-Etego	- South Zone
Mr. Atintono Akampie	- East Zone
Mr. Felix Allou Jampana	- West Zone
Mr. Isaac Amenga-Etego	- Laboratory/Field Office
Mr. Amos Bawa Agula	- Laboratory/Field Office

Data Entry/Filing Clerks
Mr. Ghana Damayira
Ms. Joana Abora Laadi

Project Driver
Mr. Justin Anao

Fieldworkers

North Zone
Ms. Alice Anecham
Mr. Isaac Weyori
Mr. Philip Akatunge

South Zone
Ms. Elizabeth Adam
Mr. Sylvester Nsoh Rainer
Mr. Ralph Azagsiya

East Zone
Mr. James Akayasi
Mr. Raymond Amogre
Mr. Ferreol Alakiya

West Zone
Ms. Esther Atigre
Mr. Justin Pwavra
Mr. Richard Latinga