

## THE EFFICACY OF PERMETHRIN-TREATED BED NETS ON CHILD MORTALITY AND MORBIDITY IN WESTERN KENYA I. DEVELOPMENT OF INFRASTRUCTURE AND DESCRIPTION OF STUDY SITE

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**Abstract.** Randomized controlled trials in sub-Saharan Africa have shown that permethrin-treated bed nets and curtains reduce all-cause child mortality by 15–33% in areas with low or high but seasonal malaria transmission. This report describes the study site for a community-based, group-randomized, controlled trial in an area of high and year-round malaria transmission in western Kenya. We outline the development of the human and physical infrastructure required to conduct this trial and discuss some of the difficulties encountered and lessons learned in conducting it.

### INTRODUCTION

Randomized controlled trials in different malaria transmission settings have shown insecticide (permethrin)-treated bed nets (ITNs) and curtains to be effective in reducing child mortality.<sup>1–4</sup> In these studies, the efficacy of treated materials appeared to be higher in coastal Kenya and The Gambia, compared with Burkina Faso and northern Ghana.<sup>5</sup> The first two sites were areas of low malaria transmission, with an average number of bites of potentially infective mosquitoes ranging between 10 and 50 per person per year, while the two latter sites were areas of intense but highly seasonal malaria transmission, with more than 300 potentially infective mosquito bites per person per year.<sup>5</sup> Since no mortality trial had been conducted in an area with intense and perennial malaria transmission, the World Health Organization recommended that a randomized controlled trial of the impact of ITNs on childhood mortality be conducted in such an area (World Health Organization Informal Consultation on Insecticide Impregnated Materials, Brazzaville, Congo, March 18–20, 1996). Much of the Lake Victoria basin, with its bimodal rainfall pattern, low elevation, and consequent intense and year round malaria transmission, is appropriate for this purpose. In western Kenya, investigators had previously measured malaria transmission pressure as approximating 100–300 infective bites per person per year.<sup>6</sup> Others had conducted a small-scale ITN project in six villages in the proposed study area<sup>7–9</sup> and had established a longitudinal study of a birth cohort of approximately 1,100 mother-infant pairs.<sup>10,11</sup> Thus, both baseline information and some skilled personnel were available to perform the trial. In this report, we describe the study site, and expansion and development of the logistical and scientific infrastructure to conduct the trial. We discuss some of the difficulties and lessons learned arising from this experience. The study design and methods of evaluation used to measure the impact of ITNs in western Kenya are described elsewhere.<sup>12</sup>

### MATERIALS AND METHODS

**The study site.** We established our initial study site in Rarieda Division, known locally as Asembo, within a subsection of the Siaya and Bondo Districts (population = 639,439, area = 2,518 km<sup>2</sup>) in western Kenya (Figure 1). Rarieda Division

covers an area of 200 km<sup>2</sup> and, according to estimates from the 1989 Kenya Government census statistics,<sup>13</sup> had a population of approximately 60,000 persons (17% less than five years old). Following our baseline census this was adjusted to 55,000 (15% less than five years old). Asembo includes all of an existing smaller study site of 15 villages (with an area of approximately 70 km<sup>2</sup>) near Asembo Bay, where a cohort of approximately 1,100 mother-infant pairs has been longitudinally monitored since 1992 (Figure 1).<sup>10,11</sup> The site was 50 km from Kisumu town, and 40 km from the Kenya Medical Research Institute in Kisian, where administrative and laboratory facilities supporting the trial were based. The field site also encompassed Saradidi, where a community-based health development project was conducted in the early 1980s.<sup>14</sup>

While the Asembo ITN project was underway, results of the efficacy trial of permethrin-treated curtains in Burkina Faso were released; the relatively low protective efficacy observed in that trial spurred us to increase the statistical power of our trial by expanding our study site to encompass the adjacent area of Gem, on the northern border of Asembo. The rationale for this expansion is described in detail elsewhere.<sup>12</sup> Gem, a 300-km<sup>2</sup> (Figure 1) area on the northern border of Asembo, was chosen for several reasons. It had a sufficiently large population (approximately 70,000)<sup>13</sup> and was culturally and environmentally similar to Asembo. Furthermore, a series of small-scale netted material projects in six villages had taken place in Gem between 1991 and 1994,<sup>7–9</sup> allowing us to take advantage of data on ITN acceptability and patterns of malaria transmission. Together, Asembo and Gem were estimated to have a population of 125,000 people (18,000 children less than five years of age) within an area of 500 km<sup>2</sup>.

Asembo and Gem comprise Rarieda, Wagai, and part of Yala Division and incorporate 33 officially designated sub-locations, which are the smallest administrative units in Kenya. Villages are social units, denoted by clan boundaries, but these are not officially recognized administrative units. Sub-locational boundaries sometimes run through village boundaries, but typically each sub-location contains 4–7 entire villages. Because of their small size and greater social cohesion, villages were the logical level at which to randomly allocate ITNs. Asembo (Rarieda Division) consists of 79 villages; 19 villages from the pre-existing cohort site and 60

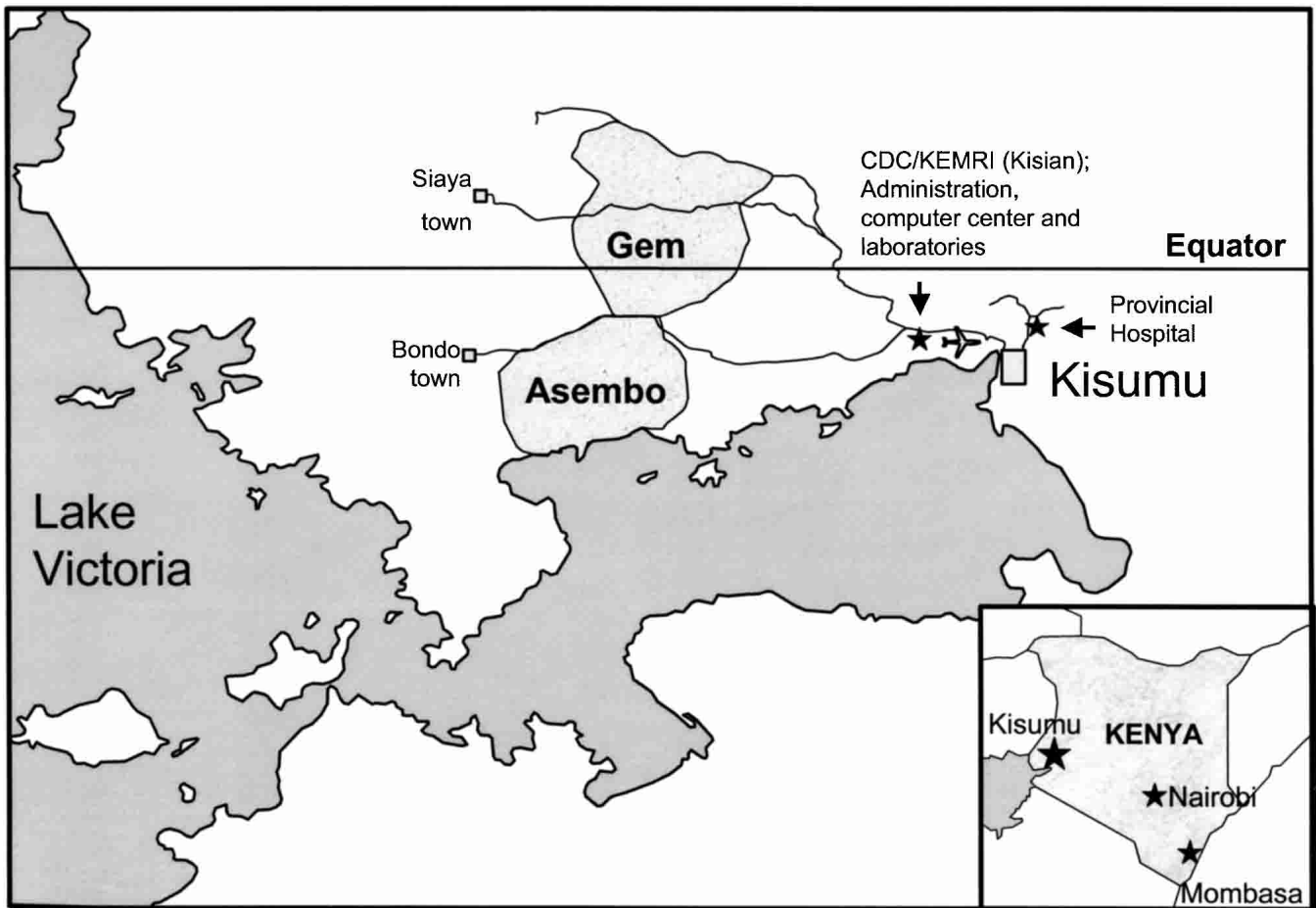


FIGURE 1. Location of the insecticide-treated bed net project in western Kenya. CDC/KEMRI = Centers for Disease Control and Prevention/Kenya Medical Research Institute.

additional villages (four of the largest of the 15 villages forming the pre-existing cohort were split using natural boundaries such as hill ranges and rivers, resulting in 19 village randomization units).<sup>10,15</sup> The Gem study site (Wagai Division and part of Yala Division) has 142 villages.

Nearly all inhabitants live in family compounds consisting of one or more (average of four) clustered houses surrounded by their agricultural holdings, resulting in a highly dispersed settlement pattern. Thus, within-village population density is homogeneous and boundaries among villages are often discernible only by asking residents where traditional boundaries lie.

**The population.** Ninety-six percent of the study population are members of the Nilotic Luo ethnic group. Most are subsistence farmers who grow maize, sorghum, cassava, millet, or vegetables and raise cattle, goats, or chicken. A few cash crops, primarily groundnuts and cotton, are also grown. Some residents fish in Lake Victoria, while others sell food and grain locally. A small proportion of adult males migrate to towns for employment, and return to their homes during holidays and at planting and harvesting time.<sup>16</sup> Most households are poor; the mean wealth index is \$600–700 per household, which reflects possession of a thatched mud and pole house, a cow, a sofa, and a bicycle.<sup>10,17</sup> Caretakers of children and heads of households typically have 7–8 years of education.<sup>10</sup>

Approximately 65% of the houses in the study area are

constructed of mud, sticks, and thatch; an additional 20% of houses have mud walls and a tin roof, while 14% of houses are made of brick with a tin roof.<sup>10,17</sup> For all house types, eaves are usually open, allowing unimpeded entrance and exit for mosquitoes, though a few houses have corrugated iron roofs with sealed eaves. The open construction of most houses enables easy hanging of project bed nets by residents given nails, a hammer, and some strong yarn. Baseline studies revealed a low level of bed net use (< 5%), and of those using bed nets, preference was given to adults and visitors to protect them against nuisance mosquitoes.<sup>18</sup> Sleeping accommodation differs by age. Children less than three years old sleep with the mother until a newborn arrives, older children sleep in the kitchen and sitting rooms, and teenagers move to the surrounding compounds of family and friends. Depending upon age and status, individuals may sleep on beds or on floor mats.

**Malaria transmission.** Malaria is holoendemic in the study area. Transmission occurs throughout the year with two seasonal peaks reflecting the normal bimodal rainfall pattern. The heaviest rains fall from March through May (long rains) with a smaller peak (short rains) in November and December.<sup>10</sup> Annual rainfall averaged 1,400 mm in the seven years prior to the trial; it was 1,342 mm in 1997 and 1,064 mm in 1998 (Figure 2). The daily maximum temperatures ranged from a high of 33.0°C to a low of 25.5°C. Most transmission is due to *Anopheles gambiae* and *An. funestus*, with the propor-

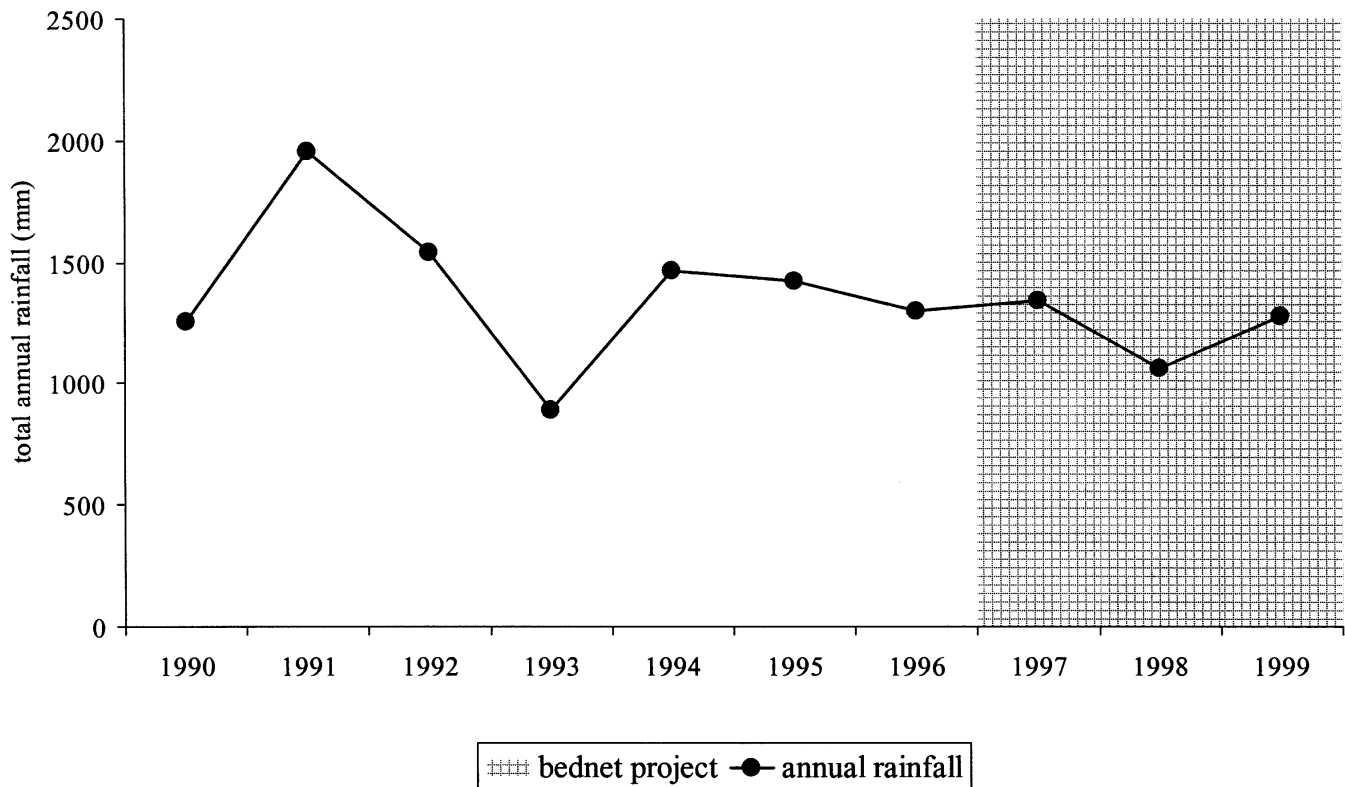


FIGURE 2. Annual rainfall preceding and during the insecticide-treated bed net project in western Kenya.

tion of infections attributed to each species varying both spatially and temporally. The small remaining balance of transmission is due to *An. arabiensis*. Sporozoite rates generally fluctuate between 5% and 10%. Entomologic inoculation rates, calculated as a crude yearly average, vary tremendously at an individual household level (Hawley WA and others, unpublished data), and their estimation depends greatly upon the collection methods used, but range from an average of 60–300 infective bites per person per year in Asembo.<sup>6–8</sup> *Plasmodium falciparum* parasite prevalence studies between June 1992 and July 1994 indicated an overall average monthly parasite prevalence of 44%, 73%, and 83%, in infants less than six months old, those 6–11 months old, and children 1–4 years old, respectively, with little seasonal variation; 88.3% were pure *P. falciparum*, 2.1% were *P. malariae*, 1.2% were *P. ovale*, and the remainder were mixed infections.<sup>11</sup>

**Disease burden.** Malaria and human immunodeficiency virus (HIV) are the two most important causes of morbidity and mortality in this population. Malaria illness accounts for nearly 50% of outpatient hospital visits, and is the cause of half of all hospital deaths in young children.<sup>19</sup> Outpatient health registers show that malaria and upper respiratory tract infection were diagnosed in 65% and 33% of sick children less than five years old visiting peripheral health facilities in Asembo in 1995–1996.<sup>20</sup> More than 80% of 6–11-month-old infants were defined as anemic in a birth cohort in the study area several years before the inception of the ITN trial, with much of this presumably due to persistent malaria infection.<sup>11,21</sup> Similarly, more than half of the pregnant women examined in Asembo have hemoglobin levels less than 11.0 g/dL.<sup>15</sup> Approximately 30%, 4%, and 20% of the children less

than five years of age are stunted, wasted, or underweight, respectively.<sup>22</sup>

In 1982, all-cause neonatal (0–28 days old), infant (less than one year old), and early childhood (1–4 years old) pre-intervention mortality rates in Saradidi were estimated to be 37, 110, and 25 per 1,000 live births, respectively.<sup>14</sup> Based on these figures, the overall mortality rate in children less than five years old is estimated to have been 135/1,000 live births. Between 1979 and 1989, the crude infant mortality rate was calculated to be 109 per 1,000 live births, with an overall mortality rate in children less than five years old of 174/1,000 live births.<sup>11</sup> Results from a retrospective evaluation of deaths from 1,303 live births monitored since 1992 indicated that neonatal, infant, and early childhood mortality rates were 32, 176, and 99 per 1,000 live births, respectively,<sup>23</sup> yielding an estimate of under-five mortality of 275/1,000 live births. Thus, child mortality appears to have increased during the 1980s and 1990s; the ITN trial may therefore have been conducted in the context of a long-term increase in child mortality. Some of this increase is due to onset of the HIV epidemic. The proportion of pregnant women infected with HIV in Asembo between 1992 and 1996 averaged 18% (Kenya Medical Research Institute/Centers for Disease Control and Prevention, unpublished data); thus, mother-child transmission of HIV will contribute to the mortality of children less than five years old. With 18% of the pregnant women infected with HIV, 40% of whom will transmit HIV in a context of prolonged breastfeeding and limited or no use of antiretroviral preventive treatment,<sup>24</sup> 7.2% ( $0.18 \times 0.40$ ) of newborns were estimated to be infected with HIV, at least 75% of whom would die before reaching five years of age in the absence of effec-

tive treatment. Thus, approximately 54/1,000 child deaths ( $0.18 \times 0.40 \times 0.75$ ), or 19.6% ( $54/275 \times 100$ ) of all child deaths, may be attributable to HIV at the onset of the ITN trial. Some part of the increase may also be due to retention of ineffective chloroquine as first-line treatment of malaria in peripheral health facilities, which was only replaced by sulfadoxine-pyrimethamine in early 1999. Although clinical resistance to chloroquine had reached 90% by 1990,<sup>25</sup> the high mortality rates observed in Asembo occurred in the context of a study in which all children had access to effective anti-malarial therapy.<sup>23</sup> The increasing trend in child mortality is likely due to a combination of factors, including a health care system faltering due to diminished funding, ineffective treatment of malaria patients, and arrival of the HIV epidemic.

**Field infrastructure.** More than 300 traditional birth attendants (TBAs) were recruited to conduct census enumeration and communication activities in their village of residence. Each village in the study had at least one resident TBA who provided the on-the-ground link between project staff and village residents. Direct supervision of TBAs was carried out by a network of 38 sector supervisors, who were located in offices serving an average of six (range = 4–9) villages. Sector supervisors were required to be literate in English and resident in the sector for which they were responsible; many sector supervisors had previous experience with Centers for Disease Control and Prevention/Kenya Medical Research Institute projects in Asembo or Gem. Sector supervisors were responsible for checking study forms completed by TBAs daily before forwarding to central offices in either Asembo or Gem.

The two central offices (one in Asembo and one in Gem) were staffed by senior managers with long experience in malaria-related projects. Staff at these sites served as the principal liaison with project scientists, organized surveys, and reviewed all forms (from the census or other surveys) before sending these to the Kenya Medical Research Institute facility at Kisian for data entry. Thus, all forms were checked twice before submission for data entry. After data entry, forms with questionable records identified through automated internal consistency checks were sent back to the central offices, which forwarded them to the relevant sector office for field verification or correction. Central offices also served as training centers for TBAs, and were the organizing points for periodic activities such as net re-treatment and cross-sectional morbidity surveys.

Sector and central offices provided the logistical infrastructure for daily transportation of samples (blood smears, blood samples, mosquitoes) from the field to the main Kisian laboratory. Smaller supplies and equipment were stored in sector offices, with larger items, such as bed nets, stored at the central offices. Nine four-wheel drive vehicles and approximately 75 bicycles were maintained for transport of forms, supplies, and personnel.

**Community mobilization and educational activities.** Prior to the trial, meetings were held with government officials (Division Officers, Chiefs, and Assistant Chiefs) to explain the purpose of the ITN trial. Subsequently, *barazas* (open community meetings) were conducted in each of the 33 sub-locations in Asembo and Gem to allow villagers to ask questions about the proposed study. Meetings were generally attended by several hundred adults, representing a substantial proportion of adult villagers, but with more men than women

in attendance. Questions were raised on a variety of topics, but at most meetings villagers asked about net ownership and use, the possibility of employment with the project, and details of malaria transmission, prevention, and treatment. Local language (*Dholuo*) and English leaflets describing the project were distributed. Although not constituting formal informed consent (which occurred later, on an individual household basis) all meetings concluded with authorization by participants that the trial could be conducted within their sub-location. In each sub-location, considerable enthusiasm for the trial was shown, since the trial offered a realistic possibility of some degree of malaria control coupled with employment opportunities for some villagers. This apparent broad support for the trial was later demonstrated by the extremely low number of villagers who refused to participate in project activities.

Following community approval, additional educational activities began. These took place in all villages, irrespective of their future status as intervention or control villages. One of the major points of these activities was the necessity of a control arm, coupled with a promise, which was carefully fulfilled at project's end, that control villages would also receive ITNs. The TBAs wrote and practiced songs about the study to perform at public meetings and other traditional functions. Ten local actors trained to perform Participatory Educational Theatre (PET) developed skits about the trial. The PET team visited all villages at least once prior to net distribution and also performed at primary schools in Asembo. Children participated in school drawing and poetry competitions describing the main activities of the study. Winning materials were used to make calendars with monthly educational messages on study activities.<sup>26</sup> Voluntary village ITN committees were established to help assist with communicating information about the trial to villagers. One volunteer from each village was elected to represent their village at the randomization lottery.

A small-scale survey of 100 villagers showed that white, followed by dark green, was the preferred color for the bed nets. Green was ultimately selected because white tends to show dirt quickly and we feared mothers would wash white bed nets too frequently, inadvertently washing out the permethrin prior to re-treatment.

**Mapping and geographic information system (GIS).** Asembo and Gem were mapped pre-intervention during 1996 and 1997, respectively. The mapping team visited each compound in the village and painted an identifying number on each house door. Mapping was performed using a differential global positioning system (GPS), as detailed elsewhere.<sup>27</sup> Family compounds, market areas, schools, health facilities, churches, study offices, boreholes, shallow wells, roads, and potential mosquito breeding sites (dams, burrow pits, and river beds) were mapped in Asembo using GPS Trimble Pro XRS GPS units (Trimble Navigation, Limited, Sunnyvale, CA). Base station and field GPS files were downloaded to a personal computer for calibration using Trimble Pathfinder version 2.01 software. Calibrated locations were exported in Dbase format for the creation of base maps of the entire study area and for linkage with all epidemiologic, clinical, entomologic, and sociologic data for spatial analysis. Information on house construction and livestock ownership was also collected during mapping.

**Data management infrastructure.** A computer network was

established at Kisian that allowed simultaneous data entry to the same dataset by several individuals, thus ensuring more rapid data entry and secure daily backup of all data files. A programmer and a hardware maintenance expert were recruited locally, as were additional data entry staff. Scientists developed coding manuals for each individual sub-study; these were used to develop data entry screens for each project. Through the National Institutes of Health/National Library of Medicine, a satellite link (VSAT system) was set up allowing faster internet linkage and improved communication. A room was dedicated to storage of data forms.

**Training.** No large-scale field trial can succeed without substantial numbers of well-trained workers to carry out essential data-gathering tasks. Training was thus an essential part of the project. At field level, experienced TBAs literate in English were recruited. The TBAs received both classroom and field training to ensure understanding and proper completion of all questionnaires used for face-to-face interviews. Refresher courses were conducted prior to each biannual census. Some TBAs received additional training to conduct newborn gestational age assessments; these TBAs became supervisory staff for pregnancy monitoring. All field supervisors had experience with previous studies, and further developed their skills through workshops and meetings with scientific staff. Exceptional supervisors received specialized training in GPS, GIS, social sciences, demography, or data management.

At the Kisian facility, teams with expertise in entomology, laboratory methods, data management, and administration were maintained. The entomology team built upon a group of individuals with many years of field experience. New recruits, all of whom were local residents literate in English, learned from their more experienced colleagues how to collect, identify, and prepare specimens for laboratory analysis. Similar on-the-job training occurred for administrative staff. In contrast, laboratory and data management staff with formal training in these fields were recruited, and many such staff received additional formal training during the course of the project. Most such training was in the form of short courses offered at various institutions (both private and public) in Kisumu or Nairobi.

Scientific training was also an important part of the project. More than 20 scientists participated, and seven of these achieved post graduate degrees while working on the trial.

## DISCUSSION

This report describes the study site used for a randomized controlled trial of ITNs in an area of intense year-round malaria transmission. A dispersed population, poor roads, and lack of telecommunications presented daily challenges. We chose a rural site where an effective research infrastructure had already partially been set up.<sup>10</sup> An alternative site, near the main administrative and laboratory facilities in Kisian, was also considered, but was rejected due to lack of experienced field personnel from the areas surrounding Kisian, and possible interference with other with other research projects being conducted in that area. To some extent, therefore, our main task was to expand the scale of the existing infrastructure rather than invent new systems. This was a tremendous advantage, but we paid a logistical cost: daily long distance

travel to and from the site was required and the effort required to transport study staff, supplies, equipment, insecticide, and bed nets throughout a 500-km<sup>2</sup> study site should not be underestimated, particularly during rainy periods, when already poor roads become nearly impassable. Long distances also reduced the direct supervisory role of senior scientists. The setting up of central field offices, as a repository for supplies and equipment, reduced the transport burden but led to some security problems. Nonetheless, the formidable challenges posed by distance were partly offset by access to an experienced, motivated cadre of field workers drawn from the study population. This core group of workers was instrumental in recruitment and training of the large numbers of new field staff needed to carry out the project.

The existing birth cohort study in Asembo used 40 field staff, and encompassed an area of about 70 km<sup>2</sup> with a study population of approximately 18,000.<sup>10,12</sup> The ITN study entailed scaling-up our infrastructure to cover 500 km<sup>2</sup> with 125,000 people. To do so required some fairly obvious efforts to increase numbers of staff, vehicles, and computers. Training and organization of staff proved more difficult. Success in staff training was very much dependent upon the efforts of experienced field staff from the cohort project. Our main planning lapse was our initial failure to understand the extent to which our data management system, which was well-adapted for small-scale studies, needed to be expanded and modified. We quickly learned that we had underestimated the time and effort needed to accurately enter and clean census data, a process that needed to be completed before beginning the next census round. Simply hiring more data entry staff and obtaining more computers did not solve the problem, nor did aggressive recruitment of trained data managers. At one point, we believed that this problem might be ameliorated by setting up an additional data entry system in the middle of the field site itself, thus allowing more rapid feedback to the field when errors were detected. However, we learned that supervision of data entry and monitoring of data quality requires a high level of skill, and we lacked sufficient number of trained personnel to adequately supervise data entry in two locations. We therefore shut down the subsidiary facility after discovery of high numbers of errors in data entry there; all data were re-entered in the central facility in Kisian. In the end, the process of strengthening and simplifying the data management system was a continuous one, and only slowly did all of the scientists involved in the study realize that the temptation to add on smaller sub-studies needed to be resisted, lest the data management personnel become overburdened and the main study, for which the census data were primary, suffer. Thus, the ultimate solution to this problem was to rein in our scientific ambitions, and conduct rigorous evaluation of our priorities before adding sub-studies to the central project.

Although we consulted with and learned from others who have conducted large-scale trials, many of the problems that arose were site-specific. The *ad hoc* process of successfully finding a solution to problems can be an important part of training, particularly if senior staff will listen to and trust the judgment of field managers. In our project, because of its massive size (especially after expansion to Gem), we had no choice but to delegate judgment to senior field staff, but this necessary strategy proved successful.

Though the principal scientists charged with the management of this study had a broad range of experience in various

field settings, none of us had previous experience in management of large-scale field trials. In the course of the project we learned a number of useful lessons that might arise in other contexts. These are:

- 1) Site selection may entail trade-offs between availability of personnel, logistical convenience, and the possibility of fruitful (or not) interaction with other research groups. But because a large-scale trial inevitably implies that many critical field-level decisions must be delegated to local staff, sites with experienced field staff should receive greater consideration. A corollary is that recruitment of capable staff and high-quality training are absolutely critical.
- 2) One must involve as many community members in the project as possible, and do this as early as possible. We worked hard on community relations, and worked as hard on this in control villages as in intervention villages. We have little to say here about problems with community relations, partly because of efforts we made to ensure that community members were involved with, or at least aware of the project.
- 3) Logistics are a time-consuming burden even with the assistance of capable middle managers.
- 4) Site expansion can change the nature of previously existing systems in unexpected ways. Simple replication of existing structures (as we tried for data management) may not be as effective as expected.
- 5) Too many sub-studies can spoil the overall effort. Given the amount of time, effort, and money invested in large-scale field trials, and the fact that one cannot start over or replicate such trials, we recommend that investigators be certain that add-on studies address questions of high scientific value and do not overly burden logistical and data management systems. A field site can address only a limited number of good ideas effectively.

**Acknowledgments:** We thank the villagers of Asembo and Gem for their participation, and the field and administrative staff for their assistance in developing the infrastructure for this study. This paper has been published with the permission of the Director of the Kenya Medical Research Institute.

**Financial support:** The ITN project was funded by the United States Agency for International Development.

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