Abstract. Effects of the distribution in space of permethrin (insecticide)–impregnated bed nets (IIBNs) on child mortality were studied in a randomized controlled trial of IIBNs in an area highly endemic for Plasmodium falciparum malaria in rural northern Ghana. Eight hundred sixty-two deaths occurred among children 6–59 months of age during 16,841 child-years-at-risk. Mortality increased with the distance from health facilities but not with proximity to identifiable anopheline breeding sites (reservoirs). The efficacy of IIBNs was independent of these distances. Mortality in users of IIBNs was independent of the proximity of nonusers, and mortality rates of nonusers and users living close to each other were similar. Poisson regression estimated a 6.7% increase in mortality among nonusers with each 100-m shift away from the nearest compound with IIBNS, indicating that the insecticide protects nearby nonusers. High coverage of IIBNs achieves maximum impact, but users of IIBNs offer some protection to less fortunate neighbors if coverage is incomplete.

Insecticide-impregnated bed nets (IIBNs) have been found to reduce malaria-related morbidity,1–3 and recently published reports from endemic areas indicate that the use of IIBNs results in a reduction of between 17% and 63% in all-cause mortality in young children.4–6

Much of the recorded variation between trials in the efficacy against all-cause mortality may be a result of differences in the proportion of deaths caused by malaria. Within any one area, the impact of IIBNs on all-cause mortality could be influenced by environmental factors affecting malaria mortality risks such as proximity to health facilities and to potential breeding sites for mosquitoes. The trials concentrated on all-cause mortality as the main outcome because of the difficulty in measuring malarial specific mortality in rural areas of Africa. Most deaths occur at home, and the only tool available for assigning the cause is verbal autopsy. This is an imprecise technique for diagnosing malaria.7,8

In the studies that have demonstrated effects of IIBNs on mortality, bed nets and/or insecticide were provided free so there was uniformly high coverage in intervention groups and no small pockets of IIBNs surrounded by unprotected individuals. In practical intervention programs, coverage is likely to be much more patchy. In principle, this could have any of several effects on malaria transmission. Mosquitoes might be diverted from families with IIBNs to families without IIBNs,9,10 thus increasing the risk of death in neighboring children without IIBNs. At the same time, nearby nonusers could provide a reservoir of hosts supporting and infecting local vector populations, thus reducing the efficacy of IIBNs below that in completely protected communities. On the other hand, IIBNs reduce vector populations and might also divert mosquitoes to animals, thereby decreasing overall levels of malaria transmission and potentially protecting nonusers in the vicinity.

We report here on the use of a geographic information system in a randomized controlled trial of permethrin-impregnated bed nets on child mortality in northern Ghana. The main analysis of mortality6 in this trial indicated that the use of IIBNs was associated with a 17% reduction in all-cause mortality in children 6–59 months of age (risk ratio = 0.83, 95% confidence interval = 0.69, 1.00 adjusted for age). The mean child mortality rate in clusters with IIBNs was 24.0/1,000 child years at risk (SD = 9.7), and in control clusters was 27.9/1,000 child years (SD = 12.7).

We examined the effect of proximity of health facilities and of water bodies (breeding sites of the secondary vector, Anopheles funestus) on the mortality rates. We also considered whether these factors affected the impact of the IIBNs. In addition, we investigate the effects on children without IIBNs of residing near families with IIBNs, and the consequences for children with IIBNs of living near unprotected families.

MATERIALS AND METHODS

Study site. The trial was carried out in the Kassena-Nankana district in Upper East Region of Ghana, which covers an area of 1,675 km² between 10°30' and 11°00’N, and 1°30’W. The area is within the guinea savannah woodland area of Ghana and has a tropical climate with a single wet season, with intense seasonal transmission of Plasmodium falciparum malaria. The main vectors are Anopheles gambiae s.s. and An. funestus.11

The district is predominantly rural, with a population currently estimated at 175,000. The town of Navrongo, which is the district administrative center, has a population of about 15,000. People live in dispersed settlements that consist of compounds containing houses made mainly of mud, with mud or thatch roofs and surrounded by farmland. Compounds are typically inhabited by related individuals from several generations with an average of 12 people per compound, but vary in size from two to 180 persons per compound.

The district is served by a hospital (in Navrongo) and three health centers located to provide the community with adequate access (Figure 1). Health service use rates are low partly because settlements are dispersed and the road network is basic. There are very few all-year-round roads and transport is predominantly by foot or bicycle using temporary footpaths.

The district is the site of a large irrigation project that covers 3,860 hectares with 42 km of canals. In addition, approximately 90 small dugout reservoirs scattered throughout the district provide water for both people and livestock.
in the center of the district is the main Tono Reservoir); contiguous compounds for the purposes of the trial. Cluster area was divided into 96 clusters (villages) of geographically facilities, and over more than reservoirs within the study area referenced positions of the 12,000 compounds, four health gation, Ltd., Sunnyvale, CA) were used to record the geo-hand-held geographic positioning systems (Trimble Navi-reservoirs, forest reserves, and rivers) were digitized. Two of 1: 50,000 (showing district boundaries, roads, irrigation Ghana. The trial was explained in detail to the district authorities and all paramount chiefs, who gave their approval. It was also explained and consent was sought from the head of each compound and the parents or guardians of each eligible child before they were enrolled in the study. No parent refused permission for their child to enter the trial. Ethical approval for the study was obtained from the Ministry of Health of Ghana.

Digital map of the district. Maps of the district at a scale of 1: 50,000 (showing district boundaries, roads, irrigation reservors, forest reserves, and rivers) were digitized. Two hand-held geographic positioning systems (Trimble Navi-gation, Ltd., Sunnyvale, CA) were used to record the geo-referenced positions of the 12,000 compounds, four health facilities, and over more than reservoirs within the study area (Figure 1).

Insecticide-impregnated bed net intervention. The details of the intervention are published elsewhere.6 The study area was divided into 96 clusters (villages) of geographically contiguous compounds for the purposes of the trial. Cluster size, which averaged 1,400 people, was set at the maximum consistent with the trial having sufficient power to detect an overall efficacy of 30%, assuming a design effect12 of 2.0, and that the clusters would be the units of analysis. Where possible, small paths or road were used to delineate the clusters. However, in most cases, the cluster boundaries did not correspond to natural barriers. Open ballots were cast at village level to randomly select 48 clusters to form each of the intervention and control areas. In June 1993, approximately 31,000 brown permethrin (50% emulsifiable concentrate; Zeneca, London, United Kingdom)–impregnated bed nets were provided to residents of the more than 6,035 compounds in the intervention area. All compounds were subsequently visited every six months to reimpregnate the bed nets during the two years of follow-up. The bed nets and insecticide were provided free of charge to all participants in the study.

Demographic surveillance. A census of the study area was conducted in 1992 and all members of the 12,000 compounds were enumerated. Each compound had a unique number painted on the wall for ease of identification. This information were entered into a FoxPro® (Microsoft, Inc., Redmond, WA) relational database, known as the Navrongo demographic surveillance system.13 The compounds were visited in a 90-day cycle to update the current status of each resident. Births, deaths, in and out migrations, and any new compounds that had been built since the last visit were recorded. Approximately 120 key informants were recruited from members of the study community and paid to record all pregnancies, births, and child deaths in their local area. These data augmented the demographic data collected in the 90-day cycle and facilitated checks for completeness of event reporting.

Data analysis. The distance from each compound to the nearest reservoir or health facility was calculated using Arcview 2.1© (ESRI, Ltd., Redlands, CA). Compounds with bed nets were grouped according to the distance to the nearest reservoir or health facility. Five categories were used (Tables 1 and 2). The grouping was chosen to allocate deaths of children 6–59 months of age in roughly equal numbers to each category.

Similarly, compounds to which bed nets were assigned were grouped according to the distance to the nearest compound without bed nets. This distance is referred to as the distances to the nearest discordant compound (D). For compounds to which no bed nets were assigned, D was the distance to the nearest compound with bed nets. Five categories of D were used: < 200 m, 200–< 300 m, 300–< 400 m, 400–<500 m, and > 500 m. These categories were chosen to allocate deaths in roughly equal numbers to each category.

Table 1

<table>
<thead>
<tr>
<th>Distance from reservoir (meters)</th>
<th>Compounds with bed nets</th>
<th>Compounds without bed nets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed deaths</td>
<td>Expected deaths</td>
</tr>
<tr>
<td>0–500</td>
<td>95</td>
<td>97.10</td>
</tr>
<tr>
<td>501–700</td>
<td>66</td>
<td>53.51</td>
</tr>
<tr>
<td>701–1,000</td>
<td>77</td>
<td>65.79</td>
</tr>
<tr>
<td>1,001–1,500</td>
<td>80</td>
<td>71.80</td>
</tr>
<tr>
<td>&gt;1,500</td>
<td>78</td>
<td>63.53</td>
</tr>
</tbody>
</table>
except for the category > 500 m. We grouped all compounds together for which D was greater than 500 m.

Mortality rates of children 6–59 months of age were available for both the preintervention and post-intervention periods in both the intervention and control areas. The intervention and control areas were tested separately for heterogeneity in mortality rates using the method of Potthoff and Whittinghill and Elliott and others. The expected numbers to give standardized mortality ratios (SMRs) was tested by Poisson regression using the program EGRET (SERC, Seattle, WA), with the expected numbers of deaths treated as an offset and distance included as a continuous explanatory variable.

The expected number of deaths for each cluster was computed by applying age-specific death rates derived from the preintervention population to the post-intervention time at risk. The observed number of deaths was divided by these expected numbers to give standardized mortality ratios (SMRs). The SMRs were divided into quintiles and plotted by cluster. They were also calculated for each category of distance from health facilities, distance from reservoirs, and of D. The statistical significance of distance effects on the SMRs was tested by Poisson regression (LR \(\chi^2\); 56.3, df = 46, \(P = 0.166\)). When the data were analyzed by compound, it was found that mortality risk in both compounds with bed nets and the controls tended to increase with distance from reservoirs but this trend was not statistically significant in either IIBN users (regression on log distance: likelihood ratio \(\chi^2 = 2.2\), df = 1, \(P = 0.14\)) or nonusers (LR \(\chi^2 = 1.8\), df = 1, \(P = 0.18\)) (Table 1).

Mortality risk increased significantly with distance from health facilities in both groups (Table 1) (regression on log distance among IIBN users, LR \(\chi^2 = 4.3\), df = 1, \(P = 0.04\); nonusers, LR \(\chi^2 = 12.9\), df = 1, \(P < 0.001\)), but the impact of IIBNs again did not show any significant trend. The relationship between SMRs to D is shown in Figure 3. Within the group with bed nets, mortality rates did not show any obvious trend with D and the absence of a trend was confirmed by Poisson regression (LR \(\chi^2 = 0.7\), df = 1, \(P = 0.4\)). However, the death rate among unprotected individuals increased with distance from the nearest compounds with bed nets (LR \(\chi^2 = 7.4\), df = 1, \(P = 0.007\)) (Figure 3). This suggests that IIBNs are protecting other individuals without bed nets who sleep close to protected compounds. This model estimated that a shift of 100 m away from the boundary was associated with an increase in risk in individuals without bed nets of 6.70/o (95% confidence interval = 1.8, 11.4%).

### RESULTS

The population density in Kassena-Nankana district is highly heterogeneous, with extensive forest reserve areas away from the main center and the majority of the population living in the northeastern corner. The health facilities are located in main centers of population, so members of isolated communities especially in the southern part of the district, have long distances to travel for health care. Dugout reservoirs (including the main Tono reservoir) occur predominantly near the centers of inhabited areas. Close to the main reservoir there is also a higher density of water bodies than elsewhere (Figure 1).

The spatial distribution of clusters allocated to the receive IIBNs is shown in Figure 1. This figure shows the locations of control areas. Since allocation was by simple randomization within villages, contiguous clusters were often allocated to the same treatment group, but there was no clear overall geographic pattern in the allocation.

Because the preintervention death rates, which were lower than those during the trial, were used for age standardization, SMR values were generally greater than unity. The spatial pattern of cluster specific SMRs is shown separately for areas with IIBNs (Figure 2A) and for control areas (Figure 2B). Clusters with IIBNs generally had lower mortality than clusters in the control areas, but there was considerable overlap in the two SMR distributions. Visual assessment of the spatial distribution of SMRs did not indicate very marked geographic patterns of clusters with extreme SMRs, although there seemed to be a tendency for the larger control clusters in peripheral areas to have the highest mortality rates. The Potthoff-Whittinghill test of spatial heterogeneity indicated that there was more variation in SMRs between control clusters than can be accounted for by chance (\(\chi^2 = 106.7\), degrees of freedom [df] = 46, \(P < 0.001\)) but there was no significant spatial variation in the SMRs for the intervention clusters (\(\chi^2 = 56.3\), df = 46, \(P = 0.166\)).

### DISCUSSION

Child mortality is high throughout the Kassena-Nankana District, in particular in remote parts distant from health facilities. A number of factors might contribute to the reduced mortality near health facilities. Children living near health facilities can in principle gain easier access to health care and potentially could be saved from dying. The decreased mortality close to health facilities may also partly be due to their location in center of the population in which socioeconomic status tends to be better.

The decrease in mortality with distance from reservoirs is likely to be a further consequence of the more socioeconomic-
Figuratively marginalized people tending to live in remote locations, since most of the reservoirs are located near to the centers of inhabited areas. Originally, we anticipated finding higher mortality near to these water bodies because there are likely to be increased biting rates of *An. funestus* in the vicinity of breeding sites in the reservoirs. However, the main malaria vector in the district is *An. gambiae s.s.* and this prefers to breed in small pockets of clean fresh water rather than the larger water bodies. Small pockets of fresh water are abundant all over the district in the rainy season especially in the millet stocks that grow around every compound.

The overall reduction in all-cause mortality in children 6–59 months of age associated with the use of IIBNs was 17%. This reduction was not limited to a small number of clusters. Visual assessment of the spatial distribution of mortality risk does not provide a formal measure of the magnitude of the variation in mortality, but did clearly indicate that the effect was spread over the whole intervention area. This was confirmed by the absence of statistically significant heterogeneity in the spatial distribution of the SMRs in the IIBN clusters.

The impact of IIBNs on mortality was independent of the proximity of the compound to a health facility or reservoir. This further suggests that the proportion of deaths that are due to malaria is not very different in remote areas from that in centers of population, consistent with widespread distribution of the main malaria vector. However, the efficacy of
IIBNs did depend on their distribution in space. The IIBNs provided very good personal protection to children using them, and also protected nonusers in nearby compounds. Among nonusers, the mortality risk increased by 6.7% with each additional shift of 100 m away from the nearest compound with IIBNs.

The clusters with high mortality risks were large control areas around the district boundary where most people were remote from intervention clusters. In contrast to the importance of the nearest IIBNs for nonusers, the mortality experience of children with IIBNs did not depend on the distance to the nearest nonusers.

Postintervention mortality in areas remote from IIBNs was higher than preintervention levels. This could theoretically be a result of long-range diversion of mosquitoes as a result of the repellent effect of permethrin. However, the increase in rainfall, which was the highest in the last 10 years, has been shown to be associated with the high mortality during this period, so we do not believe that our study provides evidence for long-range diversion of mosquitoes.

Our results support the claims of Lines and others that there are short-range protective effects of IIBNs on people sleeping nearby without them. Other studies have claimed that the use of IIBNs by some family members gave no protection to others sleeping nearby without them. However, if the protective effect in a trial extends over an entire study area, including the comparison group, it will be difficult to measure it and the effect will be to bias overall estimates of efficacy towards zero.

The ideal trial design for demonstrating the efficacy of IIBNs is to randomize well-separated villages so that each cluster has its own mosquito population and the difference in the resultant impact of IIBNs between protected and unprotected clusters is maximized. To achieve this, villages should be at least 4 km apart, the maximum dispersal range recorded by Gillies for An. gambiae. In many countries, however, villages are not so clearly separated, and in any realistic bed net distribution program nets are likely to be interspersed among families lacking personal protection.

If bed nets are dispersed sparsely throughout the population in malaria control programs, this will make it difficult to estimate program effectiveness. However, if the number of nets available is limited, this may be the distribution pattern that optimizes the overall level of protection in the community. Thinly spread IIBNs provide protection to individuals without them. This is good news for social marketing schemes, since market mechanisms will tend naturally to lead to nets being widely but sparsely distributed.

Taken at face value, our results would seem to suggest that the mass effect from a small number of highly dispersed nets would provide equivalent protection to complete coverage since we observed no efficacy in areas where IIBNs and unprotected individuals are close together. However, efficacy was highest during periods of high net usage, implying that good compliance is indeed important. It is not plausible that there is absolutely no advantage in sleeping under the net rather than nearby and our results should not encourage the belief that adequate protection can be obtained from a neighbors' IIBN.

The debate on diversion of mosquitoes from households with IIBNs to households without IIBNs has been a major concern of malaria control programs. The IIBNs cost about US $5.00, which places the intervention out of the reach of a good percentage of the rural poor. If their rich neighbors then diverted all the mosquitoes to them, the intervention would create additional social problems. Our study does not endorse this concern. We will achieve maximum impact with a high coverage of IIBNs in a village, but even if coverage is low, those protected by IIBNs offer some protection to their less fortunate neighbors.

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