COMMUNITY-WIDE EFFECTS OF PERMETHRIN-TREATED BED NETS ON CHILD MORTALITY AND MALARIA MORBIDITY IN WESTERN KENYA

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Abstract. Spatial analyses of the effect of insecticide (permethrin)-treated bed nets (ITNs) on nearby households both with and without ITNs was performed in the context of a large-scale, group-randomized, controlled mortality trial in Asembo, western Kenya. Results illustrate a protective effect of ITNs on compounds lacking ITNs located within 300 meters of compounds with ITNs for child mortality, moderate anemia, high-density parasitemia, and hemoglobin levels. This community effect on nearby compounds without nets is approximately as strong as the effect observed within villages with ITNs. This implies that in areas with intense malaria transmission with high ITN coverage, the primary effect of insecticide-treated nets is via area-wide effects on the mosquito population and not, as commonly supposed, by simple imposition of a physical barrier protecting individuals from biting. The strength of the community effect depended upon the proportion of nearby compounds with treated nets. To maximize their public health impact, high coverage with treated nets is essential.

INTRODUCTION

Although widely viewed as devices for personal protection against malaria, insecticide (permethrin)-treated bed nets (ITNs) may have community-wide effects as well. Such effects might be either beneficial or harmful for those living in houses without ITNs. Early fears that the repellant effect of the pyrethroid insecticides used to treat bed nets would divert mosquitoes to neighboring houses lacking nets have been largely allayed. No evidence exists that mosquitoes are diverted to houses without ITNs. Indeed, studies from various parts of Africa and Papua New Guinea indicate the presence of a beneficial community effect (we propose use of this term rather than the less descriptive mass effect) on malaria transmission,[1–6] severe malaria,[7] and mortality[8] in children. One study, in contrast, yielded no evidence for either beneficial or harmful community-wide effects.[9]

If use of ITNs is beneficial to near neighbors lacking ITNs, new questions arise. How strong is the community effect of ITNs relative to their individual protective effect? To what extent does the strength of the effect depend upon the proportion of homes having ITNs? Answers to these questions have important implications for policymakers trying to choose among various models for ITN distribution in African communities.

In the context of a large-scale, group-randomized, controlled trial of ITNs in western Kenya, Gimnig and others[4] have shown that mosquito abundance was reduced in compounds lacking ITNs but located close to compounds with ITNs. In the present analysis, we determine whether a beneficial community effect on the mosquito population extends to malaria-related morbidity and all-cause mortality in young children, who are profoundly affected by malaria in this area. We show how the strength of the effect varies spatially, both within villages lacking nets and in villages with ITNs. We also describe how the strength of the community effect in individual houses lacking nets varies with the proportion of neighboring houses that have nets. We show that failing to control for the community effect in standard statistical analysis of ITN efficacy results in a systematic underestimate of the true

efficacy of ITNs. Finally, we discuss implications of our results for mechanisms of ITN action.

MATERIALS AND METHODS

Design of the ITN project. The ITN trial was conducted in two phases in adjacent geographic areas: Asembo and Gem in Nyanza Province in western Kenya, as described in detail by Phillips-Howard and others.[10] Results presented here incorporate data only from Asembo, which covers an area of 200 km² inhabited by 55,000 people. In late 1996, the villages in Asembo were randomized into ITN (intervention) and control villages (Figure 1A). Distribution of nets to intervention villages was complete by December 1996. Control villages received ITNs in early 1999. All nets were allotted per sleeping space, and given free of charge in an attempt to maximize coverage of the study population. After distribution, study staff went door-to-door to ensure that nets were hung properly. Enough nets were distributed to allow every person in each house to sleep under a net. Nets were re-treated twice a year with permethrin by study staff to the recommended dose (0.5 g/m²) of the World Health Organization. Thus, for two years, 1997 and 1998, people in half of the villages (intervention villages) in Asembo had access to properly treated bed nets and half (control villages) did not. Periodic spot checks during this period showed that few (<3%) nets were sold or moved outside the study area, although adherence to net use, measured as the proportion of study participants directly seen to be sleeping under nets during early morning observational surveys, was usually approximately 70%.[11]

Study site characteristics and population distribution. Since most residents of Asembo are members of the Luo ethnic group, most settlements in the study area generally follow the traditional Luo pattern: the family compound, an open ring of houses surrounded by the family's land, is occupied by the patriarch, his wives, and his children. Animals, goats, chickens, and highly prized cattle, are kept at night in the central part of the compound for protection against predators. As sons marry and have children, they construct new compounds some distance away on the family land. The result of this
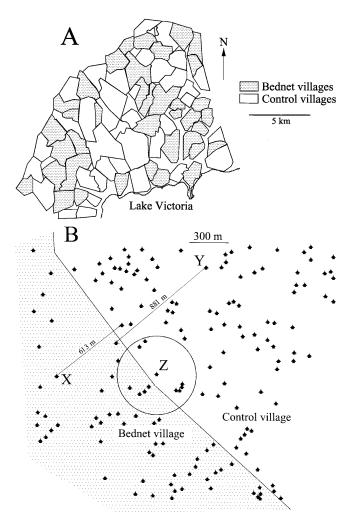
FIGURE 1.   **A**, Map of the Asembo area, showing the distribution of insecticide-treated bed net (ITN) and control villages. **B**, Map of a subset of the study area, illustrating the dispersed nature of family settlements as well as methods used to calculate geographic exposure variables. Each house symbol represents a family compound consisting of one or more separate houses. Compound X, located in an ITN village, is 613 meters from the nearest control compound. Similarly, control compound Y is 881 meters from the nearest ITN compound. The distance to the nearest compound of different intervention status was calculated for all compounds in the study area; categorization of these distances into 300-meter increments corresponded roughly to quartiles. For peripheral compounds, distance to the edge of the study area was substituted when appropriate. Calculation of the percentage of nearby compounds with ITNs is illustrated for compound Z, located in the center of a circle with a 300-meter radius. Compound Z has 10 neighbors within 300 meters, of which four are ITN compounds, yielding a coverage of 40%. Calculation of this variable was performed only for control compounds located within 300 meters of the nearest ITN compound.

settlement practice is a population that is highly dispersed over the landscape (Figure 1B). Although the study area is divided into villages with approximate boundaries as shown in Figure 1A, these are social constructs that do not reflect variation in population density.

The landscape consists of rolling hills cut by numerous seasonal rivers that flow into the lake. Underground springs bubble to the surface in parts of the area, providing water for human use, and larval habitat for mosquitoes. Rainfall follows a bimodal annual pattern, with some rain usually falling in

every month. Malaria transmission intensity mirrors the rainfall pattern, with a lag of several weeks. The annual number of infective bites sustained per person varies by year, and is highly dependent upon which field and laboratory methods are used to collect and process mosquitoes, but generally ranges from 60 to 300 infective bites per person per year (Hawley WA and others, unpublished data). Except in cases of extreme and atypical drought, some transmission occurs in every month.

Approximately 90% of the malaria infections are due to *Plasmodium falciparum*; infection with *P. malariae* makes up most of the balance, along with an occasional *P. ovale* infection. Three mosquito species transmit nearly all of the malaria here, with *Anopheles gambiae* and *An. funestus* responsible for more than 90% of the transmission and *An. arabiensis* responsible for most of the rest. Both *An. gambiae* and *An. funestus* bite primarily indoors late at night; their biting is thus diminished by use of ITNs.

Mapping of the study area and distance calculations. The Global Positioning System (GPS) was used to map the approximate center of all study compounds, clinics, boreholes, roads, rivers, schools, churches, market centers, the shore of Lake Victoria, and obvious mosquito larval habitat. A base station unit established at the Kenya Medical Research Institute in Kisian allowed correlation of readings from field GPS units. This differential processing allowed us to obtain measurements of latitude, longitude, and elevation for each point to an accuracy of less than one meter.[12,13] Positions were read into ArcView GIS[14] software for production of maps and distance calculations.

Figure 1B illustrates the method used to calculate the three geographic exposure variables used in this analysis: distance from control compounds to the nearest ITN compound, distance from ITN compounds to the nearest control compound, and proportion of compounds with ITNs within 300 meters of control compounds. Distances were calculated using an accepted standard formula.[15] The 300-meter interval for the main exposure variables was based upon the observation that this distance range divides the number of compounds of each type into approximately equal quartiles (Table 1). All distance calculations were done on the basis of intent to treat; all compounds in ITN villages were assumed to have ITNs and all compounds in control villages were assumed to lack ITNs. Other distance variables mapped and used as covariates in some analyses included distance to the shore of Lake Victoria, distance to the nearest clinic, and distance to the nearest borehole.

Measurement of morbidity and mortality. Cross-sectional surveys were conducted to assess the impact of bed nets on malaria-related morbidity in November 1996 (baseline, be-

TABLE 1
Proportion of compounds in four distance categories from compounds of different type*

Distance (meters) to nearest compound of different type	Proportion of ITN compounds	Proportion of control compounds
<300	0.18	0.26
300–599	0.28	0.31
600–899	0.25	0.22
≥900	0.29	0.21

* ITN = insecticide-treated bed net.

fore nets were distributed to intervention villages), February–March 1998, and November–December 1998. Data from the latter two surveys are used in the analysis presented here. Details of the methods used are described elsewhere.[16] The catchment area for the cross-sectional surveys included 60 of 79 villages in Asembo. The 19 villages excluded from the cross-sectional studies are in the southernmost area of Asembo, where longitudinal surveillance was ongoing. Approximately 900 children less than three years old were sampled during each survey; exact sample sizes are shown in Table 2. A simple random sampling method with households as the sampling unit was used that involved 60% of all households with children less than three years of age selected on the basis of census data. Children participated in the survey only once.

For estimation of child mortality, a complete census of the study area was conducted every six months as described in detail by Phillips-Howard and others[10,17]

Data analysis. We analyzed the effect of proximity to compounds with ITNs on six outcome measures. With the exception of mortality, all outcomes were examined in children less than three years of age. The six outcome measures were 1) mortality of children 1–59 months old; 2) moderate anemia defined as a hemoglobin level <9 g/dL; this level was chosen since cut-off values reflecting more severe anemia yielded insufficient statistical power; 3) hemoglobin level as a continuous variable (in g/dL); 4) high density of *P. falciparum* infection defined as a parasitemia >5,000 parasites/mm³; 5) clinical malaria defined as any level of parasitemia plus fever; and 6) any helminth infection, included as an internal control.

The mortality analysis was done using methods described by Phillips-Howard and others.[17] Briefly, the following covariates were incorporated in the model: year of study (year 1 or year 2), age of child, rainfall (during the previous month), and temperature (during the previous week). Weather variables were included to control for seasonality of malaria transmission while the study year variable is intended to control for temporal variation in the efficacy of the ITN intervention itself. We used survival analysis (Procedure PHREG of SAS, version 8.1)[18] and controlled for clustering by village.

For the morbidity analysis, which was based on cross-sectional data,[16] the following covariates were included in all models as categorical variables: age, sex, weight for age, cross-sectional number, and distance to the nearest clinic. In initial models, various socioeconomic indices were included as independent variables, but these were later excluded because of collinearity with the child's nutritional status. By similar logic, indices of rainfall likely duplicated the effect of controlling for survey number, so these were also excluded. Other variables examined were elevation, distance to the nearest borehole, and distance to the shore of Lake Victoria, but these were found to be neither significant nor confounding relationships of interest, so were excluded from final models.

All models controlled for clustering by village with an exchangeable correlation structure assumed for residents within a village. Dichotomous health outcomes were modeled using a logistic regression. Continuous health outcomes (hemoglobin level) were modeled using an identity link function and a normal distribution. All models were created using Procedure Genmod, a procedure within SAS, version 8.1.

The first set of models describe the relationship between health outcomes and the location of a compound within ITN and control villages relative to the distance to the nearest compound with a different intervention status. Compounds in control villages that are ≥900 meters from the nearest ITN village served as the comparison group for these analyses. A total of seven dichotomous variables were created that contained all other compounds. For control villages, we created three variables for compounds that were 0–299, 300–599, or 600–899 meters from the nearest ITN compound. For ITN villages, we created four variables for compounds 0–299, 300–599, 600–899, and ≥900 meters from the nearest control compound. The intent of this analysis was to allow us to illustrate spatial patterns of effect in a straightforward way; however, the cost of this approach was some loss in statistical power. These distance categories approximate compound distribution by quartiles as shown in Table 1. Additional tests of trend were performed using the same reference group and control compound distance categories, but combining ITN compounds into a separate variable; thus trends were evaluated only in control compounds.

Since the strongest community effect was observed in control areas within 300 meters of ITN villages, we constructed models to describe the relationship between health outcomes and the percentage of homes within 300 meters of compounds in this area. In this way, we were able to model coverage, here defined as the proportion of homes within 300 meters with ITNs, in the region of our study area where coverage varied most widely. The effect of increasing percentage coverage was modeled both categorically and by trend test.

Ethical clearance. The bed net trial was reviewed and approved by the institutional review boards of the Kenya Medical Research Institute (Nairobi, Kenya) and the Centers for Disease Control and Prevention (Atlanta, GA). Informed consent was obtained from all caregivers after the study was explained in the local language.

RESULTS

Malaria-related morbidity is common in this population of children, though somewhat lower in ITN compounds, as shown in Table 2. Approximately one-third of the population had moderate anemia, while approximately one-fourth had a parasitemia level greater than 5,000 parasites/mm³. Multivariate statistics (Table 3) confirm results presented in full elsewhere,[16] which show that ITNs significantly reduce measures of malaria-related morbidity.

The effect of the primary geographic exposure variable, distance to nearest compound of different type, is illustrated in Figure 2, which shows the effect of each of seven different

TABLE 2
Estimates of values for morbidity outcomes for insecticide-treated bed net (ITN) and control compounds used in the geographic analysis*

Outcome	ITN compounds	Control compounds
Clinical malaria	0.051 (948)	0.082 (898)
Parasitemia >5,000/mm³	0.18 (960)	0.26 (902)
Hemoglobin level <9 g/dL	0.28 (978)	0.39 (908)
Hemoglobin (g/dL)	10.0 (978)	9.5 (908)
Helminth infection	0.26 (617)	0.25 (600)

* All are estimates of prevalence except for hemoglobin level, which are mean values. Sample sizes (number of children) are shown in parentheses.

Comparison of estimates of insecticide-treated bed net (ITN) efficacy before and after adjustment for presence of a community effect in control compounds within 300 meters of intervention compounds*

Outcome	Not adjusted for community effect	Adjusted for community effect	Relative change (%)
Clinical malaria†	0.56 (0.35, 0.90)	0.52 (0.33, 0.83)	7.1
Parasitemia >5,000/mm³	0.64 (0.50, 0.81)	0.59 (0.45, 0.76)	7.8
Hemoglobin level <9 g/dL†	0.60 (0.45, 0.79)	0.53 (0.40, 0.71)	11.7
Change in hemoglobin level‡	0.50 (0.23, 0.78)	0.60 (0.31, 0.89)	20.0
Mortality§	0.75 (0.64, 0.89)	0.72 (0.60, 0.86)	4.0

* All estimates are adjusted for relevant covariates as described in the text. Point estimates and 95% confidence intervals are shown.
† Odds ratio.
‡ Regression coefficient that reflects change in hemoglobin level (g/dL).
§ Hazard ratio.

exposure categories on five malaria-related outcomes, as well as geohelminth infection. For geohelminth infection, no effect of ITN use or distance is apparent. In contrast, a protective effect of living in ITN villages (stippled area of Figure 2) is apparent at all distance categories for all-cause mortality of children 1–59 months of age and for high-density parasitemia, anemia, and hemoglobin level.

The overall pattern of effects is similar for all five malaria-related outcomes: protective effects are observed within the ITN compounds, with a similar level of protection seen in control compounds located within 300 meters of intervention compounds; these effects are statistically significant for the morbidity measures most sensitive to changes in transmission levels: anemia and hemoglobin level. The level of the protective effect appears similar for most outcomes for all four distance groups within ITN villages, although for hemoglobin level an additional benefit of living near the center of ITN villages is suggested. The spatial pattern of protection within control villages is also consistent for these outcomes. No significant protective effect is observed for any outcome in compounds located 600–899 meters from the nearest ITN compound. A suggestion of an increasing protective effect is observed in some outcomes (anemia, hemoglobin level, mortality) in the 300–599 meter category.

Results of tests of trend reflect the patterns visible in Figure 2 for clinical malaria (odds ratio [OR] = 0.92, 95% confidence interval [CI] = 0.75, 1.12, $P = 0.38$), high-density parasitemia (OR = 0.89, 95% CI = 0.78, 1.01, $P = 0.08$), moderate anemia (OR = 0.78, 95% CI = 0.69, 0.89, $P = 0.0001$), hemoglobin level regression coefficient (OR = 0.18, 95% CI = 0.06, 0.31, $P = 0.0048$), and child mortality (hazard ratio = 0.94, 95% CI = 0.90, 0.98, $P = 0.002$). For all of these malaria-related outcomes, trends are in the direction indicating greater protection in compounds closer to intervention villages, with strongly significant trends seen for mortality, anemia, and hemoglobin level. For geohelminth infection, no trend was observed (OR = 1.09, $P = 0.47$).

The relationship between coverage and the community effect are shown in Figure 3. Within the 300-meter band of control compounds nearest to ITN compounds, the strength of this community effect is dependent upon the proportion of compounds with ITNs. For high parasitemia and anemia, significant protective effects are observed only when coverage exceeds 50%. For hemoglobin level, maximal effect is seen

when coverage is greater than 50%. No effect was observed for any outcome when coverage was less than 25%; no pattern was observed for helminth infection. Results of trend tests show significantly increasing protection with increasing coverage for clinical malaria ($P = 0.027$), high-density parasitemia ($P = 0.049$), anemia ($P = 0.0024$), and hemoglobin level ($P = 0.0016$), but not for helminth infection ($P = 0.31$). Results for clinical malaria (for the analysis illustrated in Figure 3) and mortality are not presented since models did not converge due to low frequency of these end points.

The preceding results show that control homes within 300 meters of ITN villages receive protection from ITNs in nearby homes. We realized that traditional analyses of efficacy, which compare intervention groups to control groups, might underestimate the true efficacy of ITNs since, in fact, part of the population in the control group closest spatially to the intervention group also receives protection from the intervention. Thus, in the usual analysis, control homes that received the beneficial effect of neighbors' ITNs would be in the comparison group to the ITN villages, thereby reducing estimates of ITN efficacy. To assess the degree to which this reduction in estimated efficacy occurred, we produced two sets of models. The first was the traditional comparison of intervention and control compounds adjusted for potential confounders as described earlier. We then added a single dichotomous variable for control homes within 300 meters of intervention compounds to our models. This essentially allowed us to control for the greater part of the community effect by removing the homes experiencing the greatest such effect from our comparison group, thereby allowing us to estimate more accurately the true efficacy of ITNs. The effect of controlling for the community effect for the five malaria-related outcomes is shown in Table 3. Adjustment for the community effect increases the estimate of the protective efficacy of ITNs for every outcome. The relative change in efficacy ranges from 4% to 20%. Furthermore, increased precision of the estimates of effect is obtained when adjustment for the community effect is performed, as shown by the narrower confidence intervals for the community effect-adjusted estimates as compared with unadjusted estimates.

DISCUSSION

In the present study, we observed patterns suggesting existence of a community effect of ITNs for several different malaria-related outcomes using data obtained through separate methodologies: 1) the census for the mortality data covering all of Asembo; 2) cross-sectional studies for the morbidity data for a subset of Asembo villages; and 3) longitudinal entomologic studies (presented in this supplement by Gimnig and others[4]) for a different subset of Asembo villages. All three lines of evidence lead to the same conclusion, that a beneficial community effect is real, and that the hypothesis that ITNs divert mosquitoes to houses of individuals lacking ITNs is incorrect.

These results are consistent with the analysis of child morbidity and mortality data from two other large-scale ITN trials in Africa. In Ghana, Binka and others[8] showed that mortality rates of children living in control compounds increased with increasing distance from the nearest ITN compound. Similarly, rates of severe clinical malaria in coastal Kenya were
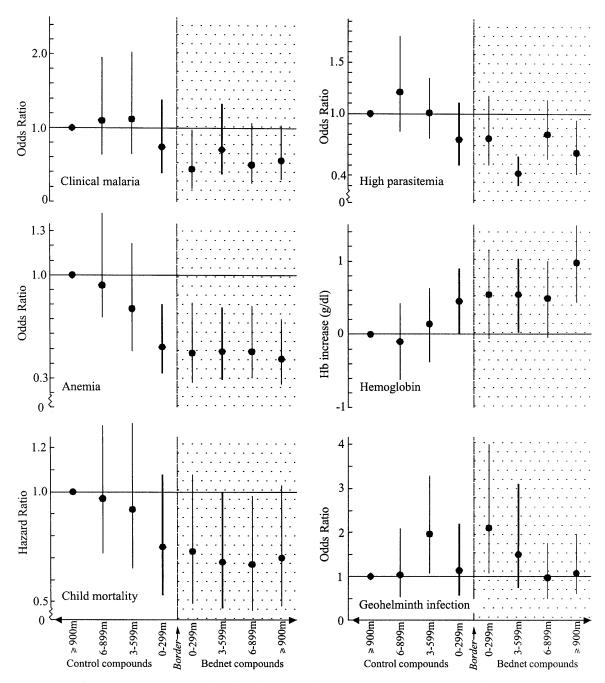
FIGURE 2.   Effect of distance to nearest compound of differing intervention status on six health outcomes. Point estimates and 95% confidence intervals are shown for compounds in each geographic exposure category. All analyses control for appropriate covariates as described in the text. The reference group for each analysis is control compounds ≥900 meters from the nearest insecticide-treated bed net compound. Clinical malaria is defined as high parasitemia plus fever, high parasitemia is >5,000 parasites/mm^3 of blood, and anemia is a hemoglobin (Hb) level <9 g/dL. For these outcomes (and for geohelminth infection, a non-malaria-related infection included for comparison) odds ratios were calculated. The effect of distance on hemoglobin level was modeled using linear regression. All of these outcomes were modeling using cross-sectional data for children less than three 3 years old. The mortality analysis is for all children 1–59 months of age in Asembo over the two-year intervention period.

lower in children living in houses lacking ITNs but living in villages where most families had nets.[7] A community effect for important health measures therefore appears to be commonly associated with use of ITNs. In our study, 23% of the population of the control villages lived within 300 meters of ITN villages. Residents of these villages received as much protection from ITNs as those living in villages within the intervention zone.

The clarity of the community effect we observed, with strongly significant trends seen for mortality, moderate anemia, and hemoglobin level, coupled with the observation that the strength of this effect is strongly correlated with coverage, lead us to consider two different models of ITN action. The prevalent view at present is that ITNs are a barrier to biting of mosquitoes, and that most of the effect of ITNs is at the level of the individual net user. Although no data support this view, it is a logical and obvious one. An alternative view is that the community effect is exceptionally strong, at least in
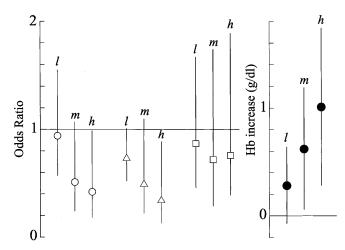
FIGURE 3. Effect of percent of nearby compounds with insecticide-treated bed nets (ITNs) (*l* = 1–24%; *m* = 25–49%; *h* = 50–75%) on odds of high parasitemia (**open circles**), anemia (**triangles**), and geohelminth infection (**squares**) for children less than three years old living in compounds without ITNs located within 300 meters of ITN compounds. A similar regression analysis of hemoglobin (Hb) level (**closed circles**) is also shown. Point estimates with 95% confidence intervals are shown.

the context of an efficacy trial with high coverage, and that most of the effect of nets stems from area-wide effects on mosquito populations. The fact that the efficacy of nets in reducing mortality and four separate measures of malaria morbidity is approximately the same in control compounds proximate to netted areas supports this conclusion. The degree to which protection of non-netted houses occurs varies in a clear dose-response, and the proportion of nearby compounds having ITNs is also consistent with this hypothesis. Low levels of coverage are associated with a weak community effect; high levels of coverage (greater than 50% of the compounds) are associated with a strong community effect.

These data support the existence of a strong community effect, but they tell us nothing directly about the relative strength of the individual barrier and community effects. To do so, we must infer a plausible mechanism of ITN action that incorporates information on the roles of three interrelated factors: the net as a barrier preventing mosquito feeding on individual net users; community coverage of nets, with effects on mosquito populations; and the insecticide. However, some level of inference is possible, based upon our data and those of other workers. Nets, when properly deployed, clearly act as a barrier to feeding, but, on a community level, sufficient reduction in mosquito feeding to cause a decrease in sporozoite rates in mosquitoes or malaria parasitemia in humans required a relatively high level of coverage in Papua New Guinea villages even when all nets were untreated.[5,6] Remarkably, effects on parasitemia in humans were more dependent upon coverage than upon individual use of nets. These investigators hypothesize that the coverage-dependent area-wide effects observed in their study were due to reduced longevity of anthropophilic vectors forced to expend extra energy in a search for blood. In our study, which found marked effects of coverage on malaria morbidity using ITNs (Figure 3), difficulties in obtaining blood are compounded by the poisonous effects of insecticide. That child mortality increased in our study with increasing time since re-treatment

with insecticide drives home the importance of the insecticide.[17] The exhaustive review of Lengeler[19] comparing effects of treated nets when controls are either no nets or untreated nets further supports the beneficial impact of insecticide. Data showing possible efficacy of untreated nets, recently reviewed by Guyatt and Snow,[20] fail to take into account coverage effects and thus may overestimate efficacy of untreated nets in areas of low coverage. It is important to note that there are no field data showing efficacy of nets, either treated or untreated, when coverage is low. Field trials of nets have usually been in the context of high coverage. If not, the extent of coverage has typically been unmeasured or not included as a covariate in estimation of the effect of nets.

We note that the relative importance of individual and community effects may depend upon an interaction of many factors including anthropophily of vectors, availability of alternative hosts, absolute distances among households, density and distribution of larval habitats in relation to blood meal sources, and the type of insecticide used.

All of the heretofore measured impact of ITNs is due to two primary factors: insecticide and coverage. If the individual protective effect of nets is relatively small, then the gap between efficacy of ITNs, as estimated through randomized controlled trials where every effort is made to ensure high coverage with properly treated nets, and effectiveness of ITN intervention programs is likely to be very large unless programs recognize and act upon the knowledge that it is the community effect of insecticide associated with large and dense population of ITNs, not the individual nets themselves, that underlies a large part of the potency of this intervention.

The conclusion that a strong community effect is associated with an ITN intervention programs helps clarify the mechanism by which this intervention works. However, it is not grounds for foolish optimism; low levels of coverage with treated nets or, worse, untreated or poorly treated nets, may do little but fritter away scarce resources. In contrast, high coverage with ITNs will do more for public health in Africa than previously imagined.

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