Sustainability of Reductions in Malaria Transmission and Infant Mortality in Western Kenya With Use of Insecticide-Treated Bednets

4 to 6 Years of Follow-up

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Context Insecticide-treated bednets reduce malaria transmission and child morbidity and mortality in short-term trials, but this impact may not be sustainable. Previous investigators have suggested that bednet use might paradoxically increase mortality in older children through delayed acquisition of immunity to malaria.

Objectives To determine whether adherence to and public health benefits of insecticide-treated bednets can be sustained over time and whether bednet use during infancy increases all-cause mortality rates in older children in an area of intense perennial malaria transmission.

Design and Setting A community randomized controlled trial in western Kenya (phase 1: January 1997 to February 2000) followed by continued surveillance of adherence, entomologic parameters, morbidity indicators, and all-cause mortality (phase 2: April 1999 to February 2002), and extended demographic monitoring (January to December 2002).

Participants A total of 130000 residents of 221 villages in Asembo and Gem were randomized to receive insecticide-treated bednets at the start of phase 1 (111 villages) or phase 2 (110 villages).

Main Outcome Measures Proportion of children younger than 5 years using insecticide-treated bednets, mean number of *Anopheles* mosquitoes per house, and all-cause mortality rates.

Results Adherence to bednet use in children younger than 5 years increased from 65.9% in phase 1 to 82.5% in phase 2 ($P<.001$). After 3 to 4 years of bednet use, the mean number of *Anopheles* mosquitoes per house in the study area was 77% lower than in a neighboring area without bednets (risk ratio, 0.23; 95% confidence interval [CI], 0.15-0.35). All-cause mortality rates in infants aged 1 to 11 months were significantly reduced in intervention villages during phase 1 (hazard ratio [HR], 0.78; 95% CI, 0.67-0.90); low rates were maintained during phase 2. Mortality rates did not differ during 2002 (after up to 6 years of bednet use) between children from former intervention and former control households born during phase 1 (HR, 1.01; 95% CI, 0.86-1.19).

Conclusions The public health benefits of insecticide-treated bednets were sustained for up to 6 years. There is no evidence that bednet use from birth increases all-cause mortality in older children in an area of intense perennial transmission of malaria.

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THE BURDEN OF MALARIA IN SUB-Saharan Africa remains intolerable, with more than 20% of all deaths of children younger than 5 years attributed to malaria,[1] resulting in up to 11.9 deaths per 1000 children living in malaria-endemic settings per year.[2] The Roll Back Malaria global partnership, founded by the World Health Organization, the United Nations Development Program, the United Nations Children's Fund, and the World Bank, aims to halve malaria mortality by 2010 through implementation of 4 key technical strategies: insecticide-treated bednets, improved case

See also Patient Page.

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management, control of malaria in pregnancy, and early warning and containment of epidemics.[3] Reductions in all-cause child mortality by an average of 17% have been demonstrated in controlled efficacy trials of insecticide-treated bednets.[4] With high coverage in malaria-endemic settings, insecticide-treated bednets could save 6 to 8 child lives (1-59 months) per 1000 protected each year, resulting in significant progress toward Roll Back Malaria goals.[1,5]

Efforts to increase insecticide-treated bednet coverage in Africa are being made[6] but questions remain concerning the long-term durability of this strategy. First, reductions in all-cause child mortality rates due to short-term bednet use may not be sustainable, because initial reductions in mortality occur as a result of the combination of reduced malaria transmission and preexisting partial immunity developed under the formerly higher levels of transmission; after transmission declines and immunity wanes, mortality rates may increase.[7] Second, pyrethroid resistance in *Anopheles* mosquitoes might compromise the long-term effectiveness of insecticide-treated bednets in killing mosquitoes.[8] Third, it is not clear whether a population of insecticide-treated bednet users will maintain proper use and deployment of bednets (adherence) over long periods, particularly when nets are distributed free of charge.[9]

Additionally, some investigators have suggested that in areas of intense perennial malaria transmission, a partial reduction in transmission due to control measures such as insecticide-treated bednets might paradoxically increase child mortality through delayed acquisition of immunity to malaria.[10-12] In areas of high perennial transmission, first malaria infections usually occur during early infancy, when maternal antibodies and physiological factors provide moderate protection from life-threatening illness.[13,14] Children who survive malaria in infancy usually gain sufficient malarial immunity to reduce the severity of later infections.[15] Reducing malaria transmission through use of bednets may shift the age of first infection out of this period of protection[16] and cause a rebound in mortality at older ages. Studies[17,18] from areas with highly seasonal transmission have not found increases in mortality in older children as a result of protection by bednets or insecticide-treated curtains during early life.

A community randomized controlled trial of insecticide-treated bednets in an area of intense year-round malaria transmission in western Kenya provided the opportunity to address questions related to the sustainability of the impact of bednets.[19] During the 2 years of the trial, insecticide-treated bednet use was found to reduce malaria transmission by 90%[20]; all-cause mortality of children aged 28 days to 11 months was reduced by 23%.[5] We report herein the results of an extended evaluation of mortality and morbidity that followed the conclusion of that trial. We assess changes in adherence to insecticide-treated bednets over time, the impact on mosquito vectors and malaria transmission rates, the effect on morbidity indicators in infants, and the cumulative impact on all-cause child mortality after up to 6 years of use.

METHODS

Study Area and Population

The study was performed along the shores of Lake Victoria in western Kenya in rural Rarieda Division (Asembo) and Yala and Wagai Divisions (Gem) with a combined population of 130 000.[21] Residents are mainly of the Luo ethnic group, who earn their living through small-holder farming, fishing, and small businesses. Residents live in scattered homesteads (compounds) consisting of 1 or more houses. A typical compound contains houses for the compound head, his wives, and unmarried sons. Sleeping spaces may be located in bedrooms, sitting rooms, and kitchens and may consist of a bed with frame and mattress or a mat on the floor.

Malaria transmission is intense and perennial in western Kenya, with entomologic inoculation rates reported between 60 and 300 infectious bites per person per year.[22] Malaria in this area primarily affects young children and pregnant women. Parasite prevalence averages 75% in children younger than 5 years, and the incidence of clinical malaria is approximately 33.9 per 100 person-months.[23] The major clinical manifestation of severe malaria in children is anemia, often profound. Before the start of this trial in 1997, insecticide-treated bednets were used by less than 5% of the study population.[24]

Study Design

In the first 2 years of the study (phase 1) in Asembo (January 1997 to March 1999) and Gem (January 1998 to February 2000), we conducted a community randomized controlled trial comparing villages with insecticide-treated bednets (intervention villages) with those without bednets (control villages).[19,25] At the beginning of the extended evaluation (phase 2), insecticide-treated bednets were distributed to all control villages. Phase 2 continued for an additional 2 years (April 1999 to March 2001 in Asembo and March 2000 to February 2002 in Gem) to permit longer-term monitoring. During phase 2, insecticide-treated bednets covered all households in both study sites. After phase 2 was completed, demographic surveillance and provision of free nets and insecticide continued in the study area (January to December 2002). Most results from phase 1 have been reported previously.[5,19,20,24-26]

The sample size for phase 1 was estimated in advance to have 90% power to detect a 20% reduction in all-cause mortality in children aged 1 to 59 months, assuming a loss to follow-up of 15% during 2 years, a 2-sided type I error probability of .05, a 1:1 ratio of intervention to control, and a design effect of 20%.[25] A post hoc analysis indicated that the sample size provided sufficient power to detect differences in all-cause mortality rates of 17.5%.

Phase 1, phase 2, and continued demographic surveillance after phase 2

received ethics approval from the Kenya Medical Research Institute, Nairobi, Kenya, and the US Centers for Disease Control and Prevention, Atlanta, Ga. Written consent was obtained from all heads of compound for participation in the adherence, entomologic, and mortality surveillance, and from caregivers of children invited to participate in the cross-sectional surveys.

Initial Randomization and Bednet Distribution and Monitoring

The methods for phase 1 have been published in detail elsewhere.[19,25] In brief, all 79 villages in Asembo and 142 villages in Gem were randomized by public lottery to receive insecticide-treated bednets at the beginning of either phase 1 or phase 2 (FIGURE 1). Every 6 to 11 months, project staff went door to door to re-treat nets with permethrin (Peripel, Hoechst Schering AgrEvo, Frankfurt, Germany) to a concentration of 500 g/m^2. Re-treatment of nets throughout phase 2 continued using the same methods as in phase 1, with all costs borne by the project.

The distribution of insecticide-treated bednets during phase 1 was accompanied by an extensive educational campaign to promote correct use of the bednets.[24] A more limited educational campaign accompanied distribution during phase 2.

Net deployment was observed between 4:30 and 6:30 AM in Asembo in selected households that were not given advance notice. Surveys were conducted quarterly through phase 1 and phase 2 for a total of 16 surveys. During phase 1, 10 intervention villages were selected with probability proportional to size. One household within each village was randomly selected and the 9 nearest neighboring houses included in the sample for a total of 100 houses in each survey.[20] During phase 2, an additional 100 houses were selected each quarter from former control villages using the same sampling method. Adherence in children younger than 5 years was defined as sleeping with the body completely covered by a hanging net.[24]

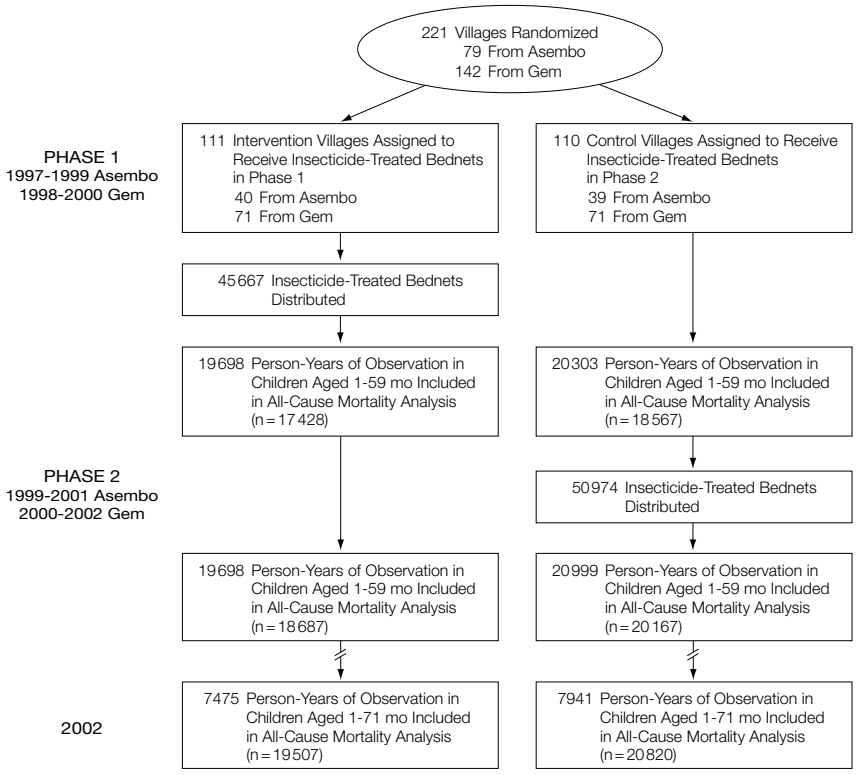
Entomologic Indices

During phase 1, entomologic indices were measured in the intervention houses included in the quarterly adherence surveys and in 100 control houses selected using the same sampling scheme.[20] Mosquitoes resting indoors were collected using standard pyrethrum spray sheet collections.[27] Indoor-resting densities were calculated as the number of blood-fed *Anopheles gambiae senso lato* and *Anopheles funestus* collected divided by the number of houses sampled. During phase 2, all households included in the adherence monitoring were sampled for indoor-resting mosquitoes using the same methods as in phase 1.

During phase 2, all study communities were covered by insecticide-treated bednets and thus no true control villages existed. To monitor entomologic indices under sustained insecticide-treated bednet use in relation to an area without bednets, we initiated entomologic monitoring in 6 villages in Asembo and in an area of approximately equal population size outside but adjacent to the study villages in Kombewa Division, where bednets had not been distributed. Pyrethrum spray collection methods were used to sample 40 houses each month from each site from November 1999 through May 2001, using cluster sampling. The number of blood-fed *Anopheles* was used to calculate the indoor-resting density.

All *Anopheles* mosquitoes were identified morphologically to species, dried, and stored for later testing. All stored mosquitoes were tested for the presence of malaria sporozoites in the head and thorax using standard enzyme-linked immunosorbent assay procedures.[28] We assumed that the number of indoor-resting blood-fed mosquitoes was a proxy measure of the human-biting rate. To estimate the population's rate of exposure to infective

Figure 1. Study Flow Diagram of Use of Insecticide-Treated Bednets and Reductions in Malaria Transmission



mosquitoes, we multiplied the average daily indoor-resting density by the number of days in the month and the proportion of *Anopheles* infected with malaria sporozoites, expressed as the number of infectious bites per person per month.

Morbidity Indicators

Malaria-related morbidity indicators were measured in postneonatal infants (aged 1-11 months) in 5 cross-sectional surveys. The first 2 surveys (1 and 2) were conducted during phase 1 from February 10 to March 24, 1998, and November 16 to December 11, 1998, respectively. The final 3 surveys (3, 4, and 5) were conducted during phase 2 from June 14 to July 8, 1999, May 22 to June 15, 2000, and May 28 to June 22, 2001, respectively. The methods for surveys 1 and 2 have been previously reported.[28] All households in 60 of 79 villages of Asembo were initially randomized to survey 1 (30% of households), survey 2 (30%), or survey 3 (40%). All children younger than 3 years (survey 1) or younger than 5 years (surveys 2 and 3) were invited to participate. The children recruited for survey 3 were asked to return annually for surveys 4 and 5. In addition to the children from survey 3, all children who were born to or who had joined the household of a participant since the last survey were invited to participate in surveys 4 and 5. Each survey therefore provides a community-based, cross-sectional sample of children aged 1 to 11 months.

Procedures for all surveys were similar to those described previously for surveys 1 and 2.[26] Caregivers were interviewed to determine the child's history of illness during the previous 2 weeks. Axillary temperature was measured using a digital thermometer. Finger-prick blood samples were taken to determine the presence of malaria parasites by microscopy and to measure hemoglobin levels using a Coulter counter (Coulter Electronics, Hialeah, Fla). Malaria blood films were prepared in the field, stained with Giemsa, and read by a trained microscopist. Malaria parasites were counted against 500 white blood cells, and parasite density was calculated assuming a white blood cell count of 8000/μL. High-density parasitemia was considered a parasite density of more than 5000/μL. Clinical malaria was defined as an axillary temperature of 37.5°C or higher and any parasitemia. Moderate to severe anemia was defined as a hemoglobin level of less than 7 g/dL.

Mortality Rates During Phase 1 and Phase 2

During phase 1 and phase 2, mortality rates in children were determined from biannual household censuses of the study population.[5] Because malaria infections may affect mortality both directly and indirectly,[7] all-cause mortality was used rather than malaria-specific mortality. For census data collection, 2 to 3 traditional birth attendants per village used standardized forms to record basic demographic information for each household. Baseline enumeration of the population took place at the beginning of phase 1. Approximately every 6 months after the baseline, the census was updated through visits to each household. All child deaths between 28 days (henceforth referred to as 1 month) and 59 months were verified to ensure that age, date of death, and village of residence were correct. Child deaths were included in the analysis if they had been resident in the study area for 1 month or longer and were aged between 1 and 59 months at the time of death. Children were included in the denominator of rate calculations if they had stayed in the study area for more than 1 month.

If mortality rates in older children protected by insecticide-treated bednets from infancy were found to be higher, it might still be possible that overall cohort mortality rates would be reduced by bednets if the increase in mortality in older children was less than the documented decrease during infancy. Because insecticide-treated bednets were distributed to control villages at the beginning of phase 2, it was not possible to follow a cohort of children to calculate a true mortality rate for those younger than 5 years in non–bednet users. We therefore constructed a synthetic cohort using age-specific death rates (ASDRs) to estimate the annual mortality rates that a cohort of children would experience with or without bednets from birth. The ASDRs were calculated using person-time contributed to each age group in the denominator and the number of deaths in the numerator. We used ASDRs from control villages during the 2 years of phase 1 to estimate the mortality in children younger than 5 years without bednets and ASDRs from former intervention villages during the 2 years of phase 2 to estimate the mortality in children younger than 5 years exposed to bednets for up to 4 years. This approach assumes that ASDRs calculated during one period are adequate approximations of mortality rates in the future.

Mortality Rates During 2002

After the conclusion of phase 2, the demographic surveillance system that had been established during the trial was reorganized to increase the frequency of data collection, make use of scanners for data processing, and begin using a relational database system specifically designed for longitudinal demographic monitoring. Because of the logistical difficulties in migrating the census data collected during the trial into the new relational database, we established new baseline censuses (Asembo in September 2001 and Gem in May 2002) that effectively prevented any direct linkage of census data during phase 1 and phase 2 of the trial and subsequent demographic surveillance.

After the baseline censuses in both areas, households were visited every 4 months by a team of trained interviewers. All births, deaths, pregnancies, in-migrations, and out-migrations were recorded. In contrast with phase 1 and phase 2, when residents were registered after living for 30 days in the study area, under the reorganized demographic surveillance system, residents were registered after they had been liv-

ing in the study area for 4 calendar months. Similarly, residents were considered to have out-migrated after an absence of at least 4 calendar months.

Data Management and Statistical Analysis

All data forms were checked for accuracy in the field before being returned to the Kenya Medical Research Institute/Centers for Disease Control and Prevention office for data entry. Data were validated with logic and range checks. Analysis was performed using SAS statistical software version 8.02 (SAS Institute Inc, Cary, NC). PROC GENMOD was used for all regression analyses, and an exchangeable correlation structure was used for all observations from the same cluster unit, either a village or village and survey. For all statistical tests, a 2-sided $P < .05$ was considered statistically significant.

To determine whether adherence differed during phase 2 between former intervention and former control villages, a logistic regression model was used with proper use of a bednet as the outcome measure and residence in an intervention or control village as the predictor variable. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The trend in adherence in children younger than 5 years over time was evaluated separately for former intervention and former control villages using a Cochran-Armitage test for trend.

For entomologic analyses, Poisson regression was used to test for differences in indoor-resting density of mosquitoes between intervention and control villages with a 2-way interaction term to analyze differences by study phase. Similar methods were used to compare differences in indoor-resting density between the study area and the adjacent area. Adjusted risk ratios (RRs) and 95% CIs were determined, and the percentage reduction in indoor-resting density was calculated as $100 \times (1 - \text{RR})$. Logistic regression was used to test for differences in the proportion of infective mosquitoes. Adjusted ORs and 95% CIs were calculated. The nonparametric Wilcoxon rank sum test was used to examine differences in the number of infective mosquito bites per person per month between intervention and control villages by study phase, and between the study area and adjacent area.

Differences in dichotomous morbidity indicators were compared between infants from intervention and control villages in phase 1 and phase 2 using a log-binomial regression model. A 2-way interaction term for trial status by study phase was used to analyze differences within and between study phases. Age in 3-month age categories was included in each model. Adjusted prevalence ratios and associated 95% CIs were calculated.

All-cause mortality rates in children from former intervention and former control villages were compared within each study phase using an extended Cox proportional hazards regression model with time-varying covariates.[29] A 2-way interaction term for trial status by study phase was used to calculate hazard ratios (HRs) for differences in mortality rates within and between study phases. The model adjusted for the potential confounders of sex, study site, age, total monthly rainfall, and average monthly temperature. Standard errors were adjusted using the empirical-sandwich estimator to account for cluster randomization at the village level.[30] Adjusted HRs and 95% CIs were calculated.

To examine differences in mortality rates in 2002 between children from former intervention and former control villages, we applied the same inclusion and exclusion criteria used for deaths and person-time in the phase 1 and phase 2 mortality analysis. Only children born from the start of the trial in both Asembo (January 1, 1997) and Gem (January 1, 1998) were included. Former trial status was determined from residence at the time of the second baseline censuses in 2001 (Asembo) and 2002 (Gem). A Cox proportional hazards regression model with a 2-way interaction term was used to calculate the HR between children from the former intervention villages and former control villages according to the period in which they were born (during phase 1 or after phase 1). The model included the potential confounders of sex and site, but rainfall and temperature were not included because the period covered was 1 calendar year.

RESULTS

Adherence

Adherence to use of insecticide-treated bednets among all children younger than 5 years increased in intervention villages from an average 65.9% in phase 1[24] to 82.5% in phase 2 ($P < .001$). During phase 2, observed adherence was higher among the former intervention villages than the former control villages but the difference was not statistically significant (OR, 1.23; 95% CI, 0.76-1.99; TABLE 1). Bednet adherence in the former intervention villages demonstrated a significant positive increase over time (Cochran-Armitage test for trend: $z = -6.69$, $P < .001$), whereas there was no change in former control villages during phase 2 ($z = -0.67$, $P = .50$; FIGURE 2).

Entomologic Indices

The major malaria vectors in western Kenya are species of the *A gambiae* complex (the members of which are morphologically identical) and *A funestus*.[22] Three quarters of the *Anopheles* captured during all entomologic surveys were of the *A gambiae* complex, and the remaining were identified to be *A funestus*. All subsequent results have been combined for the 2 species because both are important malaria vectors.

Indoor-resting densities of *Anopheles* species in phase 1 were affected by the heavy rains resulting from the El Niño event of 1997-1998. Both intervention and control houses experienced upsurges in mosquito density during late 1997 but the increase was much higher for the households without insecticide-treated bednets (FIGURE 3). During phase 1, houses with bednets experienced a 72% reduction in indoor-resting blood-fed *Anopheles* compared with houses without

bednets and a lower proportion of *Anopheles* infected with malaria (Table 1).[20] The low indoor-resting density achieved with use of bednets in intervention houses during phase 1 continued during phase 2, and there was no difference in indoor-resting density in intervention villages between study phases (RR, 1.55; 95% CI, 0.84-2.87). The reduction in indoor-resting density was also realized in former control villages after receiving nets at the beginning of phase 2 (Figure 3), and there was no significant difference between former intervention and former control households during phase 2 (RR, 1.00; 95% CI, 0.56-1.77; Table 1).

In the houses outside but adjacent to the study area, where insecticide-treated bednets had not been distributed, indoor-resting density was markedly higher. From November 1999 through May 2001 (phase 2), houses in the study area experienced a 77% reduction in indoor-resting density compared with the adjacent area (TABLE 2). The odds that an *Anopheles* mosquito from the study area was infective was 80% lower than that of the adjacent area (OR, 0.20; 95% CI, 0.10-0.42). Comparing the estimated rate of exposure with infective mosquitoes between the study area and the houses outside but adjacent, these results suggest that residents of the study area received 1.3 infective mosquito bites per year compared with 22.3 in the adjacent area, a 95% reduction.

Morbidity Indicators

A total of 1283 postneonatal infants (aged 1-11 months) were surveyed, 637 during phase 1 and 646 during phase 2. Refusals were less than 3%, and data were missing in less than 1% of participants. Caregiver-reported history of infant illness during the previous 2 weeks was similar both across study phases and within study phases between former intervention and former control villages (Table 1). Prevalence

Table 1. Results of an Extended Evaluation of Insecticide-Treated Bednets in Western Kenya (1997-2002)*

	Phase 1				Phase 2			
	Intervention Villages	Control Villages	Measure of Association (95% CI)†	*P* Value	Former Intervention Villages	Former Control Villages	Measure of Association (95% CI)†	*P* Value
Adherence monitoring								
No. of houses sampled	788				789	810		
Adherence in children <5 y, %	65.9				82.5	77.4	1.23 (0.76-1.99)	.41‡
Entomologic monitoring								
No. of houses sampled	853	682			780	806		
Anopheles indoor-resting density, No. per house	0.22	0.91	0.28 (0.16-0.51)	<.001§	0.17	0.16	1.00 (0.56-1.77)	.88§
No. *Anopheles* tested (% infective)	262 (1.2)	998 (3.4)	0.34 (0.10-1.17)	.09‡	192 (2.1)	211 (1.9)	1.06 (0.29-3.87)	.16‡
Malaria infectious bites, No. per person per month	0.08	0.93		.002‖	0.11	0.09		.80‖
Morbidity indicators, No. (%)¶								
No. of postneonatal infants surveyed	343	294			287	359		
Any history of illness	291 (84.8)	259 (88.1)	0.75 (0.44-1.27)	.25	256 (90.1)	327 (91.6)	0.82 (0.44-1.51)	.55
Parasitemic	110 (32.5)	149 (51.4)	0.43 (0.28-0.66)	<.001	96 (33.8)	137 (39.1)	0.76 (0.55-1.05)	.09
High-density parasitemia	42 (12.4)	63 (21.7)	0.51 (0.33-0.80)	.003	36 (12.8)	53 (15.1)	0.83 (0.55-1.26)	.37
Clinical malaria	15 (4.4)	27 (9.4)	0.45 (0.21-0.95)	.02	14 (5.0)	25 (7.1)	0.69 (0.37-1.28)	.22
Hemoglobin <7 g/dL	31 (9.0)	41 (14.0)	0.62 (0.34-1.13)	.12	29 (10.1)	37 (10.3)	0.97 (0.55-1.73)	.98
Mortality rates¶								
No. of deaths in children aged 1 to 59 mo	848	1025			915	931		
Person-years of observation	19 698	20 303			19 698	20 999		
Crude all-cause mortality rate (per 1000 person-years)								
Children aged 1-11 mo	99.9	128.0	0.78 (0.67-0.90)	<.001	113.1	105.4	1.07 (0.91-1.27)	.40
Children aged 12-59 mo	28.2	30.4	0.92 (0.80-1.05)	.21	29.0	28.1	1.04 (0.90-1.20)	.60

Abbreviation: CI, confidence interval.
*Phase 1, a randomized controlled trial with insecticide-treated bednets given to intervention villages only; phase 2, an extended evaluation with insecticide-treated bednets given to control communities. Phase 1 data for adherence,[24] entomology,[20] and mortality[5] have been reported previously. Numbers for mortality in this Table differ slightly from those already reported due to additional observation time in early 1999 after analysis for the previous study was closed.
†Measures of association for different comparisons are as follows: adjusted risk ratio for *Anopheles* indoor-resting density, adjusted odds ratio for adherence in children younger than 5 years and comparison of number of infective mosquitoes, adjusted prevalence ratios for morbidity monitoring, and adjusted hazard ratios for mortality rates.
‡Logistic regression, assuming an exchangeable correlation structure for individuals from the same village and survey.
§Poisson regression, assuming an exchangeable correlation structure for individuals from the same village and survey.
‖Wilcoxon rank sum test.
¶For morbidity, all *P* values are log-binomial regression, assuming an exchangeable correlation structure for individuals from the same village; for mortality, all *P* values are extended Cox proportional hazards regression model, adjusting for sex, study site, age, total monthly rainfall, and average monthly temperature with SEs adjusted using the empirical-sandwich estimator to account for village-level clustering.

of parasitemia, high-density parasitemia, and clinical malaria were all significantly lower in intervention villages than control villages during phase 1 but not phase 2. Moderate to severe anemia was not significantly different between intervention and control villages in either phase. Within intervention villages, there were no statistically significant differences in morbidity indicators between phase 1 and phase 2 ($P>.05$ for all analyses).

Mortality Rates During Phase 1 and Phase 2

We recorded 1873 deaths in children aged 1 to 59 months in phase 1 occurring in 40 001 person-years and 1846 deaths in phase 2 in 40 697 person-years. Less than 0.03% of records had to be discarded due to missing data. The reduced mortality rates of postneonatal infants (aged 1-11 months) achieved through use of insecticide-treated bednets during phase 1 (99.9 per 1000 person-years) were maintained during phase 2 in both former intervention (113.1 per 1000 person-years) and former control villages (105.4 per 1000 person-years; Table 1). Despite the higher point estimate for mortality for infants in former intervention villages in phase 2 vs phase 1, the difference was not statistically significant (HR, 1.09; 95% CI, 0.96-1.25). The mortality rates for phase 1 that are reported here are slightly different than those reported previously due to additional observation time accrued in early 1999 after the previous analysis was closed.[5]

We did not observe any significant reduction in mortality in older children (aged 12-59 months) from use of insecticide-treated bednets in phase 1 (HR, 0.92; 95% CI, 0.80-1.05). If a sustained reduction in malaria transmission during infancy led to increased rates of mortality in older children, we would have expected a higher mortality rate in children aged 12 to 59 months in the former intervention villages than former control villages during phase 2, but no significant difference was apparent (HR, 1.04; 95% CI, 0.90-1.20).

Summing ASDRs to approximate the cumulative under-5 mortality rate indicates that the absolute cumulative risk of dying between ages 1 month and 5 years was reduced by almost 3% (from 24.5% to 21.5%) when insecticide-treated bednets were used for up to 4 years compared with no use (FIGURE 4). This translates to a 12.2% relative reduction in cumulative mortality for children younger than 5 years as a result of bednet use for up to 4 years, which is comparable with the findings of other trials.[4] Therefore, sustained use of insecticide-treated bednets appears to provide an overall cohort survival benefit that is not compromised by an increase in mortality between ages 12 and 59 months.

Mortality Rates During 2002

We recorded 837 deaths in 2002 during 15 416 person-years of observation (TABLE 3). Less than 0.01% of records had to be discarded due to missing or incompatible information.

Figure 2. Proportion of Children Younger Than 5 Years Sleeping Under an Insecticide-Treated Bednet in Intervention and Control Villages During Both Phases of the Study

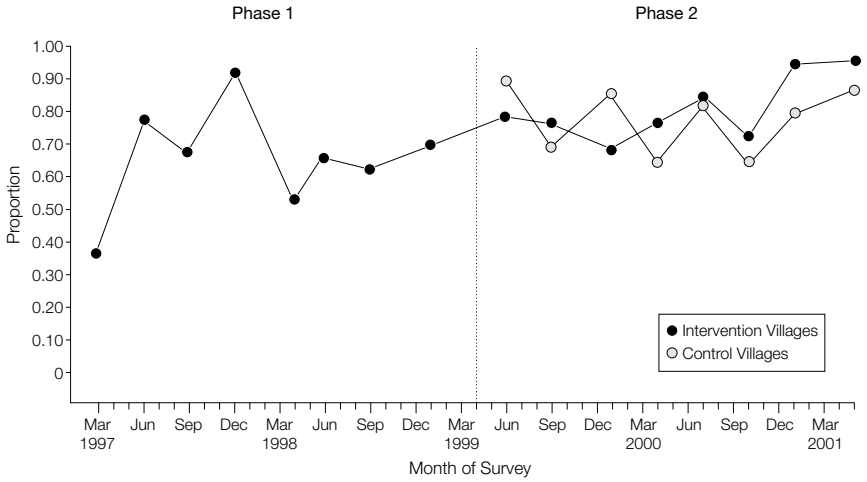
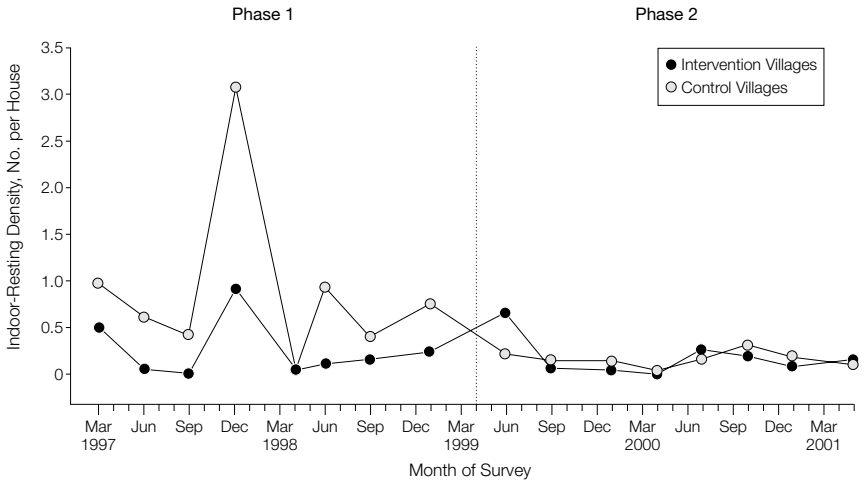


Figure 3. Mean Indoor-Resting Density of *Anopheles* Species Mosquitoes in Intervention and Control Villages During Both Phases of the Study



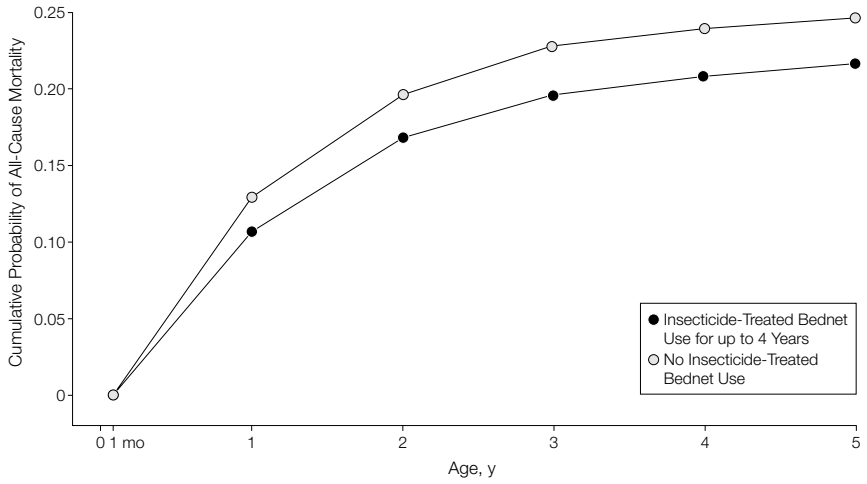
In 2002, children born during phase 1 were between 2- and 5-years-old and children born after phase 1 were 1 month to 3-years-old. Mortality rates were therefore higher in the younger children born after phase 1. Children born during phase 1 in control villages were exposed to normal levels of malaria transmission until the end of phase 1, whereas children born during phase 1 in intervention villages experienced a 90% reduction in malaria transmission.[20] Despite this difference in early exposure to malaria transmission, in 2002 there was no significant difference in mortality rates in children born during phase 1 (HR, 1.01; 95% CI, 0.86-1.19) or after phase 1 (HR, 0.97; 95% CI, 0.61-1.52).

Table 2. Differences in *Anopheles* Indoor-Resting Density, Proportion of Infective *Anopheles,* and Frequency of Infective Bites by Study and Adjacent Area*

	Study Area	Adjacent Area	Measure of Association (95% CI)†	*P* Value
No. of houses sampled	1063	1057		
Anopheles indoor-resting density, No. per house	0.17	0.76	0.23 (0.15-0.35)	<.001‡
No. tested of infective *Anopheles* (%)	424 (1.7)	1799 (7.3)	0.20 (0.10-0.42)	<.001§
Malaria infectious bites, No. per person per month	0.11	1.86		<.001‖

Abbreviation: CI, confidence interval.
*The study area was with insecticide-treated bednets and the adjacent area was without insecticide-treated bednets in Western Kenya from 1999-2001.
†Measures of association for different comparisons are adjusted risk ratio for *Anopheles* indoor-resting density and adjusted odds ratio for comparison of number of infective mosquitoes.
‡Poisson regression, assuming an exchangeable correlation structure for individuals from the same village and month.
§Logistic regression, assuming an exchangeable correlation structure for individuals from the same village and month.
‖Wilcoxon rank sum test.

Figure 4. Cumulative Probability of All-Cause Mortality by Age for Children With Up to 4 Years of Insecticide-Treated Bednet Use Compared With Children With No Insecticide-Treated Bednet Use From Synthetic Cohorts of Summed Age-Specific Death Rates



Summing age-specific death rates to approximate the cumulative under-5 mortality rate indicates that the absolute cumulative risk of dying between ages 1 month and 5 years decreased when insecticide-treated bednets were used for up to 4 years compared with no use.

COMMENT

We continued to monitor the efficacy of insecticide-treated bednets for an additional 2 to 4 years beyond the conclusion of a 2-year randomized controlled trial (for a total of up to 6 years) to address questions related to the sustainability of adherence to bednet use and the impact of bednets on malaria transmission, malaria-related morbidity indicators, and all-cause child (aged 1-59 months) mortality. Our results indicate that insecticide-treated bednets are effective in reducing malaria transmission and all-cause postneonatal infant mortality rates, and that these important public health improvements can be maintained for up to 6 years. Our results do not suggest that a reduction in malaria transmission through use of insecticide-treated bednets from birth leads to an increase in mortality after infancy.

To our knowledge, our results are the first from an area with intense perennial malaria transmission to demonstrate a lack of mortality rebound after up to 6 years of reduced malaria transmission through use of insecticide-treated bednets. Two sites in West Africa with intense but highly seasonal transmission have had similar findings. Six years after insecticide-treated curtains were distributed to households in Burkina Faso, the mortality rate ratio in children 24- to 59-months-old who lived in former intervention villages was 1.16 (95% CI, 0.83-1.60) times that of children from former

Table 3. Mortality Rates for Children Born During Phase 1 and Those Born After Phase 1 by Former Trial Status in Western Kenya, 2002

	Former Intervention Villages		Former Control Villages		
	Deaths per Person-Year	Rate per 1000 Person-Years	Deaths per Person-Year	Rate per 1000 Person-Years	Hazard Ratio (95% CI)*
Children born during phase 1 (aged 2-5 y)	44/3002	14.7	48/3197	15.0	1.01 (0.86-1.19)
Children born after phase 1 (aged 1 mo to 3 y)	365/4473	81.6	380/4744	80.1	0.97 (0.61-1.52)

Abbreviation: CI, confidence interval.
*Cox proportional hazards regression model controlling for sex and study site with SEs adjusted using the empirical-sandwich estimator to account for village-level clustering.

control villages.[17] In Ghana, 7.5 years after insecticide-treated bednets were distributed, no indication of any increase in mortality in children of any age group could be found associated with reduced malaria transmission during the original 2-year trial.[18]

The lack of a rebound in mortality is consistent with the few studies in a review article[31] of malaria chemoprophylaxis that measured mortality after the conclusion of the intervention and found no relative increase in deaths in children who had taken chemoprophylaxis. Only a few studies found any rebound in morbidity after chemoprophylaxis, although infants seemed at a slightly higher risk of rebound than older children, highlighting the importance of this age period in development of malaria-related immunity. Although the infants in our study who used insecticide-treated bednets experienced a decrease in malaria-related morbidity that was sustained over time, more than a third of them were parasitemic in cross-sectional surveys 2 to 4 years after introduction of bednets. This finding suggests that many infants under bednets continue to be exposed to malaria parasites during infancy, albeit with reduced parasite densities. This reduced exposure may improve humoral immune responses compared with normally intense levels of transmission[32] and thereby prevent any mortality increase at older ages.

For reasons of equity and community acceptance, insecticide-treated bednets were distributed to control households at the end of the randomized controlled trial in phase 1, and we continued to re-treat nets with insecticide throughout phase 2 and beyond. Our analysis of the sustainability of the impact of bednets on mortality rates was therefore conducted without the benefit of a true control group and in an environment of significantly reduced malaria transmission. As a result, we are not able to make inferences about mortality rates in children protected by bednets from birth once they are exposed to the normally high malaria transmission of this region. We continue to monitor malaria and entomologic indices in children in this study area and maintain high bednet coverage to detect any change that might occur as a result of extended reductions in malaria transmission.

Recently, there has been a call to distribute insecticide-treated bednets free of charge in the same manner that vaccines are provided free to developing countries, with the argument that bednets provide important community-level effects in addition to personal protection.[9] Our results demonstrate that populations who are given bednets for free and who do not have a history of bednet use can learn to appreciate the benefits of bednets and improve adherence after initial acceptance. However, adherence in our study area increased throughout the period that intensive health education was provided to residents of the study area. These results, therefore, may not be generalizable to other populations if free bednet distribution is not conducted in conjunction with extensive health education.

Insecticide-treated bednets are the most immediately available prevention tool to achieve substantial reductions in malaria mortality in sub-Saharan Africa. However, several major barriers to widespread bednet coverage remain to be overcome, including cost to the household, availability, initial acceptance, and the difficulty and cost of biannual net retreatments. Many of these barriers are being addressed; for example, development of wash-durable bednets may preclude the need to ever re-treat nets.[33] Several governments have removed the import tariffs and taxes on nets, thereby reducing cost to the consumer.[1] Social marketing organizations are working on increasing availability of nets and retreatment kits,[34] and novel distribution mechanisms that link insecticide-treated bednets to national immunization days are being explored.[35]

In conclusion, based on observed efficacy, wide-scale use of insecticide-treated bednets throughout sub-Saharan Africa could help to achieve Roll Back Malaria goals and save the lives of numerous infants each year. Our data suggest that free bednets can be retained, appreciated, and used by populations without negatively affecting survival of older children, at least while low malaria transmission rates are maintained. A sustained global effort to provide free or highly subsidized bednets to those experiencing the greatest burden from malaria could substantially reduce malaria transmission throughout large areas of sub-Saharan Africa for some time to come and save many young lives.

Author Contributions: Dr Lindblade had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data: Lindblade, Eisele, Alaii, Hawley, Wannemuehler, Slutsker.
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Supervision: Lindblade, Alaii, Odhiambo, Hawley, Phillips-Howard, Terlouw, Adazu, Vulule, Slutsker.
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