EFFECT OF SUSTAINED INSECTICIDE-TREATED BED NET USE ON ALL-CAUSE CHILD MORTALITY IN AN AREA OF INTENSE PERENNIAL MALARIA TRANSMISSION IN WESTERN KENYA

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Abstract. We present results from a study conducted in western Kenya where all-cause child mortality was assessed among a population with high levels of sustained insecticide-treated bed net (ITN) use for up to six years. Although ITNs were associated with significant reductions in all-cause mortality among infants 1–11 months old, there was no difference in the rate of all-cause mortality among children 12–59 months old with ITNs for 2–4 years, compared historically with children from villages without ITNs, after controlling for seasonality and underlying child mortality across calendar years (adjusted hazard ratio [AHR] = 0.91, 95% confidence interval [CI] = 0.77–1.07). There was no increase in the proportion of child deaths at older ages (12-59 months old) of all child deaths within villages with ITNs for 5–6 years (48.1%) compared historically with villages without ITNs (47.9%), after controlling for seasonality (AHR = 1.03, P = 0.834). We find no evidence that sustained ITN use increased the risk of mortality in older children in this area of intense perennial malaria transmission.

INTRODUCTION

Insecticide-treated bed nets (ITNs) have been associated with substantial reductions in malaria transmission.[1–4] Accordingly, community-randomized controlled trials conducted across a range of malaria transmission settings in sub-Saharan Africa have shown ITNs and insecticide-treated curtains (ITCs) to be associated with up to a 30% reduction in all-cause child mortality over the first 1–2 years of the trials.[5–9] However, there has been some concern that sustained use of ITNs may increase mortality rates in older children as a result of a delayed acquisition of natural immunity to malaria, especially within areas of intense, perennial malaria transmission.[10–16] Since a global effort is currently under way to scale-up coverage of ITNs to populations at risk of malaria, it is imperative that any evidence of a potential rebound in all-cause child mortality be carefully sought using a variety of epidemiologic approaches.

Recent results from two studies within areas of intense but highly seasonal malaria transmission have described the impact of long-term use of ITNs/ITCs on all-cause child mortality.[17,18] Neither showed any evidence of increased mortality in older children following sustained use of ITNs and ITCs for up to seven-and-a-half years.

Due to ethical concerns regarding withholding a proven life-saving intervention, none of these studies were able to compare mortality rates between sustained ITN users and non-users. Rather, they measured mortality rates during times when both intervention and control groups were under widespread ITN/ITC coverage, comparing children who had used ITNs/ITCs for differing lengths of time. However, it is possible that a general decreasing trend in all-cause child mortality during these studies within the general population

in the area, with or without ITNs/ITCs, could have occurred. In such a situation, a rebound in mortality in the children who had used ITNs from birth might have been masked.

We recently presented results from an area of intense, perennial transmission in western Kenya and failed to find any change in the mortality rate of children 12–59 old months 4–6 years after introduction of ITNs.[19] Here we present additional data and analyses from the western Kenya ITN trial. These data extend the previous analysis in several important ways. First, although these results primarily focus on the four-year ITN study (1997–2001) during which children were under continuous demographic monitoring, we include here an additional year of follow-up from 2002 with a health and demographic surveillance system (HDSS). Second, in addition to the comparison of age specific all-cause mortality rates, we present an analysis of the proportion of deaths occurring at older ages. Third, to address the issue of not having a contemporaneous control group of children not under ITNs, mortality rates and proportional mortality are compared historically to the original control group without ITNs. In doing so, an attempt is made to control for potential confounders of seasonality and underlying changes in all-cause child mortality across calendar years. Finally, we present data on all-cause child mortality from areas contiguous to the study sites without widespread ITN use to assess the overall trends in child mortality in the area over the course of the study.

METHODS

Study site, population, and background. A detailed overview of the study site and population are presented elsewhere.[20] Briefly, the study was conducted in western Kenya in Asembo (Rarieda Division) and Gem (Wagai and Yala Divisions), situated approximately 40 km from the city of Kisumu near Lake Victoria (approximate total population of 130,000).[21] The study population is relatively homogeneous with most (95%) members of the Luo ethnic group. Subsistence farming is the primary source of income. Total annual rainfall averaged 1,134 mm from 1997 to 2002, with 1997 ex-

periencing the heaviest rains (1,342 mm) and 2000 the least (963 mm).

Prior to the start of the study, malaria transmission was intense and perennial[3,22,23] and ITN use was low (< 5%).[24] Historically, all-cause child mortality has been extremely high in this region, since neonatal, infant, and cumulative mortality under five years old was estimated to be 32, 176, and 257 per 1,000 live births, respectively.[25] Human immunodeficiency virus/acquired immunodeficiency syndrome is a growing threat to child survival, directly and indirectly, in this area.

Study design and intervention. The ITN study was split into two distinct but continuous study phases: the initial community-randomized controlled trial (henceforth referred to as phase 1), followed by a two-year extended evaluation (henceforth referred to as phase 2). Details concerning rationale, study design, ITN allocation, and timeline have been presented elsewhere for phase 1[9,26] and phase 2.[19] Briefly, half of the 79 and 142 villages within Asembo and Gem, respectively, were randomized via public lottery to receive ITNs at the start of phase 1, which began in Asembo in 1997 and in Gem in 1998. A total of 45,667 ITNs were distributed to 60,000 people in phase 1. All remaining households within control villages (approximately 70,000 people) were allocated 50,974 ITNs two years later at the start of phase 2, which concluded in 2001 in Asembo and 2002 in Gem. The ITNs were pretreated before distribution with permethrin (Peripel, Hoechst Schering, AgrEvo, Frankfurt, Germany) and then re-treated every 6–11 months during both phases 1 and 2 and in 2002 to a target dose of 500 mg/meter^2 of netting.

Estimates of ITN coverage remained at approximately 1.5 people per net over both study phases within villages allocated ITNs. The ITN adherence (percentage sleeping under a properly deployed net) among children less than five years old within villages originally allocated ITNs increased from 66% in phase 1 to 83% in phase 2.[19,24] The ITN adherence during phase 2 among children less than five years old within former control villages was 77%.

Data collection. Continuous monitoring of child-years at risk and deaths was performed during both study phases with biannual population censuses of the study population, as described in detail elsewhere.[9,26] In summary, all children within the study area were enumerated via a baseline census conducted at the beginning of phase 1. Thereafter, biannual updates were conducted by project-trained traditional birth attendants who visited all households within their villages using pre-printed roll-call forms to record all births, deaths, and migrations.

Following the completion of the four-year ITN study, a new baseline survey was conducted to establish a new HDSS in the study area.[19] Due to incompatibilities in database structure between the demographic surveillance under the ITN study and the new HDSS, linking records and subsequent person-time was not possible.

Data from government burial records of children less than 10 years old who died between 1997 and 2002 in divisions contiguous to the study area were collected from divisional registrar offices to ascertain trends in child mortality in areas without widespread ITN use, as described elsewhere.[27] In these areas, age-specific mortality rates for each month and year of the study were estimated from reported deaths and the population figures from the 1999 Kenya National Census, and extrapolated to other time points using the reported an-

nual growth rate of 0.23%. The number of deaths reported from governmental burial records was incomplete for two of the months during the study (3%). The corresponding monthly mortality rates were inferred from the mean of monthly child mortality rates for these same months over the previous five years.

Data management and analysis. Data collection forms were checked at central field offices prior to data entry at the Centers for Disease Control and Prevention/Kenya Medical Research Institute field station using Visual FoxPro version 6.0 (Microsoft, Redmond, WA). SAS version 8.01 (SAS Institute, Cary, NC) was used for all data cleaning and analyses. Data cleaning was performed using logic checks, with subsequent error listings verified against the original data forms.

The eligibility criteria used to standardize deaths and person-time for assessing child mortality were consistent between phase 1 and phase 2.[9] A counting procedure was used to account for study subjects moving in and out of the survival risk set. The analysis was restricted to children 28–1,824 days old from birth (1–59 months) who resided in the study area for at least one month during the study period. Twenty-nine (< 1%) records with one or more conflicting critical variables that could not be resolved were excluded from analysis.

Person-time was compared using the following four groups to assess the impact of sustained ITN use on all-cause child mortality during the four-year ITN study: control villages during phase 1, henceforth referred to as the baseline (no ITNs during the first two years of the study); intervention villages during phase 1, henceforth referred to as ITN group 1 (under ITNs 0–2 years); former control villages during phase 2, henceforth referred to as ITN group 2 (under ITNs 0–2 years during phase 2 only); and former intervention villages during phase 2 henceforth referred to as ITN group 3 (under ITNs 2–4 years during phase 2). Thus, the baseline group serves as a contemporaneous control to ITN group 1 and as a historical control to ITN groups 2 and 3.

Post-neonatal infant mortality is defined as the rate of death in infants 28–364 days old (henceforth referred to as 1–11 months) per 1,000 person-years, while post-infant mortality is defined as the rate of death in children 365–1,824 days old (henceforth referred to as 12–59 months) per 1,000 person-years. Child mortality is defined as the rate of death in children 1–59 months old.

The effect of ITNs on all-cause child mortality was assessed on an intention-to-treat basis for all analyses. A two-sided P value < 0.05 was considered statistically significant for all analyses. Results of the survival analyses described below are presented as adjusted hazard ratios (HRs). Protective efficacy (PE) is defined as the percent reduction in all-cause mortality between comparison groups, calculated as (1 − the adjusted HR) × 100. Because randomization of treatment status was done at the village level, 95% confidence intervals (CIs) were derived for all survival models using a robust sandwich estimator to correct for the effect of clustering.

Survival analysis for historical comparison. Age-specific mortality rates between ITN group 3 and the baseline were compared to determine whether mortality rates had increased in children as a result of sustained ITN use of 2–4 years. ITN groups 1 and 2 are also compared with the baseline to assess the impact of ITN use for up to two years. An individual-level survival analysis was used to fit a multivariate Cox Proportional Hazard model to the data (SAS Phreg Procedure) to

control for time-dependent covariates. All person-time from Asembo and Gem was pooled for this analysis because the effect of ITNs did not differ significantly between study sites. The analysis was stratified *a priori* by 1–11- and 12–59-month age groups given the findings from phase 1 that showed ITNs to have a significant impact on infant mortality only.[9] Subsequent analyses here showed the effect of ITNs did not differ by age within each of the 1–11- and 12–59-month intervals. Dummy coding was used to establish a single model for comparing the three ITN groups to the baseline. Rainfall lagged by 60 days was included in this model to control for seasonality across calendar years. While the effect of delayed net re-treatment beyond six months was a significant factor on ITN efficacy in phase 1,[9] it was not in phase 2 and was subsequently dropped from the final model. To control for the effect of underlying changes in child mortality in this area over the course of the study, reported monthly mortality rates from the contiguous areas without ITNs were included in the model. Monthly mortality rates estimated from contiguous areas were not associated with lagged rainfall, and thus both were eligible for inclusion in the final model. The final survival model included sex, plus time-dependent covariates for age, total monthly rainfall, and monthly child mortality rates from contiguous areas. Because age in months was not a significant confounder within the model comparing children 1–11 months old, it was excluded from this analysis.

Survival analysis for birth cohorts. To further evaluate whether protection by ITNs throughout infancy was associated with increased mortality rates at an older age, we compared two cohorts of children: those born after their villages received ITNs but at least one year prior to the start of phase 2, and those born into control villages during the same time period without ITNs. The two groups differed only according to their ITN use during the first 12 months of life. Since the ITN study lasted just over four years, children within these cohorts during phase 2 were between 12 and 51 months of age, which is the age group in which a rebound in mortality would be expected following decreased malaria transmission in infancy. A multivariate Cox Proportional Hazard model was used to compare mortality rates in these two cohorts during phase 2 (SAS Phreg Procedure), adjusted by sex, plus time-dependent covariates for age, and total monthly rainfall. Since this was a contemporaneous comparison, child mortality from contiguous areas was not a significant confounder and was thus excluded. All person-time from Asembo and Gem was pooled for this analysis because the effect of ITNs did not differ significantly between study sites.

Analysis of proportional mortality. To test if sustained ITN use resulted in an upward shift in the age distribution of all-cause child mortality, as would be expected if there was a rebound in mortality at older ages, the proportion of child deaths at 12–59 months of age of all deaths at 1–59 months of age were compared between each of the three ITN groups and the baseline. Furthermore, the proportion of child deaths at 12–59 months of age of all deaths at 1–59 months of age among former intervention villages in 2002 are also compared with the baseline, providing up to six years of follow-up for detecting an upward shift in mortality following sustained ITN use. To ensure that the age distribution did not change over the period of study, the proportion of living children 1–11 months old and 12–59 months old was compared between each of the three ITN groups, the former intervention

villages in 2002 and the baseline. Logistic regression (SAS Proc Genmod) was used to compare the odds of dying at 12–59 months of age between the baseline and the four comparison groups outlined above, adjusted by study site and rainfall. Empirically estimated standard errors were derived using generalized estimating equation methods to account for the effect of clustering at the village level.

Ethical clearance. Informed consent to participate in the study was received from all compound heads for both phases of the ITN study and the new HDSS. This research was approved by the institutional review boards of the Kenya Medical Research Institute (Nairobi, Kenya) and by the Centers for Disease Control and Prevention (Atlanta, GA).

RESULTS

We observed 3,719 child deaths at 1–59 months of age among a population followed for 80,698 person-years during the four-year ITN study (1997–2002). The distribution of child deaths (1–59 months) by age for this population clearly shows that most deaths occurred within the first year of life (Figure 1). Mortality rates after the first year of life were very similar, regardless of the length of time ITNs had been used. Peaks in monthly child mortality (1–59 months) followed seasonal peaks in total monthly rainfall throughout the study, regardless of ITN status (Figure 2).

While monthly child mortality rates (0–59 months) estimated from civil registration for contiguous areas showed similar seasonal trends to those obtained from the census, they substantially underestimated child mortality; overall infant (0–11 months) mortality rates increased from 48 to 60 per 1,000, while post-infant (12–59 months) mortality increased from 13 to 15 per 1,000, over the time periods roughly covering phase 1 (1997–1999) and phase 2 (2000–2002) (Figure 2).

The efficacy of ITNs for reducing all-cause child mortality was concentrated among post-neonatal infants (1–11 months) throughout the study (Table 1). After controlling for sex, rainfall, and underlying changes in child mortality in the area, ITN use of 0–2 years was associated with significant reductions in all-cause mortality among post-neonatal infants, compared with the baseline (PEs = 22%, 95% CI = 10–33% and 24%, 95% CI = 11–35%) for ITN groups 1 and 2, respectively. The mortality rates presented here for phase I differ slightly from those previously reported by Phillip-Howards and others[9] due to the inclusion of additional follow-up time accrued since the end-point used in their analysis. Significant reductions in post-neonatal infant mortality rates were maintained among villages of ITN group 3 who had been using ITNs for 2–4 years, compared with the baseline (PE = 18%, 95% CI = 4–30%). Moreover, ITNs remained efficacious in reducing all-cause mortality among children 1–59 months old over all four years of the ITN study. There was no significant difference between post-infant (12–59 months) mortality rates among children residing in villages with ITN coverage of 2–4 years (ITN group 3), compared with the baseline of villages without ITNs, after adjusting for age, sex, rainfall, and underlying changes in child mortality in the area (HR = 0.91, 95% CI = 0.76–1.07).

There was no significant difference in post-infant (12–51 months) mortality between the birth-cohort of children who used an ITN every night of their lives (78 deaths/2,406 person-years, crude rate = 32.4/1,000 person-years), compared with
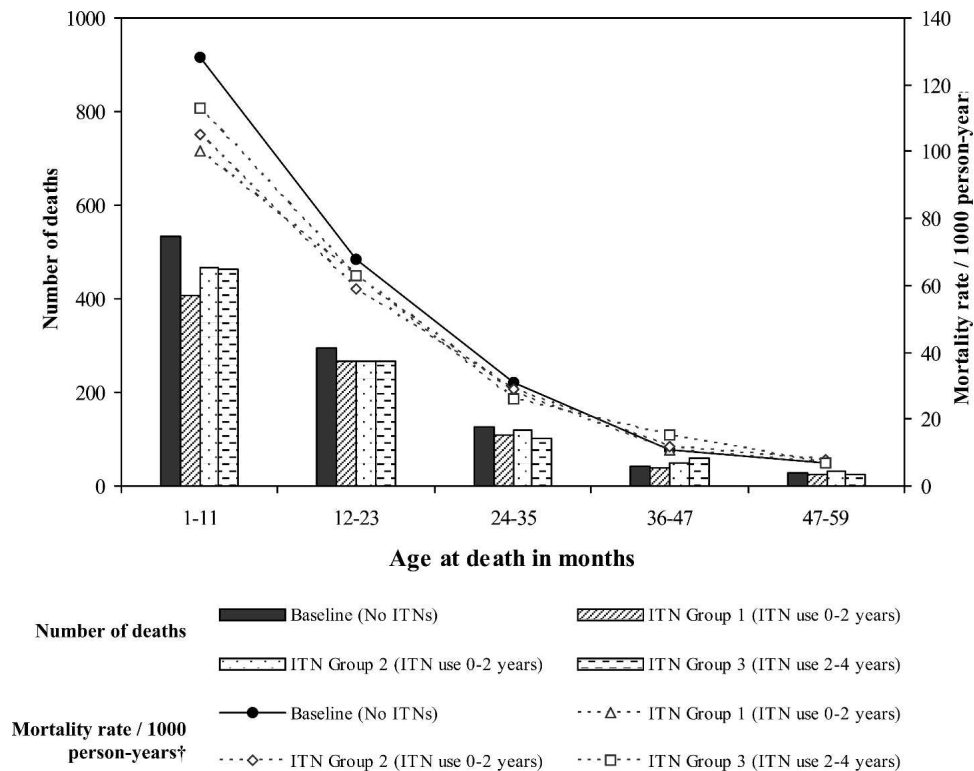
FIGURE 1. Distribution of child mortality by age according to number of years of insecticide-treated bed net (ITN) use. Each comparison group consists of approximately two years of follow-up time.

the cohort exposed to normal levels of malaria transmission for at least their first year of life (67 deaths/2,323 person-years, crude mortality rate = 28.8/1,000 person-years, HR = 1.11, 95% CI = 0.79–1.57), after adjusting for age, sex, and rainfall.

Deaths of children 12–59 months old represented roughly half of all deaths 1–59 months old, regardless of the length of time ITNs had been used (Figure 3). There were no increased odds of dying between 12 and 59 months of age among children within villages with ITN coverage of 2–4 years (ITN group 3), compared with the baseline, after controlling for study site and rainfall (adjusted odds ratio = 1.03, P = 0.733). The proportions of living children 12–59 months old of all children 1–59 months old at the start of the baseline and intervention villages in phase 2 (ITN group 3) were nearly identical at 76.5% and 77.6%, respectively. Furthermore, there continued to be no significant increase in the odds of dying among children 12–59 months old in 2002 within villages with ITNs for 5–6 years, after adjusting for study site and rainfall (adjusted odds ratio = 1.03, P = 0.834). Older children comprised a larger proportion (80.3%) of all living children 1–59 months old in 2002, compared with the baseline (76.5%).

DISCUSSION

The ITNs were shown to substantially reduced malaria transmission in our study area and this dramatic decrease was sustained for more than four years.[19] To investigate the impact of sustained ITN use on all-cause child mortality, we continued to monitor children under high levels of ITN coverage for an additional two years after the completion of a two-year community-randomized controlled trial in an area of intense, perennial malaria transmission in western Kenya. Additionally, we report results from the study population on proportional mortality from 2002, which provides up to six years of follow-up under conditions of widespread ITN use.

This study confirms that sustained ITN coverage does not increase the risk of all-cause mortality in children 12–59 months of age in this area of intense, year-round transmission. These results extend and strengthen our previous analysis.[19] First, we detected no difference in all-cause mortality of older children (12–59 months old) between those who had used ITNs for 2–4 years and those from villages without ITNs at baseline, after adjusting for seasonality as well as changes in the underlying trends in child mortality in the area. Second, the proportion of deaths among children 12–59 months old of all child deaths was nearly identical within villages that had ITNs for up to six years, compared with villages without ITNs, a finding consistent with no upward shift in the age distribution of child mortality. This was observed even though older children comprised a larger proportion of all living children 1–59 months old in 2002, compared with the baseline. Finally, all-cause post-infant mortality rates (12–51 months old), the age range in which one would expect to find any potential rebound, did not differ between the cohort of children who had used ITNs from birth and the cohort without ITNs that was exposed to natural levels of malaria transmission over their first year of life, even after six years of follow-up.[19]

The benefit of ITNs for preventing all-cause mortality was concentrated among post-neonatal infants and remained significant throughout the four-year ITN study. Based on the
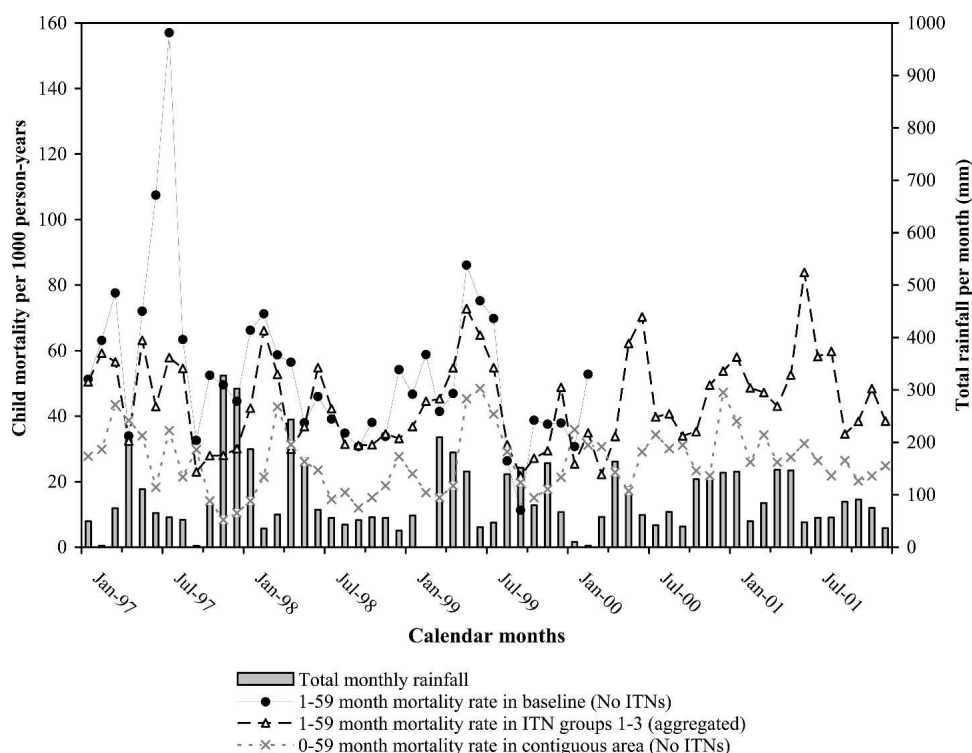
FIGURE 2. Total monthly rainfall and monthly child mortality rates within villages with and without insecticide-treated bed nets (ITNs) and contiguous areas without ITNs.

number of children saved per 1,000 protected during the four-year ITN study, we estimate that ITNs saved the lives of approximately 345 post-neonatal infants. Moreover, these children experienced no increase in mortality rates after reaching their second year of life.

Due to the proven benefits of ITNs in our initial study, it was inappropriate to maintain a contemporaneous control group of children living without ITNs during phase 2. We were therefore only able to make a historical comparison between children during phase 2 and the baseline of children

without ITNs in phase 1. This comparison could have been biased if mortality rates decreased for other reasons during phase 2. However, results from governmental burial records from areas contiguous to the study sites without widespread ITN use showed that all-cause child mortality generally increased during the four-year ITN study (1997–2002). We were able to control for this effect with the inclusion of monthly child mortality rates from these contiguous areas in our main survival model that compared follow-up time from phase 2 historically to the baseline. Adjusting for the underlying

TABLE 1
Comparison of mortality rates by age among children living in villages with varying number of years of insecticide-treated bed nets (ITNs) use compared with children living in villages without ITNs in western Kenya*

	1–11 months†	12–59 months‡	1–59 months‡
Baseline (no. of ITNs): 1997–1999			
Deaths/person-years	534/4,172	491/16,131	1,025/20,303
Crude rate/1,000 person-years	128.0	30.4	50.5
ITN group 1 (ITN use 0–2 years): 1997–1999 (contemporaneous comparison to baseline)			
Deaths/person-years	407/4,075	441/15,623	848/19,698
Crude rate/1,000 person-years	99.9	28.2	43.1
Adjusted HR (95% CI)	0.78 (0.67–0.90)	0.92 (0.80–1.05)	0.84 (0.76–0.94)
Protective efficacy (95% CI)	22% (10–33)	8% (−5–20)	16% (6–24)
ITN group 2 (ITN use 0–2 years): 1999–2001 (historical comparison to baseline)			
Deaths/person-years	466/4,422	465/16,577	931/20,999
Crude rate/1,000 person-years	105.4	28.1	44.3
Adjusted HR (95% CI)	0.76 (0.65–0.89)	0.87 (0.76–1.00)	0.81 (0.72–0.91)
Protective efficacy (95% CI)	24% (11–35)	13% (0–24)	19% (9–28)
ITN group 3 (ITN use 2–4 years): 1999–2001 (historical comparison to baseline)			
Deaths/person-years	463/4,094	452/15,604	915/19,698
Crude rate/1,000 person-years	113.1	29.0	46.5
Adjusted HR (95% CI)	0.82 (0.70–0.96)	0.91 (0.76–1.07)	0.86 (0.75–0.97)
Protective efficacy (95% CI)	18% (4–30)	9% (−7–21)	14% (3–25)

* Protective efficacy = (1 − adjusted HR) × 100. Adjusted hazard ratio (HR) estimated from multivariate survival analysis using a Cox proportion hazard model. CI = confidence interval.
† Model adjusted for sex, rainfall, and underlying changes in child mortality.
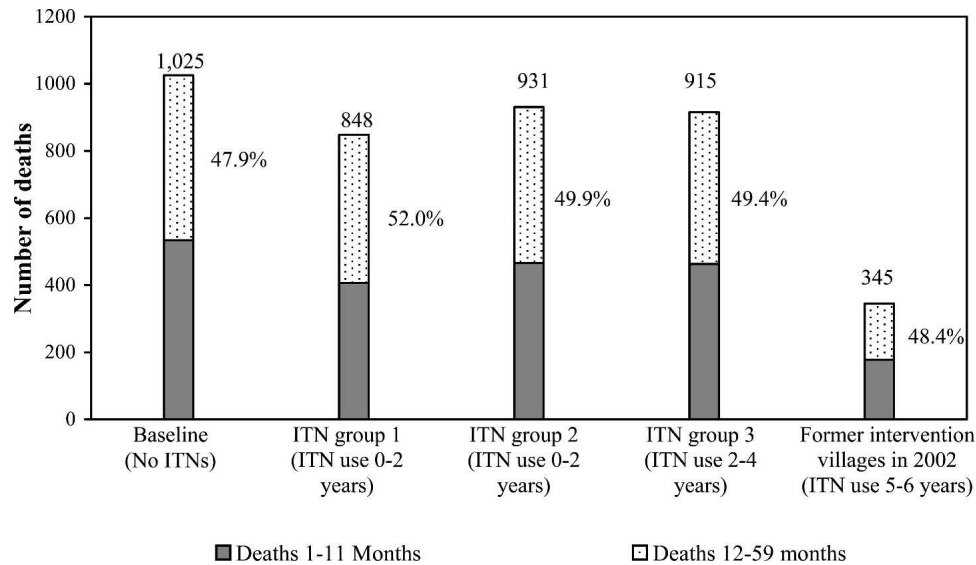‡ Model adjusted for age, sex, rainfall, and underlying changes in child mortality.

FIGURE 3.   Percentage of deaths among older children (12–59 months old) of deaths among all children 1–59 months old according to number of years of insecticide-treated bed net (ITN) use in western Kenya. The baseline and ITN groups 1–3 consist of approximately two years of follow-up time each. The number of deaths in 2002 is lower than in the other periods because they were identified during a 12-month period.

changes in child mortality was crucial in controlling for the effect of outside influences on child mortality over the course of the four year study.

There are several possible explanations why such a dramatic and sustained reduction in malaria transmission did not result in an increase in mortality in older children. First, reductions in malaria transmission have been shown to increase the age of first infection within this population.[28] Although this might delay development of anti-malarial immunity, illnesses occurring at older ages might be more likely diagnosed, treated, and challenged by a more mature immune response. Second, data suggest that significant protection against severe malaria may be acquired after only one or two infections.[29] Cross-sectional studies conducted during phase 2 of the ITN study showed that while infants experienced a sustained decrease in malaria-related morbidity, up to one-third remained parasitemic.[19] Thus, ITNs clearly do not prevent all malaria transmission and infants using them may still acquire at least some level of immunologic protection against severe malaria. Lastly, immunologic findings from this population during phase 1 have suggested lowered malaria transmission due to widespread ITN use may not necessarily compromise the acquisition of humoral immunity to malaria in young children, as a result of more efficient antibody responses.[30] While further clarification of this evidence is required from additional research, it suggests young children protected by ITNs may still garner significant immunologic protection from severe malaria.

These findings support results from a seven-and-a-half-year follow-up of an ITN study in Ghana[18] and a six-year follow-up of an ITC study in Burkina Faso,[17] which demonstrated that older children are not at an increased risk of death following sustained protection from malaria as a result of ITN/ITC use since early in life. Historically, our findings are consistent with those found from the study of the Pare-Taveta Malaria Scheme of indoor-residual household spraying in the late 1950s in an area of intense malaria transmission on the Kenya-Tanzania border. After the program was stopped after

four years, no rebound in all-cause mortality above pre-intervention levels was detected among children 1–4 years old who had previously been protected by the intervention, presumably since birth.[31] Our findings are also consistent with previous research from the Gambia and Tanzania that showed lower malaria transmission pressure during infancy to have limited adverse effects on child mortality at older ages, compared with counterparts within areas of elevated transmission.[32,33] Our findings also coincide with those of a recent study from Tanzania that demonstrated the benefit of ITNs in preventing malaria morbidity in young children is not reversed at older ages following 3–4 years of ITN coverage.[34]

While these results provide no evidence to suggest that mortality increased in older children following sustained ITN use, further investigation of the relationship between the acquisition of clinical malaria immunity during early childhood and transmission intensity is warranted. Monitoring of this study population under conditions of high ITN coverage continues, providing a unique opportunity to assess the long-term implications for malaria in children, as well as young adults, following dramatic reductions in transmission.

Results from this study demonstrate that ITNs continue to save the lives of young children, even with sustained use. Moreover, these results confirm that sustained ITN use is not associated with rebound mortality among older children. The global initiative to promote ITNs for combating early childhood deaths in malarious areas will undoubtedly result in more children surviving into adolescence and adulthood.

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