ORIGINAL ARTICLE

Mosquito Net Use in Early Childhood and Survival to Adulthood in Tanzania

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ABSTRACT

BACKGROUND
It has been hypothesized that in high-transmission settings, malaria control in early childhood (<5 years of age) might delay the acquisition of functional immunity and shift child deaths from younger to older ages.

METHODS
We used data from a 22-year prospective cohort study in rural southern Tanzania to estimate the association between early-life use of treated nets and survival to adulthood. All the children born between January 1, 1998, and August 30, 2000, in the study area were invited to enroll in a longitudinal study from 1998 through 2003. Adult survival outcomes were verified in 2019 through community outreach and mobile telephones. We used Cox proportional-hazards models to estimate the association between the use of treated nets in early childhood and survival to adulthood, adjusting for potential confounders.

RESULTS
A total of 6706 children were enrolled. In 2019, we verified information on the vital status of 5983 participants (89%). According to reports of early-life community outreach visits, approximately one quarter of children never slept under a treated net, one half slept under a treated net some of the time, and the remaining quarter always slept under a treated net. Participants who were reported to have used treated nets at half the early-life visits or more had a hazard ratio for death of 0.57 (95% confidence interval [CI], 0.45 to 0.72) as compared with those who were reported to have used treated nets at less than half the visits. The corresponding hazard ratio between 5 years of age and adulthood was 0.93 (95% CI, 0.58 to 1.49).

CONCLUSIONS
In this long-term study of early-life malaria control in a high-transmission setting, the survival benefit from early-life use of treated nets persisted to adulthood. (Funded by the Eckenstein-Geigy Professorship and others.)

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Malaria remains a major cause of disease and death worldwide.[1] More than 90% of the 409,000 malaria deaths in 2019 occurred in sub-Saharan Africa, and two thirds of deaths occurred among children younger than 5 years of age.[1] Insecticide-treated nets have been a mainstay of malaria control since the Abuja Declaration in 2000.[2] A series of cluster-randomized trials that were conducted in the 1990s showed the substantial survival benefits of treated mosquito nets for children younger than 5 years of age.[3] Largely owing to mass distribution, 46% of persons at risk for malaria in sub-Saharan Africa slept under a treated net in 2019.[1]

As evidence of the survival benefit of treated nets for young children became available in the 1990s, it was hypothesized that the long-term effect of treated nets on survival in high-transmission settings would be lower than the short-term effects and might even be negative, owing to a net-related delay in acquiring functional immunity.[4-9] However, the published evidence on this issue is limited to three studies, with no more than 7.5 years of follow-up, from Burkina Faso,[10] Ghana,[11] and Kenya.[12] None of these publications showed evidence of a shift in child deaths from younger to older ages as a result of malaria control in early childhood. Here, we report data from a 22-year prospective cohort study in rural southern Tanzania that were used to estimate the association between the use of treated nets in early childhood and survival to adulthood.

METHODS

STUDY DESIGN AND OVERSIGHT

In this prospective cohort study, we followed children from early infancy to adulthood. The study was approved by relevant ethics review boards in Tanzania, Switzerland, and the United Kingdom. Parents or guardians of young children gave oral consent for data collected from 1998 through 2003. In 2019, we obtained written consent from participants interviewed in person and oral consent from those interviewed by telephone. The first and last authors vouch for the completeness and accuracy of the data.

SETTING

This study was conducted within the Ifakara Rural Health and Demographic Surveillance Site (HDSS) in the Kilombero and Ulanga Districts, Tanzania.[13] The study area originally comprised 18 villages, which were later split into 25 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). During household visits conducted every 4 months from May 1998 through April 2003, all the children born to an HDSS resident between January 1, 1998, and August 30, 2000, were enrolled in the longitudinal cohort study. From 1998 through 2003, participants were followed by means of HDSS visits every 4 months (Fig. S2). From 2004 through 2015, the survival status of participants known to be residing in the area was recorded at routine HDSS visits. In 2019, we conducted a follow-up survey through community outreach and mobile telephones, verifying the survival status of all the participants, independent of residency and HDSS records. This survey relied on household information provided at the time of enrollment. We created search lists for each HDSS village, which showed the first and last names of all former household members for each participant, as well as the date of birth and the community leader responsible for the household at the time of enrollment. In meetings with local community leaders, this list was reviewed, and additional community members were identified to help with the tracking.

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SOCIAL MARKETING OF TREATED NETS

With support from the Swiss Agency for Development and Cooperation and the government of the United Republic of Tanzania, a program for implementation research on treated nets was set up in the study area in 1995.[14] In 1997, a social-marketing initiative to distribute, promote, and recover part of the cost of nets and net treatment was introduced.[15] A nested case–control study showed that treated nets were associated with a 27% increase in survival among children 1 month to 4 years of age (95% confidence interval [CI], 3 to 45).[15]

OUTCOMES AND VARIABLES

The primary outcome was survival that was verified during household visits. For participants who had died, the age and year of death were obtained from parents or other family members. The primary exposure variable was the use of nets between birth and 5 years of age ("early-life net use”). We analyzed both individual use and community-level availability of nets. For individual net use, the child’s mother or caregiver was asked during each household visit during the 1998–2003 period whether the child had slept under a net the previous night and, if so, whether and when the net had been insecticide-treated or washed. We summarized each child’s early-life exposure to treated nets as the percentage of visits in which children were reported to be sleeping under a treated net. For village-level ownership of treated nets, we combined all household records collected from 1998 through 2003 to compute the proportion of households in each village, and according to year, owning at least one treated net.

Data on malaria parasitemia were collected in 2000 as part of the Integrated Monitoring Project for Antimalarial Combination Therapy.[16] Parasitemia was measured by means of thick-film microscopy among all household members 6 months of age or older in a representative sample of HDSS households in May through July of 2000, 2001, 2002, 2004, 2005, and 2006.[16]

DATA QUALITY AND COMPLETENESS

To maximize data quality and completeness of follow-up in 2019, we recruited and trained a team of experienced interviewers who already possessed extensive local knowledge. For some families, information on caregiver education, household income, and time to reach a health facility was not available. Multiple imputation with chained equations was used to address missing covariate data in our main results. All the variables that are listed in Table 1 were included as predictors for these imputations. Additional complete-case analysis was conducted to ensure that the results were not sensitive to the imputation method chosen.

STATISTICAL ANALYSIS

Initial descriptive statistics included mean person-time of follow-up and mortality according to sex, year of birth, caregiver education, and household income categories. Mortality was estimated as the number of deaths per 1000 person-years.

We present data on how net coverage changed over time. To illustrate the relation between household ownership of treated nets at the village level and local malaria transmission, we created scatter plots of village-level treated net coverage against village-level parasitemia prevalence in 2000.

To estimate the associations between net use and long-term survival, we first estimated unadjusted standard Kaplan–Meier survival curves comparing survival outcomes among children reported to be sleeping under a treated net during at least 50% of the early-life visits with those among children reported to be sleeping under a treated net during less than 50% of the early-life visits. The 50% cutoff was chosen to match a simple “majority of the time” definition. To ensure that results were not driven by this arbitrary cutoff, we also estimated unadjusted standard Kaplan–Meier survival curves comparing survival outcomes among children always reported to be sleeping under a treated net with those among children never reported to be sleeping under a treated net. We estimated unadjusted Kaplan–Meier curves for these contrasts both for the full period (0 to 20 years of age) and for the post–early-childhood period (5 to 20 years of age). All the survival analyses were restricted to the time between the first survey interview and the last survey interview, which resulted in both left truncation and right censoring.

We used Cox proportional-hazards models to estimate three primary contrasts of interest conditional on observable confounders — first, the association between survival and the percentage of visits in which children were reported to be sleeping under a treated net; second, survival differences between children using treated nets at half the visits or more and those using treated nets at less than half the visits; and third, survival differences between children always reported to be sleeping under a treated net at their early-life visits and children never reported to be sleeping under a treated net at these visits. For the first association, the percentage of visits was analyzed as a linear term. Martingale residual analysis was conducted to confirm the appropriateness of this linearity assumption. Schoenfeld residual analysis[17] was used to verify the proportional-hazards assumption. To address confounding concerns, all multivariable estimates for these first three contrasts were adjusted for household income category, time to the nearest health facility, the caregiver’s education category, the child’s sex, and the child’s year of birth. All multivariable models also included 25 village-

Table 1. Characteristics of the Participants.*

Characteristic	Participants (N=6706)	Mean Age at Enrollment	Lost to Follow-up, 2019	Mortality	Mean Period of Observation
	no. (%)	*mo*	*%*	*deaths per 1000 person-yr*	*person-yr*
Sex					
Male	3303 (49)	11	11	6.2	16.0
Female	3403 (51)	12	11	6.4	16.0
Year of birth					
1998	2592 (39)	16	12	5.8	16.4
1999	2452 (37)	10	10	6.8	15.9
2000	1662 (25)	7	10	6.4	15.6
Maternal education†					
None	772 (12)	13	11	7.4	15.5
1–6 yr of schooling	1528 (23)	10	11	7.1	15.8
7 yr of schooling	4056 (60)	11	11	5.8	16.3
≥8 yr of schooling	200 (3)	13	14	4.4	15.9
Missing	150 (2)	32	13	8.4	13.8
Time to health facility†					
<0.5 hr	1060 (16)	5	9	6.9	16.5
0.5–1 hr	1502 (22)	5	8	6.5	16.7
>1–2 hr	1221 (18)	6	8	6.5	16.7
>2–3 hr	629 (9)	6	9	7.9	16.4
>3 hr	279 (4)	4	11	9.2	16.1
Missing	2015 (30)	26	16	4.5	14.7
Household income category†‡					
No income	1746 (26)	12	12	5.8	15.9
Quartile 1	1617 (24)	11	9	4.7	16.7
Quartile 2	1280 (19)	11	9	4.8	16.8
Quartile 3	917 (14)	11	11	6.2	16.1
Quartile 4	599 (9)	11	11	6.7	15.8
Missing	547 (8)	14	14	19.5	12.7
Water source†					
River, pond, or spring	583 (9)	13	10	5.5	16.3
Pump, pipe, or well	6123 (91)	11	11	6.4	16.0

* Percentages may not total 100 because of rounding.
† Shown are values at the time of enrollment in the study.
‡ Participants in quartile 1 had the lowest household income, and those in quartile 4 had the highest household income.

specific intercepts, which allowed us to rule out systematic differences in unobservable village-level factors as potential confounders. To ensure the robustness of the presented results with respect to the empirical model chosen, we also estimated the two binary contrasts using kernel, caliper, and exact matching algorithms.

Given that early-life use of treated nets could be explained by unobserved household or caregiver traits such as health knowledge or individual ability to access health services, we also estimated a village-level model as a fourth contrast. For this contrast, we used village-level mean household ownership of treated nets in

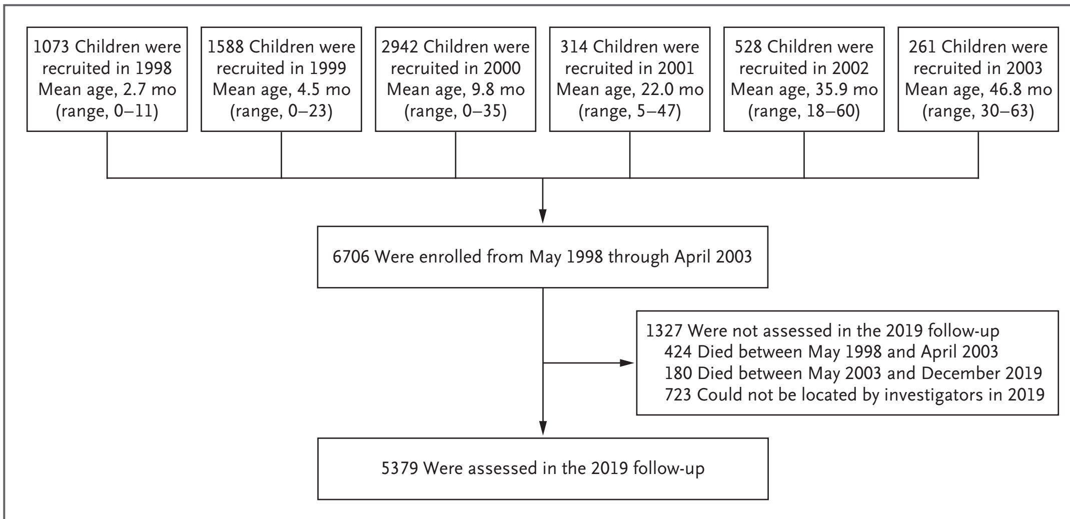

Figure 1. Recruitment, Enrollment, and Follow-up.

the first 3 years that the child was observed (entered as a linear term) as our primary exposure variable. Village-level exposure has the advantage of being less dependent on individual or household-level covariates and should thus be less subject to confounding. Conceptually, increasing village-level coverage should yield larger protective effects than increasing individual coverage owing to larger effects on mosquito populations and malaria transmission.[18]

To account for village-level net treatment as well as village-level correlations more generally, standard errors were calculated with the use of Huber's cluster-robust variance estimator. Results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive associations. Our primary analysis was not prespecified; therefore, no P values were reported. The statistical analysis was conducted with the use of Stata SE software (StataCorp), version 16.0.[19]

Results

Study Population

A total of 6706 participants born between January 1, 1998, and August 30, 2000, were enrolled in the cohort from May 1998 through April 2003 (Fig. 1). The age at enrollment ranged from 3 to 47 months, with a mean of 12 months. A total of 424 participants died between May 1998 and April 2003. In 2019, we verified the vital status of 5983 participants (89% of those enrolled). A total of 180 participants died between May 2003 and December 2019, which resulted in an overall crude mortality of 6.3 deaths per 1000 person-years.

As shown in Table 1, the sample was balanced with respect to sex; on average, children were enrolled just before their first birthday and were followed for 16 years. Most caregivers had completed primary education, and most families had access to piped water or water from a well. Table S1 provides further information on the representativeness of the study sample. The number of deaths per 1000 person-years observed was lowest among children with highly educated caregivers (4.4 per 1000 person-years) and highest among children living more than 3 hours from a health facility (9.2 per 1000 person-years) as well as among households with missing information on education (8.4 per 1000 person-years) or income (19.5 per 1000 person-years).

Exposure to Treated Nets

Table 2 summarizes the main exposure variables. Roughly one quarter of the study participants were reported never to have slept under a treated net, a further quarter were reported at every early-life visit to have slept under a treated net, and the remaining half were reported at some but not all visits to have slept under a treated net. The percentage of children always sleeping under a

Table 2. Cumulative Exposure to Treated Nets.*

Variable	Participants	Mean Age at Enrollment	Lost to Follow-up, 2019	Mortality	Mean Period of Observation
	no./total no. (%)	*mo*	*%*	*deaths per 1000 person-yr*	*person-yr*
All participants					
Never slept under treated net	1515/6700 (23)	12	14	14.9	13.7
Sometimes slept under treated net†	3492/6700 (52)	8	8	3.5	17.5
Always slept under treated net	1693/6700 (25)	18	13	6.3	15.1
Sleeping under treated net reported during <50% of visits	2590/6700 (39)	10	12	9.1	15.3
Sleeping under treated net reported during ≥50% of visits	4110/6700 (61)	12	10	4.6	16.5
Participants born in 1998					
Never slept under treated net	608/2590 (23)	16	15	14.2	14.0
Sometimes slept under treated net†	1438/2590 (56)	11	9	3.3	17.9
Always slept under treated net	544/2590 (21)	27	15	5.1	15.3
Sleeping under treated net reported during <50% of visits	1066/2590 (41)	13	12	8.4	15.8
Sleeping under treated net reported during ≥50% of visits	1524/2590 (59)	17	11	4.0	16.9
Participants born in 1999					
Never slept under treated net	548/2451 (22)	11	14	16.1	13.5
Sometimes slept under treated net†	1275/2451 (52)	7	8	3.8	17.3
Always slept under treated net	628/2451 (26)	15	12	7.0	15.2
Sleeping under treated net reported during <50% of visits	952/2451 (39)	9	12	9.8	15.1
Sleeping under treated net reported during ≥50% of visits	1499/2451 (61)	11	10	5.1	16.4
Participants born in 2000					
Never slept under treated net	359/1659 (22)	8	11	14.3	13.7
Sometimes slept under treated net†	780/1659 (47)	4	8	3.4	16.9
Always slept under treated net	520/1659 (31)	11	13	6.7	14.8
Sleeping under treated net reported during <50% of visits	572/1659 (34)	6	11	9.5	14.8
Sleeping under treated net reported during ≥50% of visits	1087/1659 (66)	8	9	4.9	16.0

* A net that had ever been treated was classified as a treated net, regardless of washing or time since treatment. Data on net use were missing for 6 children.

† Children in the "Sometimes" category were reported to have slept under a treated net at least once and reported not to have slept under a treated net at least once.

treated net increased from 21% of children born in 1998 to 31% of children born in 2000.

Table S2 provides further details on overall trends in net use from 1998 through 2003. Although 34% of children were reported to have slept under a treated net the previous night in 1998, this number increased to 77% of children by 2003. Figure S3 shows the frequency of treated net use in early life. Figure S4 shows the high variability in ownership, with less than 25% of households owning a treated net in 1998 in the village of Iragua and more than 50% of households owning a treated net in the villages of Igota, Kivukoni, and Lupiro in the same year.

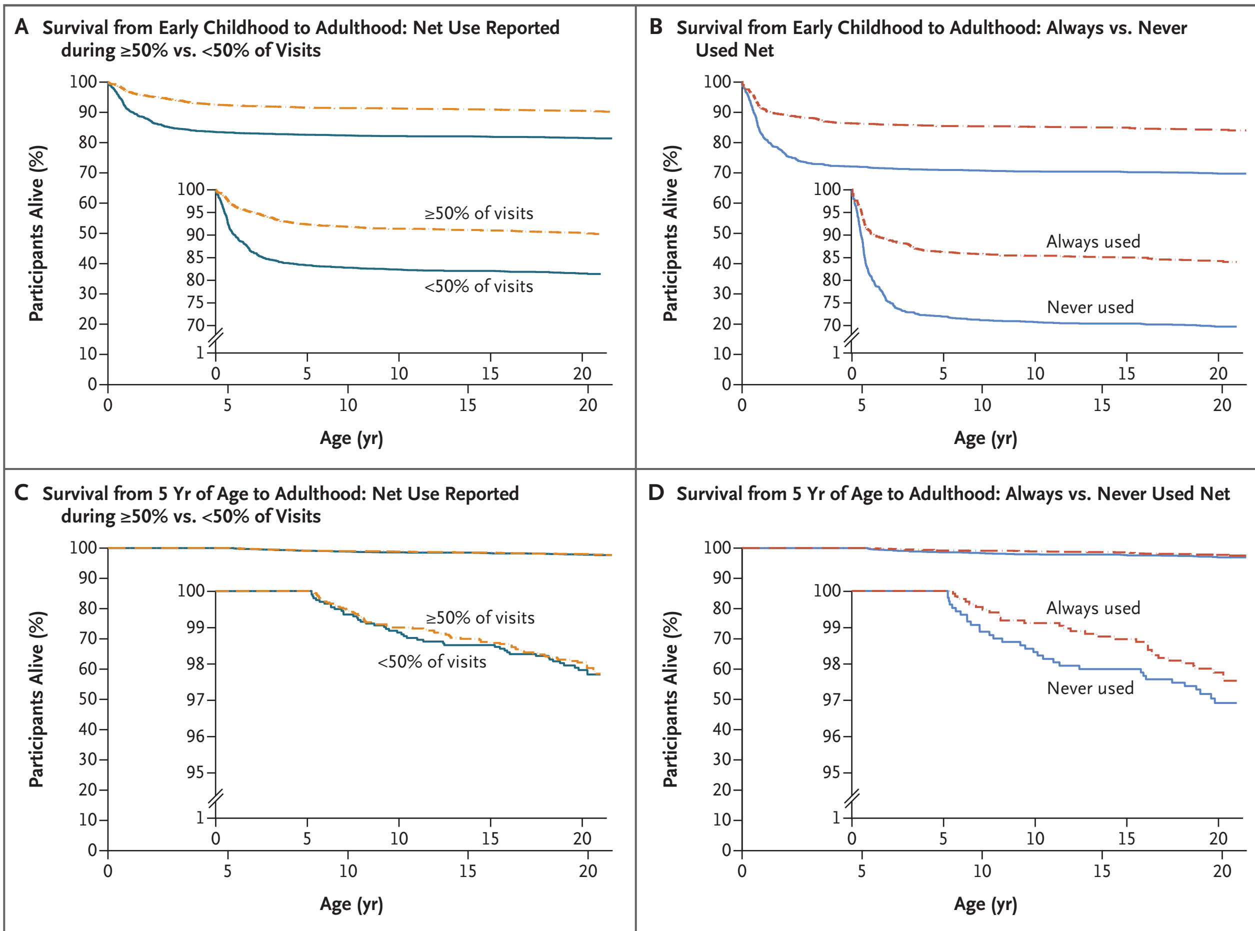

Figure 2. Kaplan–Meier Estimates of Survival to Adulthood According to Use of Treated Nets in Early Childhood (<5 Years of Age).

Unadjusted Kaplan–Meier survival curves are shown. Panels A and C compare the (unadjusted) survival trajectories of children reported to be using treated nets at least half the times visited with those of children with less frequent use. Panels B and D compare the (unadjusted) trajectories of children never reported to be sleeping under treated nets (23% of the sample) with those always reported to be sleeping under treated nets (25% of the sample). Insets show the same data on an enlarged y axis.

ASSOCIATION BETWEEN NET USE AND SURVIVAL

Figure 2 compares the survival trajectories to adulthood of participants according to early-life use of treated nets, including the survival estimates for the full period (Fig. 2A and 2B) and survival curves conditional on surviving to 5 years of age (Fig. 2C and 2D). A total of 604 deaths were recorded during the study period; 485 (80%) occurred during the first 5 years of life. The risk of death peaked in the first year of life, rapidly decreased until age 5, then remained relatively low but with a small increase at approximately 15 years of age (Fig. S6). A total of 91% of the participants who had always used a treated net survived to adulthood; the same was true for only 80% of the children with no early-life use of treated nets (Table 2 and Fig. 2B). Parasite prevalence in 2000 showed a strong negative correlation with household ownership of treated nets both for children younger than 5 years of age (correlation coefficient, −0.63) and for children 5 years of age or older (correlation coefficient, −0.51) (Fig. S5).

Each 10-percentage-point increase in early-life use of treated nets was associated with a 10% lower risk of death (hazard ratio, 0.90; 95% CI, 0.86 to 0.93) conditional on a full set of caregiver and household covariates as well as village fixed effects (Table 3). Children who used treated nets at half the early-life visits or more had a 43% lower risk of death than those using treated nets at less than half the visits (hazard ratio,

Table 3. Associations between Treated Net Use in Early Childhood (<5 Years of Age) and Survival to Adulthood.*

Time Frame and Exposure Variable	Reference Group	Hazard Ratio for Death (95% CI)	No. of Participants
Survival from early childhood to adulthood			
10-percentage-point increase in early-life visits with child reported to be sleeping under treated net	Continuous	0.90 (0.86–0.93)	6697
Sleeping under treated net reported during ≥50% of early-life visits	Sleeping under treated net reported during <50% of visits	0.57 (0.45–0.72)	6697
Child always slept under treated net	Child never slept under treated net	0.54 (0.39–0.74)	3204
10-percentage-point increase in village households owning treated net in first 3 yr observed	Continuous	0.91 (0.82–1.01)	6697
Survival from 5 yr of age to adulthood			
10-percentage-point increase in early-life visits with child reported to be sleeping under treated net	Continuous	0.97 (0.91–1.03)	5799
Sleeping under treated net reported during ≥50% of early-life visits	Sleeping under treated net reported during <50% of visits	0.93 (0.58–1.49)	5799
Child always slept under treated net	Child never slept under treated net	0.69 (0.37–1.30)	2591
10-percentage-point increase in village households owning treated net in first 3 yr observed	Continuous	1.03 (0.84–1.26)	5803

* All coefficients correspond to hazard ratios estimated with the use of Cox proportional-hazards models. All models control for the child's sex, the caregiver's educational-attainment category, and household income and include specific intercepts for year of birth (3 years) and village (25 villages). Standard errors that underline confidence intervals are clustered at the village level to allow for correlation within households and villages over time. Missing values for education, income, and time to a health facility were imputed with the use of the Stata mi package. A total of 250 replications were used to generate the final estimates. The null hypothesis of proportional hazards was not rejected on the basis of Schoenfeld residual analysis.

0.57; 95% CI, 0.45 to 0.72). Similarly, children who always slept under a treated net had a 46% lower risk of death than children who never slept under a net (hazard ratio, 0.54; 95% CI, 0.39 to 0.74). At the village level, each 10-percentage-point increase in the ownership of treated nets was associated with a 9% lower risk of death (hazard ratio, 0.91; 95% CI, 0.82 to 1.01).

Reported use of treated nets during at least half the early-life visits was associated with a hazard ratio for death of 0.93 (95% CI, 0.58 to 1.49) between 5 years of age and adulthood (Table 3). In the initial period of 1998 through 2003, sleeping under a treated net was associated with a 40% lower risk of death (hazard ratio, 0.60; 95% CI, 0.47 to 0.76) when we adjusted for age, caregiver education, household income and wealth, year of birth, and village of birth (Table S3).

Table S4 shows alternative propensity-score and exact matching estimates for our two binary exposure variables, with results almost identical to those presented in Table 3. Table S5 shows survival differences stratified according to the number of early-life visits. Although relatively few observations of at least four early-life visits are available, the estimated protective effect appears to be larger among children with more visits than among those with fewer visits. Table S6 shows the results of the complete-case analysis; these results are almost identical to those of our main analysis, with slightly greater precision for the village-level estimates.

DISCUSSION

Although there is robust evidence of survival gains from treated nets among children younger than 5 years of age, the long-term effects remain little studied, particularly in areas of high transmission.[20] Our results suggest substantial long-term benefits of childhood use of treated nets. These results are robust across a wide range of empirical specifications and imply that concerns regarding increased mortality in later childhood or adolescence — which might, in theory, result from delays in developing functional immunity — are not warranted. Although our study included no direct measure of immune function, it could be argued that survival to adulthood in a malaria-endemic area is itself a reflection of functional immunity.

The strengths of our study include the sample size, with more than 6500 children enrolled; the length of follow-up, with a mean follow-up period of 16 years; the unexpectedly low losses to follow-up (11%); and the consistency of the results from different analyses. The high rate of follow-up is probably due to an unusual combination of factors, such as the wide availability of mobile telephones, the cohesive nature of rural communities in the study area, and the deep and positive social connections made between study staff and local communities through the HDSS.

Our study has certain limitations, which include a lack of individual follow-up between 2003 and 2019; no information on children who died before the first study visit, which means that cohort survival rates are not fully representative of all births in the same period; and the observational analysis. Even though our models included a substantial number of covariates, residual confounding cannot be ruled out. Given these limitations, we suggest that further research is needed on the effect of consistent use of nets over time, as well as on the public health importance of untreated nets, particularly given current concerns about insecticide resistance.

This long-term study of survival associated with malaria control in early childhood suggests that the survival benefits of insecticide-treated nets were large and persisted to adulthood given a moderate level of community coverage.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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