

IMPACT OF PERMETHRIN-TREATED BED NETS ON THE INCIDENCE OF SICK CHILD VISITS TO PERIPHERAL HEALTH FACILITIES

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Abstract. During a randomized controlled trial of insecticide (permethrin)-treated bed nets (ITNs) in an area with intense malaria transmission in western Kenya, we monitored 20,915 sick child visits (SCVs) by children less than five years of age visiting seven peripheral health facilities. The SCVs were monitored over a four-year period both before (1995–1996) and during the intervention (1997–1998). Results are used to estimate the effect of ITNs on the burden of malaria in this community and to evaluate the potential role of these facilities in assessment of the impact of large-scale public health interventions. Compared with baseline, a 27% greater reduction in the incidence of SCVs was seen in ITN villages than in control villages (37% versus 10%; $P = 0.049$). A similar reduction was observed in SCVs diagnosed as malaria (35% reduction in ITN villages versus 5% reduction in controls; $P = 0.04$). Two-hundred sixteen SCVs per 1,000 child-years were prevented; three-fourths of these were in children less than 24 months old. As a consequence of lack of laboratory facilities, severe anemia was rarely (< 2%) diagnosed, regardless of intervention status. No effect of ITNs on the incidence of respiratory tract infections, diarrhea, and other commonly diagnosed childhood illnesses was observed. The ITNs reduced the number of SCVs due to malaria, but had no effect on other illnesses. Routine statistics from these facilities provided useful information on trends in malaria incidence, but underestimated the burden of severe anemia.

INTRODUCTION

Randomized controlled trials of insecticide (permethrin)-treated bed nets (ITNs) and curtains have demonstrated their efficacy in reducing child mortality in various transmission settings in Africa.^{1–5} Other studies have shown that ITNs reduce by approximately half the risk of malaria parasitemia, clinical malaria, and severe anemia in these areas.^{6–9} Morbidity studies associated with ITNs use active surveillance, thus allowing measurement of disease-specific incidence. While these studies provide useful estimates of the protective efficacy of ITNs on malaria morbidity, they provide no information on the actual number of sick children seeking care at peripheral health facilities, which is an important indicator of the public health burden of malaria in endemic areas.

Most morbidity studies associated with ITNs have relied on active surveillance. However, routine active surveillance to monitor efficacy is problematic for large-scale control programs.^{10,11} In contrast, routine passive surveillance by national programs, while simple and cheap, is generally considered less reliable, though efforts are underway to strengthen district level surveillance.¹² During the course of a randomized controlled trial of ITNs in western Kenya, we analyzed data from peripheral health facilities to determine the impact of ITNs on all-cause and malaria-associated sick child visits (SCVs). We also explore the potential role of these facilities for passive morbidity surveillance in this rural setting.

MATERIALS AND METHODS

Study site and population. The study population, design, and methods used in the trial are described elsewhere.^{13,14} Briefly, randomization of ITNs to residents living in half of the villages was conducted through public lottery held during a district-wide meeting to launch the intervention in August 1996. Bed nets (Siamdutch Mosquito Netting Co., Bangkok,

Thailand) pre-impregnated with a target dose of 0.5 g of permethrin/m² of netting were distributed in Asembo during the fourth quarter of 1996 to cover all sleeping places (beds or mats) in 40 of the 79 villages. Bed nets were re-treated biannually by the study staff. The mortality trial was conducted from January 1997 to December 1998, but was extended for morbidity studies to March 1999 when control households received bed nets. The project achieved a bed net coverage rate of 1.46 persons per bed net, and an adherence rate (persons directly observed to be sleeping under bed nets) of 66% in children less than five years old.¹⁵

Passive surveillance in peripheral health facilities. A passive surveillance system was established in 13 of 15 peripheral health facilities in Asembo. Three-fourths of these facilities were government funded. Drugs were equally available to peripheral health facilities serving control and ITN villages and all facilities served both control and ITN-treated communities. Two facilities that did not routinely examine at least five sick children each day were excluded. Monitoring began in June 1996 with the assignment of one project staff per facility who interviewed the caregiver accompanying each sick child using a pre-coded questionnaire. In addition to demographic information and data on ITN use, details of the child's illness were recorded using local disease terminology based upon baseline ethnographic studies. At the end of each day, the staff member transcribed to the questionnaire data from facility records on symptoms, diagnosis, and treatment of each child. Project staff did not participate in diagnosis or provide treatment or advice. Facility personnel were unaware of the randomization status of children. Retrospective review of SCVs prior to intervention was conducted in each facility. Project recorders transcribed all visits listed in health facility registers by date of visit, child's name, age, village of residence, diagnosis, and treatment.¹⁶ Of 13 health facilities surveyed, seven that monitored SCVs continuously from January 1995 through March 1999 were selected for this analysis. The

period January 1995 to December 1996 is the pre-intervention period; January 1997 to March 1999 is the intervention' period, and for simplicity of reporting, January 1998–March 1999 is referred to as 1998.

Statistical analysis. Surveillance forms were collected weekly, checked, coded, and forwarded to the Kenya Medical Research Institute/Centers for Diseases Control and Prevention main office for data entry. Analysis was performed using Statistical Analysis System (SAS System for Windows, Release 8.01; SAS Institute, Cary, NC). The incidence of SCVs was calculated as the number of visits per 1,000 child-years. Each child could contribute multiple times to the numerator. The denominator was based on census data for the ITN study for the first quarter of 1997. The analysis assumed that the population remained constant over the intervention period regardless of intervention status.

All analysis was based on intention to treat. Data from children residing in four villages that were split into two for purposes of randomization were therefore excluded from the analysis, since their randomization status could not be accurately determined from village names. Preliminary analysis of pre-intervention data showed that the incidence of SCVs was higher in villages randomized to receive ITNs, compared with subsequent control villages. This complicated the interpretation of post-intervention comparisons between ITN and control villages since analysis had to take into account historical differences: the change in incidence was expressed as a percentage reduction; $100 \times (1 - \text{incidence rate ratio [IRR]})\%$, where the ratio represents incidence during the intervention divided by pre-intervention rate. The difference in the percentage reduction in ITN and control villages was defined as the ITN-associated reduction: $100 \times (\text{IRR}_{\text{control villages}} - \text{IRR}_{\text{ITN villages}})\%$. The statistical significance of the differences over time between ITN and control villages was assessed using the Wald chi-square statistic of the interaction term between randomization status (ITN or control village) and time effect (pre- or during intervention). A significant interaction term indicates that the change over time is different between the ITN and control villages. The impact of

ITNs by age group and by intervention study year (1997 versus 1998) was assessed using analogous interaction terms.

We estimated the potential number of SCVs prevented by ITNs per 1,000 child-years by multiplying the estimate of the bed net-associated reduction described earlier by the crude overall incidence rate in the entire pre-intervention study population. The potential rather than the actual number of visits prevented was calculated because use of the latter would have overestimated the effect of ITNs due to the unequal pre-intervention distribution of SCVs between subsequent ITN and control villages.

Poisson regression using GEE methods in the GENMOD procedure in SAS software was used. Because the trial used village as the unit of randomization, all *P* values and 95% confidence intervals were corrected for clustering at this level, assuming an exchangeable correlation structure for measures from the same village. Two sided *P* values < 0.05 were considered statistically significant.

Ethical clearance. The ITN trial was reviewed and approved by the institutional review boards of the Kenya Medical Research Institute (Nairobi, Kenya) and the Centers for Disease Control and Prevention (Atlanta, GA).

RESULTS

Between January 1995 and March 1999, children 0–59 months old made 23,898 visits to the seven peripheral health facilities. Of these visits, 2,983 (12.4%) were excluded since village of residence could not be determined. Of the 20,915 SCVs used in the analysis, 11,378 were made in the two years pre-intervention and 9,537 were made during the intervention period. Nearly half (9,352; 44.7%) of the SCVs involved children less than 12 months old, 5,221 (25.0%) were 12–23 months old, and 6,342 (30.3%) were 24–59 months old. Monthly SCV incidence for the entire study population over the four-year monitoring period showed distinct seasonal trends in child morbidity (Figure 1). The SCVs generally increased 2–3 months following biannual peaks in rainfall. Be-

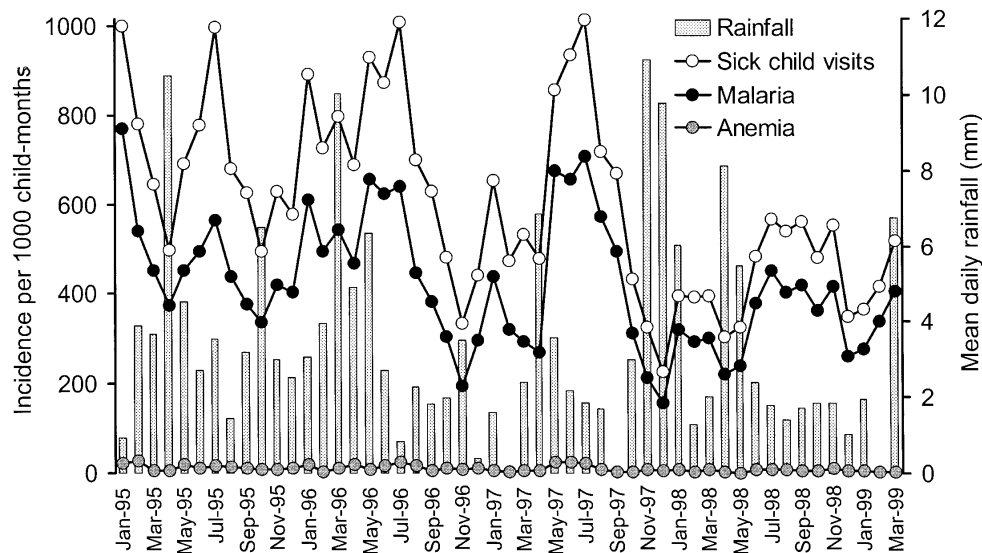


FIGURE 1. Trends in rainfall, sick child visits, and diagnoses of malaria and anemia at seven peripheral health facilities, before and during the insecticide-treated bed net intervention.

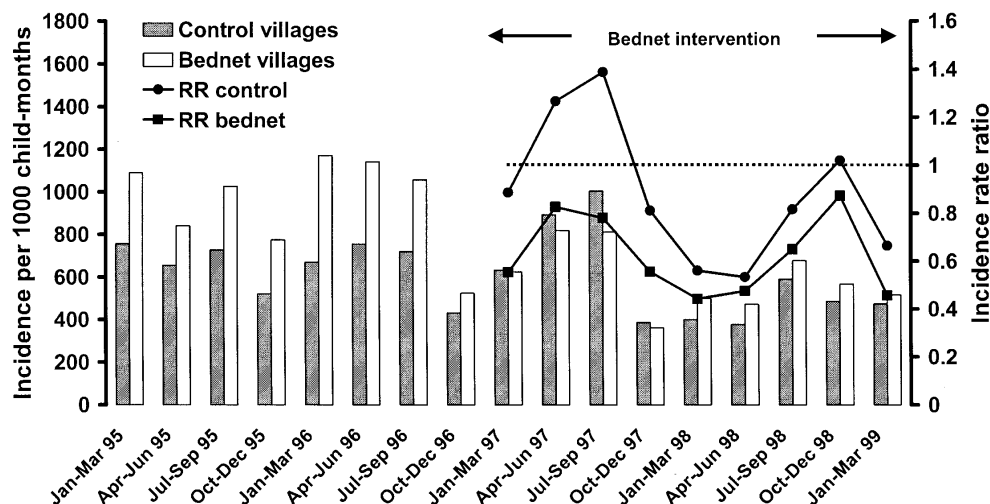


FIGURE 2. Incidence per 1,000 child months of sick child visits to seven peripheral health facilities before and during the insecticide-treated bed net intervention, by intervention status. The two solid lines represent the ratio of the incidence during and before the intervention period. Each quarter from January 1997 onwards is compared with the average incidence in the same quarter in 1995 and 1996. The dashed horizontal line represents the reference incidence rate ratio of 1. RR = rate ratio.

tween 55% and 80% of the SCVs were diagnosed as malaria (Figure 1).

Impact of ITNs on all cause SCVs. In the pre-intervention period, the incidence of SCVs was higher among children from villages randomized to receive ITNs compared with those from villages randomized to the control arm (IRR = 1.41, 95% confidence limits [CL] = 0.81–2.44). Following the introduction of ITNs in 1997, the IRR (95% CL) decreased to 0.86 (0.56–1.31) in the first year, and increased again in the second year to 1.11 (0.75–1.66) (Figure 2). Overall, the IRR (95% CL) was 0.97 (0.66–1.44) during the intervention period. When we compared intervention and pre-intervention rates, the SCV incidence decreased by 27% more in ITN villages (37% [95% CL = 26–46]) than in control villages (10% [95% CL = -23–34]) ($P = 0.049$) (Table 1). The ITN-associated reduction in SCV incidence was significantly greater in 1997 than in 1998 ($P = 0.0048$) (Table 2). Although the reduction in incidence of SCVs associated with ITN use did not differ by age, many more SCVs were prevented in young children because the absolute number of SCVs is higher in this group (Table 1). Thus, three-fourths of 216 potential SCVs prevented occurred in infants and children less than 24 months of age.

A total of 19,999 prescriptions for antimalarials, antipyret-

ics, and antibiotics were issued to sick children following the introduction of bed nets. Of 10,617 sick child visits with drug treatment recorded, a total of 7,748 (73%) were prescribed chloroquine, 749 (7.1%) were prescribed sulfadoxine-pyrimethamine (SP), and 508 (4.8%) were prescribed amodiaquine. Only 28 (<1%) were given quinine. Eighty-six percent of all antimalarial treatments issued was chloroquine, 8.3% was SP, 5.6% was amodiaquine, and less than 1% was quinine. There was no significant difference in the frequency of treatment with an effective antimalarial by intervention status.

The incidence of prescriptions was reduced 30% more in ITN than control villages in parallel with the same overall reduction in the incidence of sick child visits. Thus, sick children from both from ITN and control villages who attended a health facility were each issued an average of 2.1 drugs per illness episode. Similarly, of children diagnosed with malaria, an average of 2.4 drugs were issued per malaria episode diagnosed, again regardless of their randomization status.

Impact of ITNs by diagnosis. Similar to the overall number of SCVs, a 30% greater reduction in the incidence of SCVs diagnosed as malaria was observed among visits from children living in ITN villages (30% versus 5%; $P = 0.04$) (Table 3). Diagnoses of severe malnutrition and anemia were rare and

TABLE 1
Reduction in incidence of overall sick child visits in insecticide-treated bed net (ITN) and control villages

Age (months)	No. followed	ITN villages			No. followed	Control villages			Difference in ITN-associated reduction*	Potential effect	
		Crude incidence rate per 1,000 child-year	95–96	97–98		Reduction (95% confidence limit)	Crude incidence rate per 1,000 child-years	95–96		97–98	Reduction (95% confidence limit)
0–5	450	1,757	886	50% (38–59)	489	1,229	971	21% (-5–41)	29%	1,482	423
6–11	415	1,640	1,168	29% (16–40)	468	1,077	1,086	-1% (-37–26)	30%	1,341	397
12–23	729	1,045	822	21% (5–35)	705	741	822	-11% (-49–18)	33%	896	289
24–59	1,890	574	326	43% (30–53)	1,964	379	294	22% (-14–47)	21%	474	98
Overall‡	3,484	952	603	37% (26–46)	3,626	654	590	10% (-23–34)	27%	800	216

* Percentage reduction in ITN villages minus percentage reduction in control villages.

† Based on the bed net-associated reduction and the overall incidence pre-intervention in ITN and control villages combined.

‡ $P = 0.0491$ for the difference in change over time in sick child visits in ITN versus control villages, adjusted for age.

TABLE 2

Age-adjusted reductions in incidence of overall sick child visits in insecticide-treated bed net (ITN) and control villages by study year*

Study year	Observed effect			Difference in ITN-associated reduction‡	Potential effect	
	ITN	Control	P		Incidence 95–96 ITN plus control villages	Potential no. of visits per 1,000 child-years prevented§
97 versus 95 + 96	31 (20–40)	–14 (–55–17)	0.0053	45%¶	800	360
98 versus 95 + 96	43 (29–54)	27 (1–47)	0.2201	16%¶	800	128

* Values in parentheses are 95% confidence limits.
 † P value for the difference in change over time between ITN versus control villages.
 ‡ Percentage reduction in ITN villages minus percentage reduction in control villages.
 § Based on the ITN-associated reduction and the overall crude incidence pre-intervention in ITN and control villages combined.
 ¶ P = 0.048 for the difference in change over time in sick child visits between ITN and control villages by study year.

constituted only 1% and 2% of all SCVs, respectively, among children from the entire study population. The incidence of anemia, diarrhea, malnutrition, respiratory tract infections, and other illnesses in any age group also decreased with time, and this decrease was greater in intervention villages. However, none of these differences were statistically significant. Comparison by diagnosis of the potential number of SCVs prevented shows that the greatest reduction was in children diagnosed with malaria (Figure 3).

DISCUSSION

In this study, we evaluated the impact of ITNs on SCVs to peripheral health facilities in rural western Kenya. Prior to intervention, the incidence of SCVs was higher in villages randomized to subsequently receive ITNs than in those villages destined to be controls. During the intervention, this trend reversed. Though incidence of SCVs in children less than five years old decreased in both ITN and control areas during the intervention phase, the extent of this decrease was substantially greater in ITN compared with control villages. The proportional reduction in SCVs was similar in all age groups, but the greatest benefit in terms of absolute number of SCVs prevented was in children less than 24 months of age, particularly in infants.

The reduction in SCVs from bed net villages was higher in the first year of the study compared with the second year, but it is possible, for a variety of reasons, that this does not reflect an actual decrease in efficacy. In May–September 1998, the number of SCVs decreased markedly in both ITN and control villages, possibly due to reduced rainfall during this part of

the year,¹³ resulting in lower malaria transmission. Lower malaria transmission may also have resulted from a strong community effect by ITNs observed in this study, reducing malaria associated morbidity in children living within 300 meters of intervention villages (25% of the control population).¹⁷ A stronger community effect in the second study year resulting from the cumulative effects of insecticide on reducing mosquito densities over time may also partly explain the reduced morbidity in the control villages in the second year.¹⁷ In addition, because this analysis was based on data generated from routine statistics, we used a fixed denominator over time. However, the ITNs were found to have a marked impact on mortality in the first year in Asembo (reduction of 34%).¹⁸ Thus, the overall number of children, particularly infants, in ITN villages, but not in control villages, increased over time, as more children survived the first year to contribute to the second year. The use of a fixed, instead of time-dependent, denominator will thus underestimate the true denominator, leading to an overestimate of the incidence of SCVs in ITN villages in the second year, and thus an underestimate of the efficacy measurement. Other possible explanations for this apparent decrease in efficacy are the Hawthorne effect,¹⁹ and selective survival; high-risk children in control villages may die in the first year, and the surviving cohort contributing to the second year consists of a healthier selection of older children. Time to re-treatment with insecticide is unlikely to be a contributing factor because most delayed re-treatment occurred in Gem, not Asembo.¹⁸ It is unlikely that delayed acquisition of immunity resulting in increased malaria morbidity in older children played a role since no shift in the age distribution of SCVs over time was observed. There was also

TABLE 3

Reduction in incidence by diagnosis in insecticide-treated bed net (ITN) and control villages*

Diagnosis	ITN villages			Control villages			Difference ITN versus control		Potential effect	
	Crude incidence rate per 1,000 child-years	Crude incidence rate per 1,000 child-years	Age-adjusted reduction (95% confidence limit)	Crude incidence rate per 1,000 child-years	Crude incidence rate per 1,000 child-years	Age-adjusted reduction (95% confidence limit)	P†	ITN-associated reduction‡	Incidence 95–96 ITN plus control villages	Potential no. of visits per 1,000 child-years prevented§
Malaria	628	414	35% (19–48)	445	450	5% (–77–26)	0.0413	30%	534	160
Anemia	17	8	55% (34–70)	12	8	34% (0.4–57)	0.1892	21%	14	3
Malnutrition	10	3	73% (61–82)	6	3	53% (8–76)	0.2183	20%	8	2
Diarrhea	63	38	41% (04–64)	41	33	23% (–48–60)	0.5262	18%	52	9
Pneumonia	62	37	42% (21–57)	46	31	38% (–1–62)	0.8169	4%	54	2
URTI	322	206	37% (23–49)	230	199	19% (–3–36)	0.1229	18%	275	50
Other	286	223	23% (12–33)	197	212	–2% (–35–23)	0.0861	25%	241	60

* Multiple diagnoses are possible per child. URTI = upper respiratory tract infection.
 † P value for the difference in age-adjusted reductions in ITN versus control villages.
 ‡ Percentage reduction in ITN villages minus percentage reduction in control villages.
 § Based on the ITN-associated reduction times the overall crude incidence pre-intervention in ITN and control villages combined.

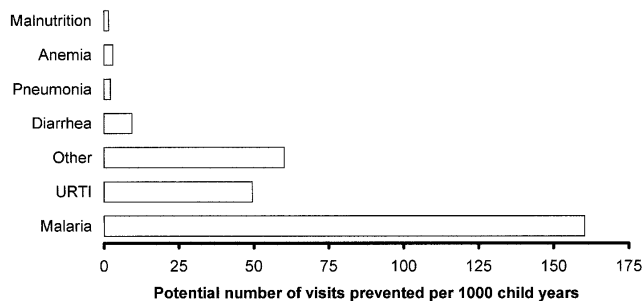


FIGURE 3. Potential number by diagnosis of sick child visits prevented following the introduction of insecticide-treated bed nets in children less than five years of age. URTI = upper respiratory tract infection.

no evidence that the reduction in malaria resulted in increased morbidity due to other non-malaria related illnesses (replacement morbidity).

It is unlikely that our results were influenced by the type of health facility or the type of antimalarial treatment issued by these facilities. The health facilities were equally dispersed between intervention and control villages and none exclusively served children randomized into either intervention or control. Data from this, and the baseline study of diagnosis and prescribing practices,¹⁶ illustrated that the 86% of the sick children visiting health facilities received chloroquine, which was the first-line treatment of uncomplicated malaria at the time of the study. Sulfadoxine-pyrimethamine was made available as first line treatment of uncomplicated, microscopically confirmed *Plasmodium falciparum* malaria to children participating in longitudinal monitoring in the 19 cohort villages.¹³ However, the villages were randomized equally between intervention and control arms in both the cohort and remaining villages.¹⁴

Although none of the clinics had facilities for microscopy or assessment of hemoglobin concentrations, we found a significant reduction in the proportion of SCVs diagnosed to have malaria, but no reduction in the proportion of diagnosis for other common childhood illnesses including respiratory tract infection, diarrhea, measles, or helminth infection. This overall result is consistent with findings of detailed cross-sectional and longitudinal surveys in the same population,²⁰ suggesting that statistics gleaned from peripheral health facilities can provide useful estimates of efficacy of public health interventions in this rural setting. An ITN trial in coastal Kenya also showed that records from Kilifi district hospital could be used to detect a reduction in crude hospital admission rates, malaria admissions, and severe malaria admissions. An important advantage of passive surveillance through routine facilities is that an estimate of the effect of an intervention on actual numbers of children seeking health care may be obtained.

This study also illustrates the limitations of statistics from rural health facilities for monitoring of illnesses requiring laboratory diagnosis. Malaria is one of the main causes of severe anemia in this area, particularly in young children.²¹⁻²³ In concurrent cross-sectional surveys, the prevalence of any anemia (hemoglobin level <11 g/dL) and severe anemia (hemoglobin level < 7 g/dL) was 70% and 6.9%, respectively, with 34% of children exhibiting detectable pallor.²³ In the same study, a reduction of 39% in severe anemia in children

less than three years old was associated with ITN use,²⁰ and in a birth cohort of 900 infants a reduction of 60% was observed.²³ However, no reduction in anemia was reflected in health statistics. This was most likely due to the low prevalence of anemia detected (2%) in the absence of laboratory capabilities. With this diagnostic limitation, it is unlikely that anemia can effectively be used as a key indicator for measuring the impact of a malaria control intervention through rural health facilities.

Two important conclusions can be drawn from this study. First, and most important, is the observation that ITN use was associated with a reduction of 27% in SCVs at peripheral health facilities, reflecting substantial amelioration of the malaria burden on both the children of Asembo and the health care system of Asembo. Second, we confirmed that passive surveillance in peripheral health facilities provided information on disease trends that was sufficiently sensitive to detect a substantial ITN-related reduction in malaria-associated SCVs (though not anemia) among pre-school children.

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