The Combination of Indoor Residual Spraying and Insecticide-Treated Nets Provides Added Protection against Malaria Compared with Insecticide-Treated Nets Alone

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Abstract. Both insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS) reduce malaria in high malaria transmission areas.[1–3] The combined effect of these interventions is unknown. We conducted a non-randomized prospective cohort study to determine protective efficacy of IRS with ITNs (ITN + IRS) compared with ITNs alone (ITN only) in preventing *Plasmodium falciparum* parasitemia. At baseline, participants provided blood samples for malaria smears, were presumptively treated for malaria, and received ITNs. Blood smears were made monthly and at sick visits. In total, 1,804 participants were enrolled. Incidence of *P. falciparum* parasitemia in the ITN + IRS and ITN only groups was 18 and 44 infections per 100 persons-years at risk, respectively (unadjusted rate ratio = 0.41; 95% confidence interval [CI] = 0.31–0.56). Adjusted protective efficacy of ITN + IRS compared with ITN only was 62% (95% CI = 0.50–0.72). The combination of IRS and ITN might be a feasible strategy to further reduce malaria transmission in areas of persistent perennial malaria transmission.

INTRODUCTION

Malaria continues to be a leading cause of morbidity and mortality in Africa. In 2008, there were over 247 million cases of malaria and nearly 1 million deaths.[4] International goals have been set to dramatically reduce malaria illness and death.[5] To achieve these goals, effective tools to prevent malaria, including indoor residual spraying (IRS) and insecticide-treated nets (ITNs), are being scaled up across Africa.

ITNs reduce malaria morbidity and all causes of malaria mortality across a variety of transmission settings.[1] African Ministries of Health have used innovative means to increase ITN number and use, and reductions in morbidity and mortality have been observed in Kenya and elsewhere coincident with ITN scale up.[6,7]

IRS also reduces malaria morbidity and mortality.[3,8] Until recently, IRS was not considered feasible in areas of perennial transmission because of the logistical complexity and considerable resources required to conduct a spray campaign, which in an area of perennial transmission, would need to be done several times per year. Consequently, IRS had been relegated to seasonal transmission or epidemic-prone areas. Recently, longer-lasting residual insecticide formulations have become available,[9] a development that might make IRS a feasible option in areas of perennial transmission.

There has been considerable debate about the relative merits of ITNs and IRS. Review of previous intervention trials, including direct comparisons of ITNs and IRS, indicates that ITNs and IRS have similar efficacy, whereas the cost effectiveness of each intervention is dependent on the unique setting where it is implemented.[8,10,11] A recent Cochrane review concluded that, in areas of perennial malaria transmission, there are insufficient data to conclude whether IRS or ITN provides better protection against malaria.[2]

As each intervention is scaled up within Africa, it is increasingly likely that many people will be protected by both ITNs and IRS. It is unknown whether the combination of these interventions reduces malaria transmission beyond the reduction that would be seen by one of these interventions used alone. Recent data from cross-sectional surveys seem to indicate an added benefit of IRS with ITNs.[6] If ITNs and IRS have additive or synergistic effects when applied in combination, then a strategy of combined IRS plus ITNs may be an effective way to drive transmission to very low levels. However, if there is no added benefit of combining ITNs and IRS, then implementation of both is an inefficient use of scarce resources.

Kenya began an IRS program in Rachuonyo District in Western Kenya in 2008. We used this opportunity to conduct a non-randomized prospective cohort study to compare the combined effectiveness of ITNs and IRS with ITNs alone in preventing *Plasmodium falciparum* parasitemia in areas of perennial malaria transmission. We compared Rachuonyo District with Nyando District, an adjacent district with similar malaria transmission levels[12] where IRS was not conducted.

METHODS

Study site and population. Rachuonyo and Nyando Districts are located in Nyanza Province in Western Kenya. A community-based survey conducted in April of 2008 before the initiation of IRS in Rachuonyo District showed similar malaria prevalence in the two districts (9% in Rachuonyo and 11% in Nyando) and lower ITN use in Rachuonyo, where 37% of compound members reportedly slept under an ITN the prior night compared with 50% in Nyando (Kenya Medical Research Institute [KEMRI]/Centers for Disease Control and Prevention [CDC], unpublished data). Malaria transmission in Nyanza Province is high and perennial, with seasonal peaks in April to July and November to December. The main malaria vectors in this region are *Anopheles gambiae* s.s., *An. arabiensis*, and *An. funestus*. Historically, *An. arabiensis* has been the predominant vector in Rachuonyo and Nyando.[13] Both districts have benefited from heavily subsidized distributions of ITNs targeting pregnant women and children.

The majority of the population in both districts are members of the Luo ethnic group who earn their living through subsistence farming and fishing.[14] The region has been described elsewhere in detail.[15]

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Procedures. The Kenya Ministry of Health (MOH) supported an IRS campaign from July to September of 2008 using λ-cyhalothrin capsule suspension (ICON CS; Syngenta, AG, Midrand, South Africa), a longer-lasting residual insecticide.[16] Every living space in Rachuonyo District was targeted for IRS. The IRS campaign was repeated in April and May of 2009 using alphacypermethrin (Fendon).

We randomly selected households within 1 km of three health facilities in Rachuonyo and within 1 km of three health facilities in Nyando for inclusion in the cohort study. Health facilities in the two districts were similar with respect to type, approximate use rate, and elevation. We limited the radius of enrollment to 1 km around each health facility to improve likeliness that every febrile illness would present to the health facility.

In November of 2008, 2 months after the first IRS campaign was completed, all members of randomly selected compounds were informed about the study. All non-pregnant compound members aged > 6 months were eligible for enrollment, and if they provided consent (or assent if aged 13–17 years), they were enrolled for participation. Women aged 13–45 years were provided a urine pregnancy test if their last menstrual period was not within the prior 4 weeks. Pregnant women were excluded to avoid exposure of the fetus to antimalarial drugs provided to participants at baseline. A questionnaire was administered to assess the use of antimosquito measures and antimalaria drugs. A new long-lasting insecticide-treated net (LLITN) was provided for every sleeping space, and participants were encouraged to replace older ITNs to ensure uniformity of insecticide and durability. All participants provided blood samples for baseline malaria detection by microscopy and hemoglobin measurement by Hemocue.

To ensure that all *P. falciparum* infections were cleared, including subpatent infections, participants were provided a treatment course of artemether-lumefantrine (AL) at baseline. Participants with a positive blood smear at baseline had a repeat blood smear after 2 weeks to ensure parasite clearance. Anemic participants were provided hematinics according to MOH guidelines.

Participants were visited monthly and encouraged to present to the clinic when sick. At monthly and sick visits, a blood smear was made, and hemoglobin was measured for endpoint analysis. A rapid diagnostic test for malaria (RDT) was made for clinical care. Anyone found to be RDT-positive received AL, anyone found to be blood smear-positive received AL and completed the study, and anyone with a hemoglobin < 11 g/dL was treated with hematinics. Participants were followed for up to 9 months.

Microscopy. All blood smears were stained using Giemsa and read independently by two microscopists. Discordant results were resolved by a third microscopist.

Entomological monitoring. Each month, an index house was randomly selected from the study area, and pyrethrum spray catches (PSCs) were conducted on the index and neighboring houses, whether or not study participants inhabited the selected houses, to measure adult anopheline mosquito numbers. In total, 20–30 houses were included for PSC per month. All mosquitoes collected were identified to species morphologically[17,18] and by polymerase chain reaction (PCR) for the identification of *An. gambiae* s.l.[19] to sibling species level.

Throughout the study period, we measured effectiveness of residual insecticide in Rachuonyo by exposing susceptible mosquitoes in plastic cones attached to the walls of 10 houses according to recommended procedures, and measuring mosquito mortality 24 hours after exposure.[20]

Statistical analysis. Primary outcome measures were incidence of *P. falciparum* parasitemia, incidence of moderate anemia (hemoglobin < 8), and differences in entomological indices in the ITN + IRS and the ITN only groups. Measurement of time at risk and *P. falciparum* parasitemia events began 10.5 days after enrollment to account for the half life of AL.[21] If a participant was RDT-positive and received AL but was blood smear-negative, we decreased time at risk by 10.5 days. The primary analysis was by intention, to treat; data were also analyzed according to protocol. Kaplan–Meier survival plots were used to describe time to first *P. falciparum* infection censored at the subject's last study visit. We compared anemia prevalence, ITN usage (having slept under an ITN the prior night), and other categorical variables between the groups at enrollment using log-binomial regression models. We compared time to *P. falciparum* infection and moderate anemia using Poisson regression models. Follow-up time was truncated at last study date or first *P. falciparum* infection. In the adjusted analysis, we controlled for study clinic, housing type (Table 1 shows housing types), baseline *P. falciparum* parasitemia, and seasonality, and ITN use as time-varying covariates. Generalized estimating equations were used in the above regression models to account for correlation within compounds when calculating 95% confidence intervals. Entomological data were analyzed using Poisson regression controlling for clustering at the village levels. Comparisons of species composition and sporozoite rates were done using logistic regression controlling for clustering at the village level. All analyses were done using SAS statistical software (SAS 9.1).

Ethical review. Informed consent was obtained from all human adult participants and the parents or legal guardians of minors. This protocol was approved by the ethical review boards of KEMRI and CDC.

Role of the funding source. The sponsor had no role in the study design, data collection, analysis, interpretation, or writing the report.

RESULTS

Baseline. In total, 1,804 household members were enrolled, 919 in the ITN + IRS group and 885 in the ITN only group. Of those people enrolled, 86% completed the 9-month follow-up period, with no difference between study groups (*P* = 0.92) (Figure 1). Study groups differed at baseline; in the ITN + IRS group, household heads were less likely to have completed primary school education, houses were more likely to be traditional mud and less likely to be semi-permanent structures, overall ITN use was higher, and participants were more likely to have had a fever in the prior 2 weeks than those participants in the ITN only households (Table 1). Children < 15 years of age in the ITN + IRS group had a higher mean hemoglobin. Parasite prevalence did not differ significantly between the two study groups. Clinical malaria, defined as *P. falciparum* parasitemia accompanied by reported fever in the prior 24 hours, was low in both study groups. In total, 74% of households in Rachuonyo and 6% in Nyando reportedly received IRS.

Follow up. Participants were followed for 1,197 person-years, 627 and 570 person-years in the ITN + IRS and ITN

TABLE 1
Study population characteristics at enrollment of ITN + IRS versus ITN only

	ITN + IRS (N = 919)	ITN only (N = 885)	P value
Median age in years (range)	12 (0.5–105)	12 (0.6–91)	0.61
Female (%)	57	56	0.57
Head of household completed primary school (%)	20	32	0.03
Mother completed primary school (%)	21	29	0.05
Household type			
Traditional mud hut (%)	10	3	0.002
Semi-permanent (corrugated iron roof) (%)	64	84	0.002
Permanent (concrete or stone walls) (%)	26	12	0.39
Eves open (%)	90	94	0.25
Mosquito prevention methods			
Mosquito coils, insecticide spray, or repellents used in prior week (%)	6	6	0.96
Received IRS (%)	73	6	< 0.001
At least one bed net in house (%)	71	72	0.95
Slept under an ITN the prior night (%)			
< 5 years	36	30	0.24
5–14 years	20	15	0.20
≥ 15 years	30	22	0.05
Overall	28	21	0.04
Fever in prior 2 weeks (%)			
< 5 years	51	44	0.18
5–14 years	34	21	< 0.002
≥ 15 years	60	38	< 0.001
Overall	49	33	< 0.001
Took antimalarial in prior 2 weeks (%)	21	28	0.08
Took ACT in prior 2 weeks (%)	6	10	0.09
Mean hemoglobin (g/dL)			
< 5 years	11.2	10.5	< 0.001
5–14 years	12.6	12.3	0.008
≥ 15 years	12.6	12.6	0.95
Overall	12.3	12.0	0.009
P. falciparum parasitemia prevalence (%)			
< 5 years	8	6	0.48
5–14 years	12	9	0.37
≥ 15 years	2	2	0.95
Overall	7	5	0.39
Geometric mean *P. falciparum* parasite density per microliter) among participants with parasites	1,136	835	0.45
Clinical malaria (*P. falciparum* parasitemia with fever; %)			
< 5 years	1.9	0.5	0.24
5–14 years	2.4	0.5	0.05
≥ 15 years	0.3	0.6	0.55
Overall	1.4	0.5	0.05

only groups, respectively. There were 114 and 251 events of *P. falciparum* parasitemia among those participants in the ITN + IRS and ITN only groups, respectively, resulting in 18 and 44 events per 100 person-years, respectively (unadjusted rate ratio [RR] = 0.41, 95% confidence interval [CI] = 0.31–0.56). The overall adjusted protective efficacy (aPE) of ITN + IRS compared with ITN only was 62%. ITN + IRS provided significant protective efficacy in every age category, with the greatest protective efficacy (67%) observed in those 6 months to 4 years of age (aPE = 0.67, 95% CI = 0.38–0.82) (Table 2). Kaplan–Meier curves showing time to first *P. falciparum* parasitemia by age group are shown in Figure 2.
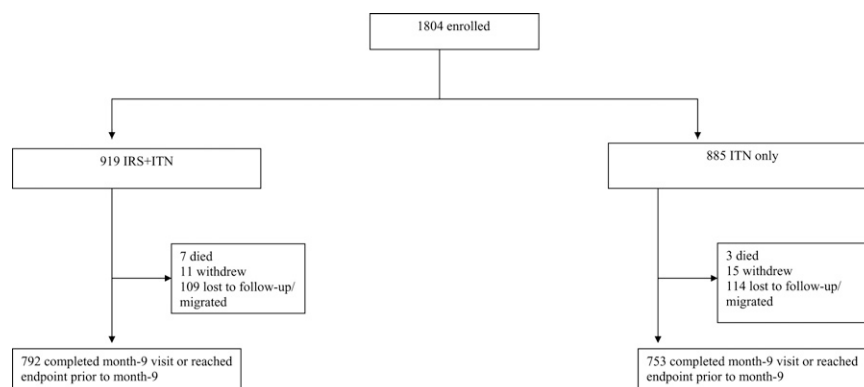

FIGURE 1.   Study profile.

TABLE 2
Unadjusted and adjusted malaria parasitemia incidence and anemia incidence in ITN + IRS and ITN only by age group*

	ITN + IRS			ITN only					
	Events	Person-years at risk	Rate per 100 person-years	Events	Person-years at risk	Rate per 100 person-years	RR (95% CI)	Adjusted RR* (95% CI)	aPE* (95% CI)
Malaria incidence									
Overall	114	627	18	251	570	44	0.41 (0.31–0.56)	0.38 (0.28–0.50)	62 (0.50–0.72)
6 months to 4 years	21	146	14	57	133	43	0.34 (0.20–0.56)	0.33 (0.18–0.62)	67 (0.38–0.82)
5–14 years	70	220	32	137	186	74	0.43 (0.30–0.62)	0.37 (0.26–0.54)	63 (0.46–0.74)
≥ 15 years	23	261	9	57	251	23	0.39 (0.23–0.65)	0.34 (0.18–0.64)	66 (0.36–0.82)
Anemia incidence (hemoglobin < 8)									
Overall	38	633	6	46	583	8	0.76 (0.49–1.19)	0.83 (0.51–1.34)	17 (−0.34–0.49)
6 months to 4 years	14	144	10	18	133	14	0.72 (0.35–1.47)	0.99 (0.43–2.29)	1 (−1.29–0.57)
5–14 years	3	228	1	6	196	3	0.43 (0.10–1.84)	0.50 (0.15–1.70)	50 (−0.70–0.85)
≥ 15 years	21	260	8	22	255	9	0.93 (0.50–1.73)	0.85 (0.42–1.73)	15 (−0.73–0.58)

*Adjusted for study clinic, baseline parasitemia, and housing type at baseline and seasonality and ITN use as time-varying variables.

Clinical malaria likewise was reduced in the ITN + IRS compared with ITN only group, with 57 and 157 events of clinical malaria recorded, respectively, resulting in 9 and 27 events per 100 person-years (unadjusted RR = 0.34, 95% CI = 0.24–0.49). Incidence of moderate anemia was low, with no difference between the study groups overall or by age group (Table 2).

We also assessed the incidence of *P. falciparum* parasitemia in a per-protocol analysis, removing those participants who reported at all follow-up visits that they did not sleep under an ITN the prior night ($N = 58$), who lived in the ITN + IRS area but did not have their house sprayed during the initial IRS campaign ($N = 242$), or who lived in the ITN only area who reported having their houses sprayed ($N = 54$) from the analysis. Results from this per-protocol analysis (data not shown) were similar to the results from the intention to treat analysis.

During follow up, participants in the ITN only group who developed *P. falciparum* parasitemia had significantly higher geometric mean parasite density than those participants in the
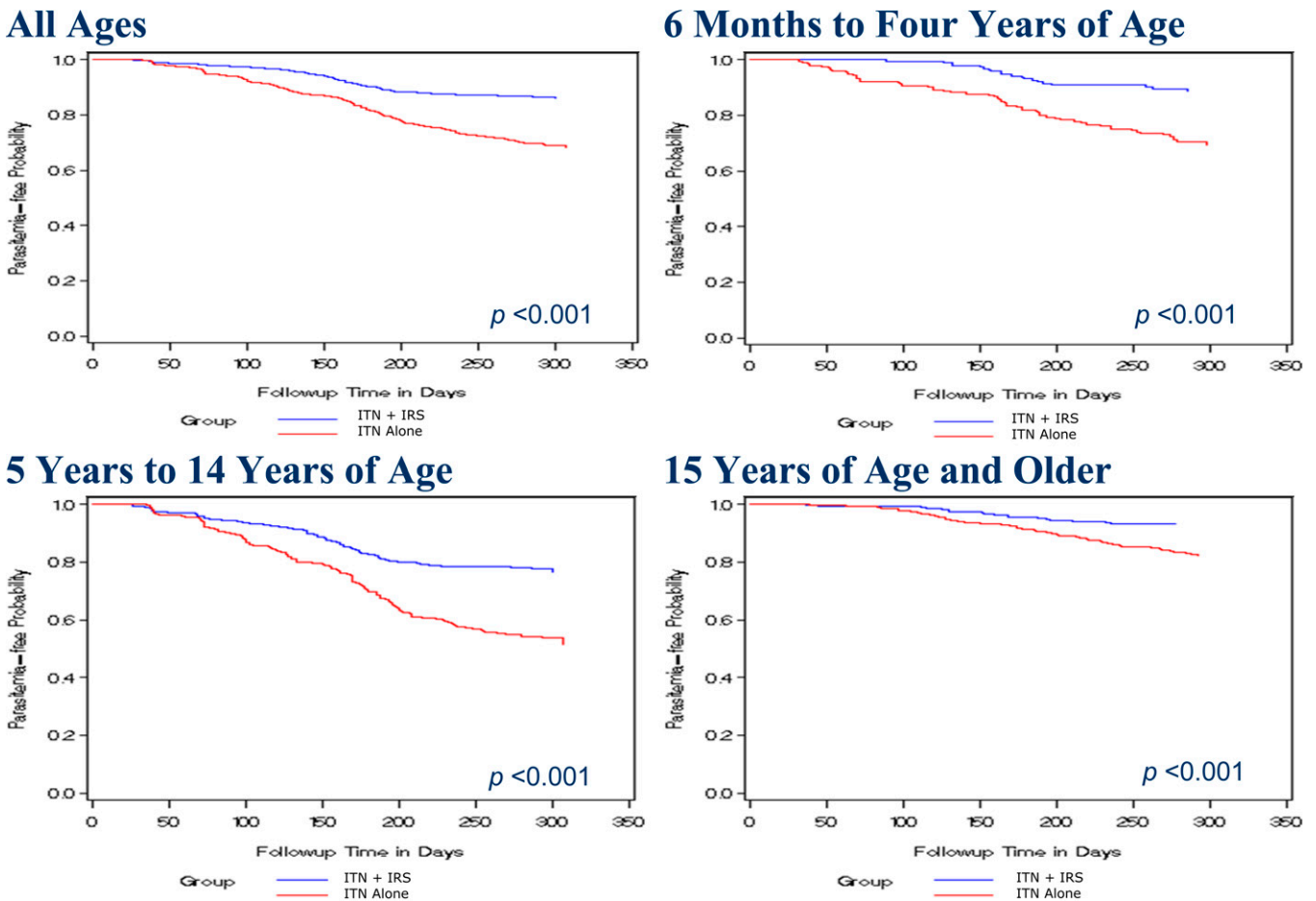
All Ages

6 Months to Four Years of Age

5 Years to 14 Years of Age

15 Years of Age and Older

FIGURE 2. Time to first malaria parasitemia (ITN + IRS versus ITN alone) in Nyanza Province, Kenya.

ITN + IRS group (4,266 versus 1,760 parasites/μL, $P < 0.0001$). ITN use differed at month 9, with 72% of participants in the ITN + IRS group and 98% of participants in the ITN only group reportedly using ITNs ($P < 0.001$).

Incident rates for first or only *P. falciparum* malaria varied between study clinics; participants enrolled near the three study clinics in the ITN + IRS area experienced 10, 14, and 29 events per 100 person-years, whereas those participants enrolled near the three study clinics in the ITN only area had 17, 46, and 87 events per 100 person-years.

Entomologic data. The average number of anopheline mosquitoes collected in pyrethrum spray catches is shown by month in Figure 3. In April of 2008, before the IRS campaign began, there was no difference in the total number of anopheline mosquitoes collected from houses in the two districts (RR = 0.91, 95% CI = 0.67–1.23, $P = 0.71$). After the IRS campaign, anopheline density was low in Rachuonyo relative to Nyando District through October of 2009 with the exception of two months (May and June of 2009). These months corresponded to the peak transmission period, during which the second round of IRS was being conducted, and may indicate waning efficacy of the first IRS round before the second round was completed. Overall, from September 2008 to October 2009, there were significantly fewer anopheline mosquitoes in Rachuonyo compared with Nyando District (RR = 0.40, 95% CI = 0.22–0.72, $P < 0.001$).

In both districts, *An. gambiae* s.l. was the primary species captured, although there was a higher proportion of *An. funestus* in Nyando compared with Rachuonyo both pre- and post-IRS. Before IRS was implemented, *An. funestus* accounted for 15.0% of the anophelines collected from Nyando and 1.6% of the anophelines collected from Rachuonyo (odds ratio [OR] = 0.09, 95% CI = 0.02–0.49, $P = 0.03$). From August of 2008 to October of 2009, *An. funestus* accounted for 9.2% of anophelines collected from Nyando and 2.7% of anophelines collected from Rachuonyo (OR = 0.36, 95% CI = 0.12–1.22, $P = 0.06$). Of 121 *An. gambiae* s.l. collected in April 2008, 120 were determined by PCR to be *An. arabiensis*. From August of 2008 to October of 2009, the proportion of *An. gambiae* s.l. that was identified as *An. arabiensis* was 97.5% in Rachuonyo and 96.8% in Nyando (OR = 2.27, 95% CI = 0.32–16.16, $P = 0.45$). Sporozoite enzyme-linked immunosorbent assays (ELISAs) were done on 483 anopheline mosquitoes collected after spraying began. Sporozoite rates were lower in Rachuonyo (1.5%) compared with Nyando

(3.1%), but the difference was not statistically significant (OR = 0.48, 95% CI = 0.12–1.91, $P = 0.34$).

Wall bioassays were conducted each month from September of 2008 to September of 2009. Valid data were obtained for 12 of 13 months; adjusted mortality was > 50% for all 12 months and > 75% for 10 of 12 months.

DISCUSSION

We found that the combination of IRS and ITNs provided significantly greater protection than the protection provided by ITNs alone in preventing malaria *P. falciparum* infection. Participants who received both interventions experienced a 61% reduction in *P. falciparum* parasitemia compared with those participants who had ITNs and no IRS, and the benefit extended to all household members, regardless of age. Moreover, those participants in the ITN + IRS group who developed malaria infection had a lower parasite density. The added benefit provided by IRS was observed, despite only 74% of households in the IRS + ITN group having received IRS.

Entomologic data show that IRS was effective in reducing anopheline mosquito numbers within households, and the anopheline mosquitoes remained highly susceptible to the lethal effects of the applied insecticide throughout the study period. Surprisingly, wall bioassays resulted in high mosquito mortality for the full 8 months between the first and second IRS campaigns, considerably longer than the 6-month expected effectiveness of λ-cyhalothrin described by the World Health Organization (WHO),[9] suggesting that, with proper timing, a yearly application of this insecticide could be a feasible control strategy.

Despite a significant difference in malaria incidence in the two study groups, we did not find a difference in incidence of moderate anemia, and development of moderate anemia overall was infrequent. This finding likely was because of the study design; hemoglobin was measured monthly and at sick visits, iron supplementation was provided whenever hemoglobin was found to be < 11.0 g/dL, and malaria was detected and treated early.

We observed a reduction in ITN use among participants in the ITN + IRS group, which may have been a consequence of reduced mosquitoes in the house or the perception of reduced malaria risk. Any program that aims to promote the combination of the two strategies will need to include an educational campaign to promote continued ITN use.

Implementation of IRS is not suitable for every setting; it is resource-intensive and requires well-trained, well-coordinated spray teams and homes accessible to those teams. Our data show that a well-planned strategy, implemented under programmatic conditions, can result in reduced *P. falciparum* infection even in the setting of high ITN coverage. In fact, the combination of IRS and ITNs may be particularly effective in East Africa and similar areas where the primary malaria vectors include anthropophagic, endophilic vectors, such as *An. gambiae* s.s. and *An. funestus*, and a more zoophagic, endophilic vector such as *An. arabiensis*. High ITN coverage was associated with a dramatic decline of *An. gambiae* s.s. and *An. funestus* and near replacement by *An. arabiensis* in the KEMRI/CDC demographic surveillance area near the study site described in this report.[13] Despite an overall decline in vector numbers, malaria transmission has been sustained at relatively high levels; community surveys indicate over 40% of children
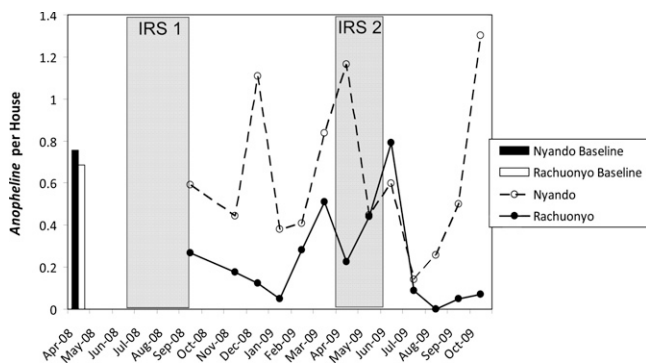

FIGURE 3. Number of anopheline mosquitoes per house before and after IRS in Rachuonyo (IRS) and Nyando Districts (no IRS), Kenya.

< 5 years of age have *P. falciparum* parasitemia (KEMRI/CDC, unpublished data). The current primary vector, *An. arabiensis*, has more varied feeding options and may survive by feeding on alternate hosts when humans are unavailable. IRS reduces the post-feeding resting place options for all anophelines, including *An. arabiensis*, which will often rest indoors after feeding outdoors.[22] Thus, the combination of IRS and ITNs may work synergistically to eliminate both vector species simultaneously, providing a means to efficiently drive down malaria transmission.

Currently, the Kenyan Malaria Control Program relies on pyrethroid insecticides for both IRS and ITNs, and the development of insecticide resistance is a major concern. Resistance to pyrethroids in *An. gambiae* and *An. funestus* has been detected in several sites throughout Africa[23–26] and has been documented to reduce the effectiveness of IRS in Bioko Island[27] and South Africa.[28] An advantage of IRS is that four classes of insecticides are available for application on walls; currently, only pyrethroids are considered safe, effective, and long-lasting for use on ITNs. Insecticide resistance management strategies include rotations, where insecticides are switched at regular intervals, and mosaics, where different insecticides are applied in different locations at the same time. The use of non-pyrethroids for IRS in combination with ITNs may represent a form of mosaic application of insecticides, where pyrethroids are on ITNs and non-pyrethroids are on walls, and should be explored as an approach to manage insecticide resistance.

Our study had limitations. First, because of the programmatic nature of the intervention, we were unable to randomize households or blind study staff. We controlled for known confounders, but there is always the risk that unknown confounders exist. We are reassured that the areas are adjacent, with similar population-based parasite prevalence before the introduction of IRS, and the areas have similar access to healthcare. Second, malaria incidence rates varied between study clinics within study areas. Ideally, we would have had pre-intervention incident rates from each study clinic to compare with post-intervention rates, but these rates are not available. Third, because ITNs have proven efficacy in areas of high transmission, we did not include an IRS only group, which could have provided information about whether the effects of ITNs and IRS act synergistically. Without an IRS only treatment arm, we cannot conclude whether the effects of IRS in the context of high ITN ownership would have been observed in the absence of ITNs. If so, the rationale for combining these interventions would be lacking, and vector control in Africa should be directed towards IRS. Given the progress in scaling up ITNs, this question may be difficult to answer definitively. Finally, the follow-up period was limited; over the years, insecticide resistance may develop, resulting in limited use of particular families of insecticide.[28]

In summary, this study provides the first prospectively collected data on the combined benefit of IRS and ITNs. These findings confirm several observational cross-sectional surveys that indicate an additive benefit from the combination of IRS and ITNs.[29] The protective efficacy was substantial, suggesting that the combination of IRS and ITNs could be an effective intervention to further reduce malaria transmission in areas with persistent perennial malaria. These findings should be confirmed through a randomized controlled trial. Additionally, to help determine the best use of finite resources, a cost-effectiveness analysis would be useful and should explore the benefit of providing more protection to a limited number of homes through the combination of IRS and ITNs and less protection with ITNs alone to a larger number of homes. Until those data are available, our data support the deployment of the combination of IRS and ITNs or the introduction of IRS in an area with high ITN coverage where funds permit.

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