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Combining Indoor Residual Spraying and Insecticide-Treated Net Interventions

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Abstract

Does scaling up of malaria control by combining indoor residual spraying (IRS) and long-lasting insecticidal nets (LLIN) enhance protection to populations? Results from a literature search and from recent household surveys in Bioko, Equatorial Guinea, and Zambezia, Mozambique are presented. Five out of eight previous studies reported a reduced risk of infection in those protected by both interventions compared with one intervention alone. Surveys in Bioko and Zambezia showed strong evidence of a protective effect of IRS combined with nets relative to IRS alone (odds ratio [OR] = 0.71, 95% confidence interval [CI] = 0.59–0.86 for Bioko, and OR = 0.63, 95% CI = 0.50–0.79, for Zambezia). The effect of both interventions combined, compared with those who had neither, was OR = 0.46, (95% CI = 0.76–0.81) in Bioko and 0.34 (95% CI = 0.21–0.56) in Zambezia. Although the effects of confounding cannot be excluded, these results provide encouragement that the additional resources for combining IRS and LLIN are justified.

INTRODUCTION

Malaria control and elimination interventions are being scaled up and intensified in current efforts to attain World Health Assembly, Roll Back Malaria, and Millennium Development universal access and coverage targets, to reduce and interrupt disease transmission in countries.^{1,2} The major malaria intervention tools now include long-lasting insecticidal nets (LLIN), artemisinin-based combination therapy (ACT), indoor residual spraying of insecticide (IRS), and intermittent preventive treatment in pregnancy (IPT). Since 2007, there have been increasing global efforts toward sustainable scaling up of malaria control to bring about rapid reductions in transmission and move toward long-term goals of malaria elimination and global eradication.³

Insecticide-treated nets (ITNs) and IRS have each been shown to be highly effective methods of malaria vector control in their own right. A recent review of the evidence of cost and consequences of large-scale vector control for malaria⁴ concluded that both ITNS and IRS are highly cost-effective

vector control strategies. ITNs have been the mainstay of vector control in many countries in which the disease is endemic and where infrastructure limits or precludes the implementation of IRS.⁵ Despite extensive evidence of their proven efficacy in reducing malaria morbidity and mortality,⁶ ITN ownership and use remains low in many of these countries.⁷

In 2006, the World Health Organization (WHO) recommended that, where appropriate, IRS with *dichloro-diphenyl-trichloroethane* (DDT) or other insecticides should be a central part of national malaria control strategies.⁸ Synthetic pyrethroids are safe alternatives to DDT especially in modern housing surfaces and in low and seasonal transmission areas. Where malaria vectors are resistant to DDT or pyrethroids, more expensive, shorter duration insecticides have to be used (carbamates and organophosphates). In Africa, sustained IRS has historically been used mainly in the southern part of the continent, where it has been successful in controlling malaria and reducing transmission.⁹ With current efforts to scale up malaria control in Africa, IRS has been introduced in a number of countries with initially high levels of transmission.¹⁰⁻¹³ However, IRS requires more complex and costly operational delivery systems than ITNs and claims of sustained high coverage often remain unproven.

In some countries where more resources have become available, malaria control programs have deployed both IRS and LLIN in the same malaria risk areas. The reasons for this combined approach are 1) to reduce transmission and hence the malaria burden of disease more rapidly than may be feasible with one method alone; 2) to increase overall coverage of vector control protection, for example when full IRS or ITN coverage is difficult to sustain¹⁴; and 3) to delay the emergence of insecticide resistance¹⁵ by using different classes of insecticide for IRS and LLINs.

This study reports on a review of current evidence on whether the use of both interventions in combination versus one method alone affords enhanced protection to exposed populations. Results of a literature search and of analysis of recent household survey data from Bioko, Equatorial Guinea,¹⁰ and from Zambezia province, Mozambique, are presented.

METHODS

Forty articles or reports were identified searching the databases Ovid/Medline and Ovid/Global Health for publications that mentioned both IRS and nets in the same report. Eight of these studies compared health or entomologic outcomes between areas or individuals using mosquito nets in IRS-treated houses, and IRS or mosquito nets alone.^{12,16-22} Nine were reports on studies in which a comparison was made between areas using nets and areas using IRS, either in terms of efficacy or in terms of cost-effectiveness.^{4,23-30} The remaining articles dealt with aspects of malaria vector control not directly relevant to the question of combined use of IRS and mosquito nets. There were no reports of studies in which combined interventions and use of one intervention alone were randomly allocated either to individuals or to houses or to areas. None of the published reports gave any assessment of combined vector control coverage achieved in areas benefiting from the use of both methods together.

Data from five household surveys undertaken between 2006 and 2008 in Bioko, Equatorial Guinea, and in Zambezia, Mozambique were analyzed to estimate the combined effect of IRS and nets on prevalence of infection, compared with IRS alone. In each of these surveys rapid diagnostic tests (RDT) were used to determine infection with *Plasmodium falciparum* in children 2 to < 15 years of age. Questionnaires were used to record whether the house in which the child lived had been sprayed with insecticide in the previous 12 months, whether the child had slept under a mosquito net the night before the survey, and what household goods and services were available in the house. The condition of nets as to whether they were new, or had recently been treated with insecticide, or were LLIN was determined in only some of the surveys, and we report on these separately.

The three surveys in Bioko were carried out in 2006, 2007, and 2008 as part of monitoring and evaluation of the Bioko Island Malaria Control Project (BIMCP).^{10,22,31} Bioko is situated in the equatorial tropics in the Gulf of Guinea with high rainfall throughout most of the year. The BIMCP introduced IRS in 2004 with initially a single round of pyrethroids, followed from 2005 onward by two rounds per year of bendiocarb. LLINs were distributed by the BIMCP to cover all sleeping areas in all households in 2007, though nets had previously been distributed on a smaller scale and their use was monitored in surveys from 2006. All BIMCP surveys were carried out on randomly selected households in 18 sentinel areas that cover almost the entire Island.¹⁰ Households were selected from sampling frames constructed by listing all houses in sentinel areas using personal digital assistants (PDA) or from census enumeration lists. All children between 2 and < 15 years of age in selected households who were present at the time of the survey were tested for *P. falciparum*.

The surveys in Zambezia, Mozambique in 2006 and 2007 were carried out through the malaria decision support system project (MDSS), based at the Medical Research Council of South Africa.³² Zambezia province is situated in south-central Mozambique and is characterized by seasonal rainfall from November to June. Surveys were conducted at 19 sentinel sites established in 2006 for monitoring and surveillance of the malaria control program. Before 2006 the only vector control intervention in the area was mosquito nets. IRS was introduced in 2006, initially by the national malaria control program and later supported by President's Malaria Initiative.¹¹

Permission to carry out the surveys was obtained from the Ministry of Health and Social Welfare in Equatorial Guinea, and from the Ministry of Health Ethics Committee in Mozambique. Informed consent was obtained from a responsible adult in each participating household, and from children who were tested, where appropriate.

For each of the five surveys, prevalence of infection was calculated for four groups of children: 1) those whose house had not been sprayed in the past year and who did not sleep under a net the night before the survey, 2) those whose house had been sprayed in the past year but who did not sleep under a net, 3) those who did sleep under a net but whose house had not been sprayed in the past year, and 4) those who slept under a net in a dwelling that had been sprayed. For each survey the odds ratio (OR) of infection with *P. falciparum* for those protected directly by IRS combined with nets relative to those who were protected by IRS alone was calculated separately for those sites in which parasite prevalence was under 35%, and for those sites in which prevalence was 35% and over. Sentinel sites were specified as the primary sampling units in statistical analysis that allowed for complex survey designs in the statistical package Stata.^{33,34}

For the most recent survey data for each of the two programs (2008 for Bioko and 2007 for Zambezia) multiple variable logistic regression was used to assess whether sleeping in an IRS-treated house and sleeping under a net were independently associated with infection status of a child, and whether these associations were the result of confounding by the wealth status of the house. For the analysis of the 2008 data from Bioko, net use was restricted to mean ITN or LLIN use (rather than any net) since the status and type of each net was known and because the number of ITN/LLIN users was sufficiently large. For the analysis of the 2007 data from Zambezia, net use was taken as any mosquito net, because treatment status of nets was not verified by interviewers. For the Bioko analysis whether the house had electric lights was used as a proxy indicator of household wealth; similarly, for the Zambezia data whether the household had a radio was used as a proxy indicator of household wealth. The logistic regression models were also used to test whether there was modification (interaction) of the effect of IRS treatment by the effect of sleeping under a net/ITN, and *vice versa*.

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RESULTS

The three surveys in Bioko and two in Zambezia show ORs of < 1 for prevalence in children protected by both IRS and nets relative to IRS alone ([Table 1](#)). There was generally moderate to strong evidence of this effect across both high and low prevalence sites. Pooling the data for each project, there was strong evidence of a protective effect of IRS combined with nets relative to IRS alone (OR = 0.71, 95% CI = 0.59–0.86, $P = 0.001$ for Bioko, and OR = 0.63, 95% CI = 0.50–0.79, $P < 0.001$ for Zambezia).

Table 1

Prevalence of infection in children 2 to < 15 years of age in Bioko, Equatorial Guinea, and Zambezia, Mozambique between 2006 and 2008 by indoor residual spraying (IRS) status of house and whether the child slept under a mosquito net the night before the survey

Study	Survey year	Low or high prevalence sites	Unprotected	IRS only	Net only	IRS + net	Number in sample	Odds ratio IRS + net relative to IRS only
Bioko	2006	low	28 (22–36)	21(16–27)	21(15–28)	13 (10–17)	4094	0.56 (0.43–0.72); <i>P</i> < 0.001
	2006	high	56(41–70)	51 (45–57)	39 (30–49)	38 (27–50)	902	0.59 (0.36–0.96); <i>P</i> = 0.036
	2007	low	25 (19–32)	20(15–25)	32 (21–45)	19 (14–26)	2506	0.99 (0.75–1.30); <i>P</i> = 0.92
	2007	high	52(40–64)	43 (35–51)	51 (36–65)	30 (25–34)	785	0.56 (0.41–0.76); <i>P</i> = 0.001
	2008	low	26 (15–42)	22 (15–31)	24 (19–31)	17 (14–21)	3012	0.74 (0.53–1.06); <i>P</i> = 0.093
	2008	high	61 (51–70)	53 (52–54)	45 (39–52)	35 (18–56)	476	0.48 (0.20–1.15); <i>P</i> = 0.094
All Bioko			33 (20–31)	25 (19–33)	30 (26–36)	19 (15–24)	11,775	0.71 (0.59–0.86); <i>P</i> = 0.001
Zambezia	2006	low	31 (23–40)	32 (21–44)	40 (26–55)	19 (16–24)	693	0.52 (0.33–0.81); <i>P</i> = 0.006
	2006	high	76 (65–85)	58(44–71)	77 (68–85)	49 (32–67)	1450	0.71 (0.51–0.99); <i>P</i> = 0.045
	2007	low	48(44–51)	32 (31–34)	30 (6.9–71)	23 (15–35)	286	0.63 (0.38–1.03); <i>P</i> = 0.064
	2007	high	76 (66–84)	64 (52–67)	67 (47–67)	53 (42–53)	2147	0.64 (0.49–0.84); <i>P</i> = 0.001

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Multiple variable analysis showed that living in an IRS-treated house had a protective effect on infection corresponding to an OR of 0.68, 95% CI = 0.48–0.94 in Bioko and of 0.49, 95% CI = 0.28–0.88 in Zambezia, regardless of whether the child was also sleeping under an ITN/net or not (Table 2). Similarly, sleeping under an ITN/LLIN or any net had protective effects on infection (OR = 0.68, 95% CI = 0.48–0.97 for ITN/LLIN on Bioko, OR = 0.70, 95% CI = 0.54–0.90 for any net in Zambezia) regardless of whether the child simultaneously slept in an IRS-treated house or not. In Bioko, there was

no evidence of an association between infection and the house having electric lights; including this variable in the model did not alter the effects of IRS and ITNs, respectively (not tabulated). In Zambezia there was only weak evidence of an association between infection and the household having a radio, and including this variable in the model did not alter the effects of IRS or net use, respectively. There was no evidence of interaction between the effects of IRS and of ITNs in Bioko ($P = 0.976$) or between IRS and nets in Zambezia ($P = 0.493$).

Table 2

Effects of sleeping in an IRS-treated house, sleeping under net/ITN, unadjusted, and adjusted for each other and effect of proxy for wealth status of household on infection with *Plasmodium falciparum* in children 2 to < 15 years of age in Zambezia province, Mozambique, and Bioko, Equatorial Guinea*

	Percent infected	Number	OR	95% CI	P value	Adjusted OR	95% CI	P value
Bioko, 2008								
Living in IRS-treated dwelling [#]								
No	29	496	1.00			1.00		
Yes	21	2631	0.65	0.46–0.92	0.017	0.68 [†]	0.48–0.94	0.024
Slept under ITN [#]								
No	27	860	1.00			1.00		
Yes	20	2267	0.66	0.46–0.94	0.025	0.68 [‡]	0.48–0.97	0.033
Electric lights [§]								
No	22	1076	1.00			¶		
Yes	22	2051	1.02	0.62–1.66	0.940			
Zambezia, 2007								
Living in IRS-treated dwelling ^{††}								
No	71	827	1.00			1.00		
Yes	55	1617	0.50	0.28–0.87	0.018	0.49 ^{**}	0.28–0.88	0.019
Slept under net ^{††}								
No	64	1622	1.00			1.00		
Yes	55	822	0.71	0.53–0.95	0.025	0.70 [‡]	0.54–0.90	0.009
Household has radio [§]								
No	64	991	1.00			¶		
Yes	58	1453	0.77	0.59–1.01	0.056			

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*IRS = indoor residual spraying; ITN = insecticide-treated net; OR = odds ratio; CI = confidence interval.

[†]Adjusted for effect of sleeping under an ITN or long-lasting insecticidal net (LLIN).

[‡]Adjusted for effect of sleeping in an IRS-treated house.

[§]Proxy for wealth of household.

[¶]Electric lights and household radio not included in multiple variable models due to absence of effect as confounder, and large *P* values.

[#]No evidence of effect modification (interaction) between IRS and net use effects (*P* = 0.493).

^{**}Adjusted for effects of sleeping under any net.

^{††}No evidence of effect modification (interaction) between IRS and ITN use effects (*P* = 0.976).

Previous studies that compared IRS combined with ITN vector control with one method alone give contradictory results. Some studies reported that there was no incremental benefit in terms of lower risk of infection, lower incidence of cases, or lower vector abundance and infectivity associated with the use of ITNs/LLINs, or untreated nets in areas that had been IRS treated.^{12,19,20} Other studies^{16–18,21,22} do report evidence of lower risk of infection for children who used nets (treated or untreated) and lived in an IRS-treated house, compared with those living in an IRS-treated house without nets.

Rowland and others¹⁶ reported substantially lower rates of *P. falciparum* and of *Plasmodium vivax* infections in Afghan refugee clinic attendees who claimed using ITNs, compared with those admitting not using any nets, in villages in which spraying had also been carried out.

Yadav and others¹⁷ reported reductions in malaria incidence and prevalence of infection in Indian villages that were supplied with either treated nets or untreated nets compared with villages that were not supplied with nets in an area in which the standard control strategy consisted of IRS alone using DDT.

Protopopoff and others,¹² reporting on a combined IRS and LLIN intervention in Burundi found that LLINs combined with IRS had an incremental effect in reducing the density of *Anopheles* mosquitoes when compared with IRS alone, but had no observable effect in reducing the number of infective bites per house. The authors argue that high coverage with effective IRS had already reduced sporozoite rates to such a low level that nets were unable to make any additional impact.

In the same intervention in Burundi, the effect of IRS and LLINs on prevalence of infection was studied by Protopopoff and others.¹⁹ Although there was strong evidence of an overall intervention effect in IRS-treated areas, there was no indication that those who also slept under nets in the IRS-treated areas had any additional protection against infection compared with those who did not sleep under a net (OR = 0.88, 95% CI = 0.60–1.31 for the 1- to 9-year-old group). The authors argue that the absence of an additional effect may be caused by high IRS coverage (90%) recorded by spray managers.

A study by Nyarango and others²⁰ evaluating a combination of malaria control measures in Eritrea concluded that “combining ITN use with IRS or other vector control measures did not confer added value to the outcome in malaria mortality and morbidity.”

In a study on a malaria epidemic during civil unrest in Burundi, Protopopoff and others¹⁸ described a vector control intervention consisting of IRS and ITN campaigns. The evaluation of this intervention showed no difference in prevalence of infection between sprayed and non-sprayed areas, but a reduced prevalence of infection in individuals sleeping under ITNs in one of the two zones in which IRS was deployed.

A study analyzing district level data from Eritrea²¹ found that ITN use and IRS were independently associated with reductions in malaria cases in multiple variable regressions after adjusting for differences in climate implying that combined use of IRS and ITNs did provide additional protection, compared with their single use. [Table 3](#) summarizes the studies that have compared IRS combined with mosquito nets versus one intervention alone.

Table 3

Summary of studies comparing the effect of IRS combined with net use vs. one intervention alone*

Study	Country and time period	How effect was measured	Effect of nets/ITNs combined with IRS vs. IRS only	Nets untreated, treated, or both	ITN coverage measured by household survey, by number distributed or not at
Rowland ¹⁶	Pakistan	Case control study	<i>P. falciparum</i> OR = 0.22 (0.09–0.55); <i>P. vivax</i> OR = 0.31 (0.19–0.51)	Treated	Not measured
Yadav ¹⁷	India, mid-1990s	Incidence and prevalence (all ages)	Significant reduction	Both	Not measured
Protopopoff (2007a)	Burundi, 2002–2005	Vector density and infectivity	a) Vector density: –56% b) Infectivity: no effect	Treated	household
Protopopoff ¹⁹	Burundi, 2002–2005	Prevalence, 1–9 years	Prevalence OR = 0.88 (0.60–1.31)	Treated	household
Protopopoff (2007b)	Burundi, 2000 (epidemic)	Prevalence (all ages); vector density	a) Prevalence: OR = 0.36 (0.15–0.88) [†] b) Vector density: no effect	Treated	household
Nyarango ²⁰	Eritrea, 2000–2004	Incidence of cases; mortality	No effect (in multivariable analysis)	Both	household
Graves ²¹	Eritrea, 1999–2003	Incidence of cases	“Significant reduction”	Treated	Number distributed
Previously unpublished [‡]	Equatorial Guinea, 2006–2008	Prevalence, 1 to 15 years	Prevalence OR = 0.71 (0.59–0.86)	Both	household

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* ITN = insecticide-treated net; IRS = indoor residual spraying; OR = odds ratio.

†One zone only.

‡Includes data from Kleinschmidt and others. [22](#)

DISCUSSION

On the basis of previously published studies, the evidence of the effect of using IRS in combination with ITNs (or nets) compared with one method alone has been varied with some studies showing a positive combined effect and others no combined effect. Because none of these studies have been able to fully control for confounding effects, and none were based on experimental study designs, it is not possible to draw firm conclusions regarding the benefits of a combined vector control strategy based on ITNs and IRS.

For example, some of the studies (Rowland, Yadav) show a lower incidence of malaria cases in those using nets combined with IRS compared with those given IRS alone, but the additional protection of the nets may have been because of patchy or ineffective spray programs that were not monitored separately. This may also explain the effect observed in the epidemic outbreak in Burundi in 2000,¹⁸ in which there were no differences in prevalence of infection between individuals in IRS-treated and untreated houses but a reduced prevalence of infection in individuals sleeping under nets. These results could be explained as being caused by poor implementation of spraying, which despite reported high coverage in some cases, showed no benefit.

The results from Bioko and from Zambezia make a more convincing case for the combined use of IRS and treated nets. In Bioko, overall prevalence of infection had decreased from 26% (95% CI = 21–33) in 2007 to 22% (95% CI = 17–28) in 2008 in the 2 to < 15 year age group, possibly because of an increase in the proportion protected by both methods (IRS + any net in 2007, IRS + ITN in 2008) from 18% in 2007 to 62% in 2008.

Those who lived in IRS-treated houses in 2008 were overwhelmingly less likely to be infected compared with those who were not living in such houses (OR = 0.68, 95% CI = 0.48–0.94) regardless of whether they slept under a net or not, whereas those sleeping under ITNs were similarly better off (OR = 0.68, 95% CI = 0.48–0.97) regardless of whether they slept in an IRS-treated house or not. Those benefiting from the combined effect of both measures had an odds of infection equivalent to the multiplicative effect of the two measures (OR = 0.46, 95% CI = 0.26–0.81) relative to those unprotected by either method.

In Zambezia, there was some evidence of an overall increase in prevalence at all sites combined from 52% in 2006 to 62% in 2007 in children 2 to < 15 years of age ($P = 0.053$). However, those who lived in IRS-treated houses in 2007 were considerably less likely to be infected compared with those not living in such houses with an OR = 0.50, 95% CI = 0.28–0.87, whereas the protective effect of sleeping under a net had an OR of 0.71, 95% CI = 0.53–0.95, relative to those who were unprotected by a net. The effect of both measures combined was again multiplicative with an OR of 0.34, 95% CI = 0.21–0.56, relative to those who were unprotected.

Because there was no random allocation of vector control measures in these studies, individuals not receiving either of the two interventions may be viewed as a control group consisting of those who either did not comply, or who were missed by the control program. Although they may be thought of as unrepresentative and socio-economically different, our analysis does not support this view. In both Bioko and Zambezia, the results appear to be unaffected by potential confounding by the proxy indicators that we used for the wealth status of the household. Nevertheless, in observational studies the effect of confounders cannot be ruled out, and prevalence of malaria infection or incidence of disease can be influenced by many other factors including access to diagnosis and treatment, and the

perception of risk by net users or health providers. More rigorous studies should randomly allocate study clusters to single or combined vector control so that confounding factors can be balanced between study arms.

It would be plausible if in combined IRS and ITN use the effect of one method alone was modified by the presence of the other. However, in the 2007 Zambezia and 2008 Bioko surveys there was no evidence of such interaction, i.e., the effect of one intervention was neither reduced nor magnified by the presence of the other.

All of these results need to be interpreted with caution, however, because community effects are likely to be substantial when ITN and/or IRS coverage is high. In Bioko in 2008, 95% of children less than 5 years of age were sleeping either in a house that had been IRS-treated, or under an ITN. In such circumstances risk of infection is substantially reduced for everyone, regardless of whether they slept under a net or whether their individual house was sprayed. Mass effects of IRS and ITN vector control extending to those not sleeping under nets and not living in sprayed houses therefore complicates the interpretation of data from observational studies.

It is noteworthy that studies in which infection status was analyzed in relation to protection by IRS or net use at individual level, did show evidence of a beneficial effect of IRS + net use, relative to IRS alone. The strongest evidence comes from our data ([Table 1](#)), which show that in most surveys in Bioko and Zambezia, infection prevalence was not only lower in children benefiting from the combined vector control measures compared with those benefiting from IRS alone, but that IRS alone was also beneficial compared with those not receiving any intervention. The lower prevalence in the IRS + net group is therefore an additional benefit because of the nets, and not simply the effect of a functioning intervention added to a primary non-functioning one.

CONCLUSION

Future studies that address the question of whether combined use of ITNs and IRS provide additional protection, need to ensure that each intervention is effective on its own in a particular setting by including program implementation indicators that are adequately and independently monitored. This can be a challenge for IRS implementations that use ineffective insecticides, or suffer from poor spray applications or low coverage because such program deficiencies cannot be readily measured through household surveys. Poor ITN implementation, however, can be gauged more easily from household survey responses.

Because combined interventions are more costly than single ones, their sustainability needs to be taken into account when they are implemented. In some countries it may be sensible to use combined IRS and LLIN for a limited period, and switch to LLIN alone once transmission rates have been reduced to previously defined targets.³⁵

Despite the limitations that are inherent in non-experimental studies, the analysis reported in this study provides remarkably consistent evidence of added protection offered to individuals who sleep under a mosquito net or ITN in an IRS-treated house in settings with as different climatic conditions as those in Bioko and in Zambezia. This suggests that in areas where funding is adequate to offer a combined approach as a means of accelerating the transmission reduction process, or in areas where malaria control is challenging because of very high transmission intensities, or where high vector control coverage using one method alone has remained illusive or where preparation for elimination is a medium term goal, the option of combining these two vector control interventions should be considered. At the same time, there is an urgent need to back up our evidence with rigorous randomized controlled studies.

There is a growing global demand for sustainable scaling up of malaria control and for elimination. This will have to balance the need for equity in delivery of cost-effective malaria control interventions against the demands for more intensified malaria control including combinations of vector control interventions. Because the implementation of IRS combined with LLIN means increases in cost, it is important that the deployment of such additional resources is based on good evidence of their efficacy, and on cost-effectiveness estimates of costs per person protected, per infection averted, and per life saved. Such information can only come from well-designed prospective multi-country studies in different transmission settings.

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