Combining LLINs and IRS: the evidence of added benefit and the benefit of added evidence

Immo Kleinschmidt

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ITN and IRS

- Two proven methods of vector control, that have each been shown to be highly effective in controlling malaria
- Both methods have operational limitations, particularly in achieving and maintaining high coverage
- In some settings sustainability of IRS is severely challenged where it is dependent on insecticides of short residual
- Effectiveness of both methods is threatened by insecticide resistance

ITN effectiveness

- Strong evidence of **protective efficacy** from numerous CRTs on several endpoints[1]
  - child mortality: 17%
  - uncomplicated malaria episodes: 50% (areas of stable malaria); 62% (areas of unstable malaria)
  - severe malaria: 45%
  - parasite prevalence: 13%

[1]Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews* 2004, Issue 2

IRS effectiveness

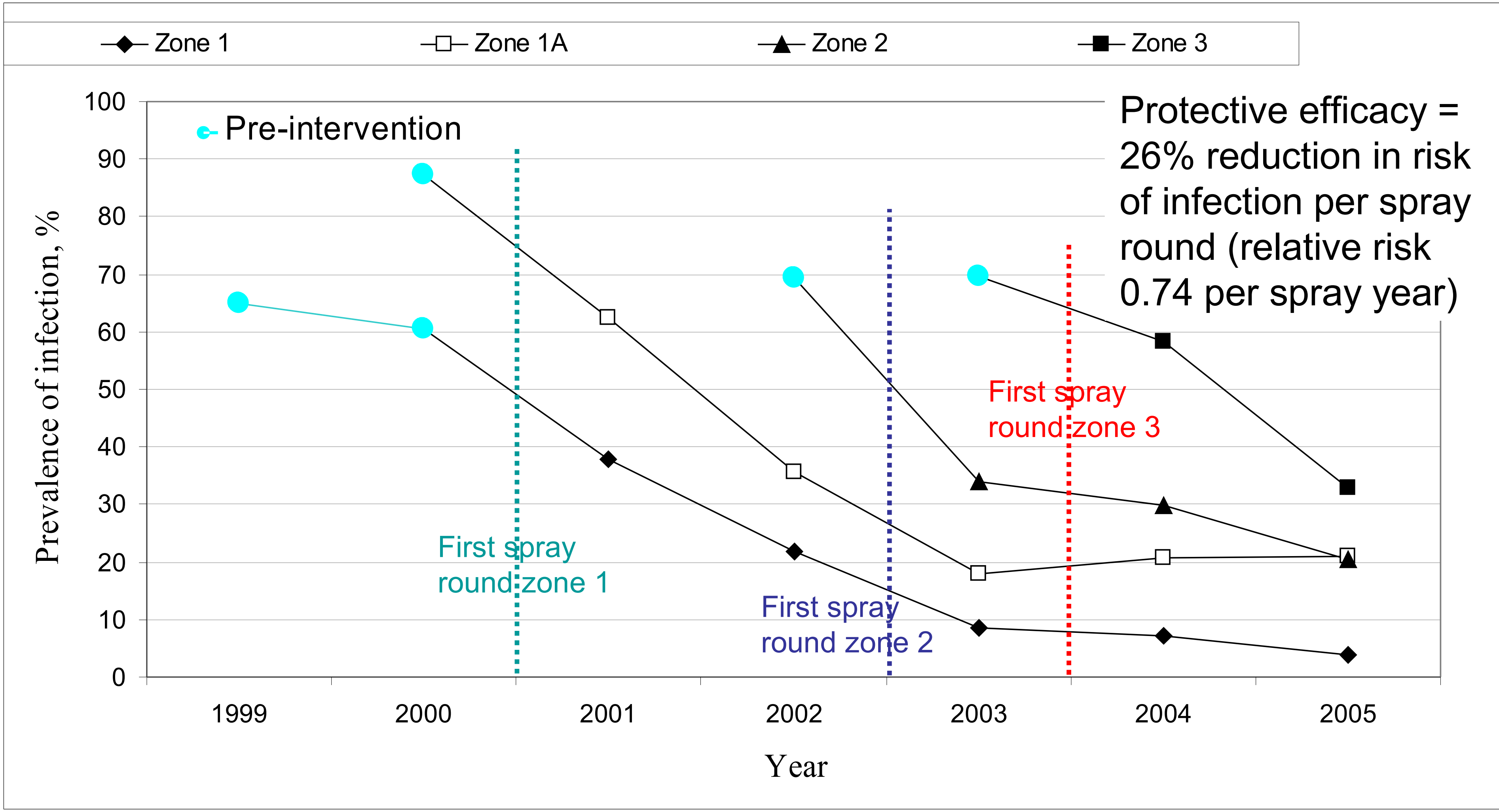
- Very limited CRT evidence
- "The number of high-quality trials are too few to quantify the size of effect in different transmission settings"[1]
- Extensive evidence of effectiveness from programme evaluations, mostly 'after versus before comparisons'

[1]Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. *Cochrane Database of Systematic Reviews* 2010, Issue 4.

Two examples of IRS effectiveness from programmatic evaluations

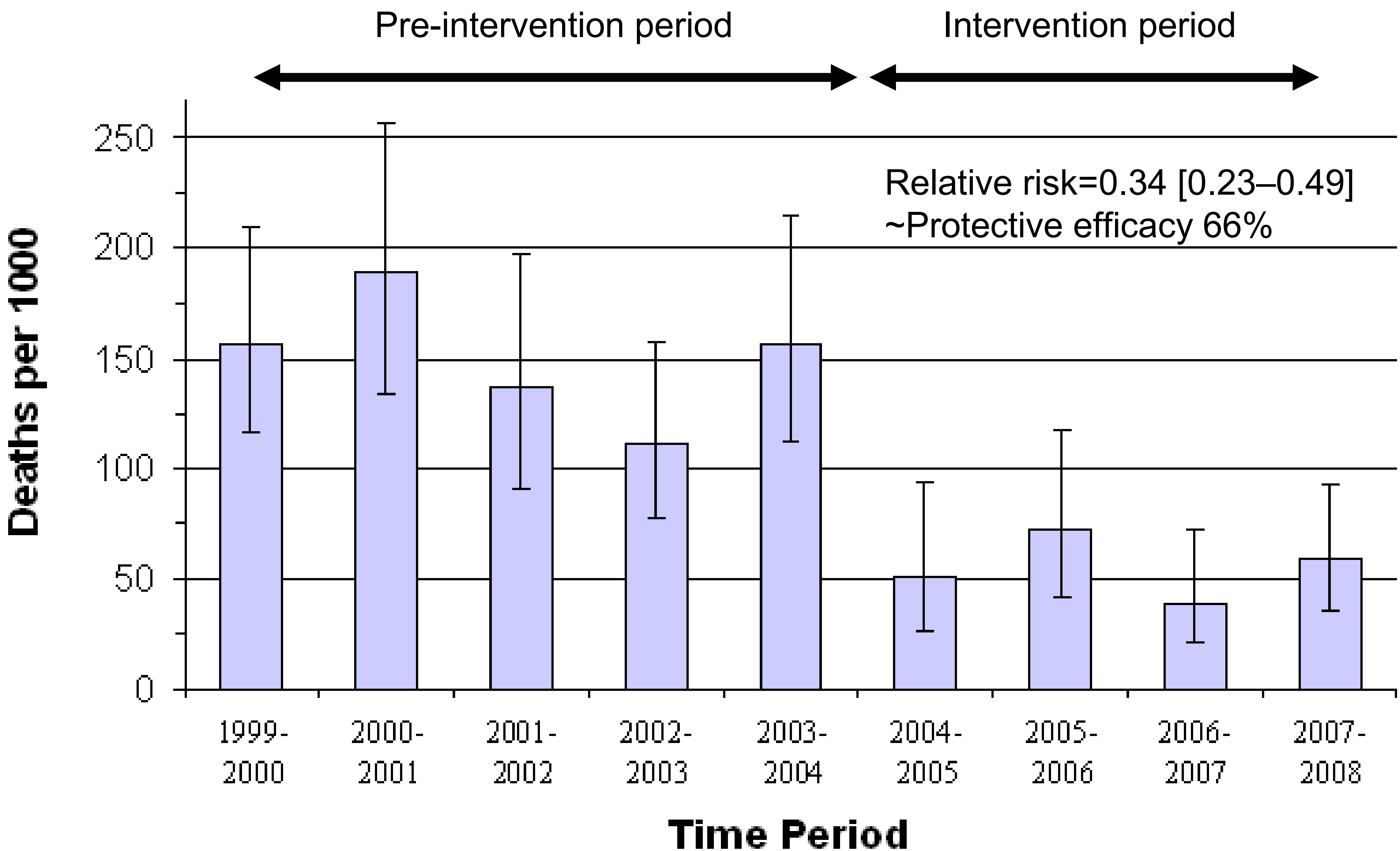
1. LSDI (Southern Mozambique), impact prevalence of infection estimated over 7 years
2. Bioko island, Equatorial Guinea: impact on under five mortality

LSDI (Southern Mozambique): prevalence monitored over seven years



Sharp BL, Kleinschmidt I, Streat E, Maharaj R, Barnes KI, Durrheim DN, Ridl FC, Morris N, Seocharan I, Kunene S, La Grange JJP, Mthembu DJ, Maartens F, Martin CL , Barreto A. Seven Years Of Regional Malaria Control Collaboration - Mozambique, South Africa And Swaziland. *Am. J. Trop. Med. Hyg.*, 2007, 76(1): 42–47

Bioko: All cause under 5 mortality by year



IRS+ITN

- If one is good on its own, are the two together even better?
- Since 2007 there have been increasing global efforts towards sustainable scaling up of malaria control
- Should such escalation of malaria control include combining vector control methods by introducing indoor residual spraying (IRS) and insecticide treated nets (ITN) alongside each other?

Reasons for combined approach

- to reduce transmission and hence burden of disease more rapidly than may be feasible with one method alone
- to increase overall coverage of vector control protection, for example when full IRS coverage is difficult to sustain
- to delay insecticide resistance development by using different insecticides for IRS and for ITNs

Results from published studies to date

- No CRT evidence
- Observational studies provide some limited and fairly weak evidence comparing
  1. One district or area versus another
  2. Before versus after
  3. Compliers versus non-compliers

Results from published studies

- No evidence 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 was reported in 3 studies (Protopopoff (2007a), Protopopoff (2008), Nyara)
- Evidence of lower risk of infection for children who used nets (treated or untreated) and lived in an IRS treated house, compared to those living in an IRS treated house without nets was documented in 5 reports (Yadav (1998), Protopopoff (2007b), Graves (2008), Kleinschmidt (2009))

Results from published studies

Study	Country and time period	Outcome measure used	Effect of nets/ITNs combined with IRS versus IRS only[†]	Nets un-treated, treated or both	ITN use by survey, by number distributed, or not at all	IRS coverage by survey, sprayer data, quantity used, or not at all	IRS/ITN known for individual
Yadav (1998)	India, mid 1990s	Incidence and prevalence (all ages)	Significant reduction	Both	Not measured	Not measured	No
Protopopoff (2007a)	Burundi, 2002-05	Vector density and infectivity	a)Vector density: -56% b)Infectivity: no effect	Treated	household	Sprayer data	No
Protopopoff (2008)	Burundi, 2002-05	Prevalence, 1-9 years	Prevalence OR=0.88[0.60-1.31]	Treated	household	Sprayer data	Nets yes; IRS no
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	Household survey	Yes

Results from published studies (continued)

Study	Country and time period	Outcome measure used	Effect of nets/ITNs combined with IRS versus IRS only†	Nets untreated, treated or both	ITN use by survey, by number distributed, or not at all	IRS coverage by survey, sprayer data, quantity used, or not at all	IRS/ITN known for individual
Nyarango (2006)	Eritrea, 2000-2004	Incidence of cases; mortality	No effect (in multivariable analysis)	Both	household	Quantity insecticide used	No
Graves (2008)	Eritrea, 1999-03	Incidence of cases	"Significant reduction"	Treated	Number distributed	Quantity insecticide used	No
Kleinschmidt (2007) + new data§	Equatorial Guinea, 2006-2008	Prevalence, 1 to 15 years	Prevalence OR= 0.71[0.59-0.86]	Both	household	Household survey	Yes
Previously unpublished	Mozambique, 2006-2007	Prevalence, 1 to 15 years	Prevalence OR= 0.63[0.50-0.79]	Both	household	Household survey	Yes

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Bioko, Zambezia and Malawi data

- Data from eight household surveys: 3 from Bioko, Equatorial Guinea, and 3 from Zambezia, Mozambique and 2 from Malawi provide information on effect of IRS combined with nets, compared to IRS alone
- Outcome measure:
  infection with *P.falciparum* in children 2 to <15 years by RDT
- Intervention questions
  1. had the house in which child lived been sprayed in previous 12 months?
  2. had the child slept under a mosquito net the night before the survey , and
- proxy information for household wealth
- Type of net and condition determined in only some surveys

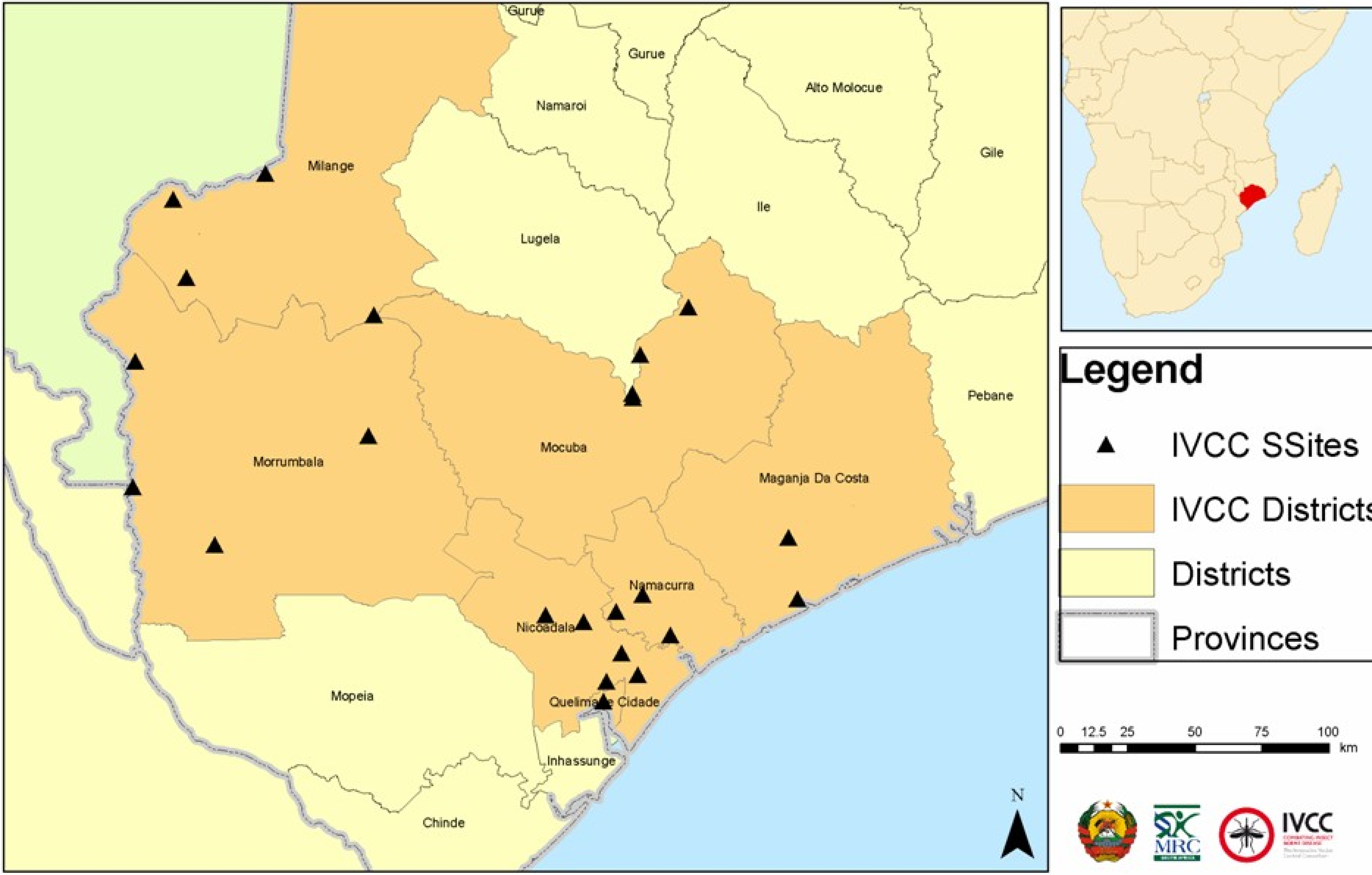
Bioko Island Malaria Control Project (BIMCP)

- BIMCP introduced IRS in 2004 with initially a single round of pyrethroids, followed from 2005 onwards by two rounds per year of bendiocarb
- LLINs were distributed by the BIMCP to cover all sleeping areas in all households in 2008
- Nets had previously been distributed on a smaller scale
- Net use was monitored in surveys from 2006
- All BIMCP surveys were carried out on randomly selected households in 18 sentinel areas covering the entire Island


Algeria
Libya
Western Sahara
Mauritania
Mali
Niger
Chad
Senegal
Sudan
Gambia, The
Guinea-Bissau
Burkina Faso
Guinea
Benin
Nigeria
Sierra Leone
Togo
Ivory Coast
Ghana
Liberia
Central African Republic
Cameroon
Equatorial Guinea
Congo
Gabon
Zaire
Angola

Zambezia (Mozambique) surveys

- Surveys 2006, 2007 & 2008 carried out through the malaria decision support system (MDSS), based at the Medical Research Council of South Africa
- Surveys conducted at nineteen sentinel sites established for monitoring and surveillance of the malaria control program
- Before 2006 the only vector control intervention in the area was mosquito nets
- IRS introduced in 2006, initially by the national malaria control program, later supported by Presidents Malaria Initiative



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Prevalence of infection in children 2 to <15 years from recent household surveys in Bioko, Equatorial Guinea and Zambezia, Mozambique

	Prevalence of infection by vector control protection, % [95% CI]				Odds Ratio: IRS + Net versus IRS only
	Un-protected	IRS only	Net only	IRS + Net	
Bioko, Equatorial Guinea, 2006/7/8	33 [20-31]	25 [19-33]	30 [26-36]	19 [15-24]	0.71[0.59-0.86], p=0.001
Zambezia, Mozambique, 2006/7/8	61 [49-72]	46 [38-55]	59 [43-74]	34 [26-43]	0.60[0.49-0.72]

Combined IRS+ITN effect on infection in Bioko 2008

- Effect of IRS compared to no IRS:
  OR= 0.68, 95% CI 0.48-0.94 (adjusting for ITN)
- Effect of ITN compared to no ITN:
  OR=0.68, 95% CI 0.48-0.97 (adjusting for IRS)
- **Combined effect** of both measures:
  OR= 0.46, 95% CI 0.26- 0.81, relative to those unprotected by either method
- No evidence of effect modification (interaction) between IRS and ITN effects ($p=0.976$)

Malawi

	Prevalence of infection in children<5 years by vector control protection, % [95% CI](N)				Odds Ratio: IRS + ITN versus IRS only
	No protection	IRS only	ITN only	IRS + ITN	
2009 and 2010	65 [40-84] (105)	52 [34-70] (169)	60 [51-59] (63)	38 [25-54] (175)	0.57 [0.27-1.19]

Overall vector control coverage and combining IRS & Nets (Bioko)

	Vector control coverage (percent of children 2 to <15 protected)			
Year	**IRS**	**Net use**	**IRS AND Net use**	**IRS OR Net use**
2006	79 [76-82]	29[23-37]	24 [19-31]	83 [80-86]
2007	67 [62–71]	32 [25–39]	22 [18-27]	73 [68-77]
2008	81 [77-84]	77[72-81]	63 [60 – 67]	95[93-96]

- Combining IRS and Nets may increase overall coverage

Discussion

- Remarkably consistent evidence of added protection of combination in Bioko and in Zambezia (Mozambique)
- Some studies found no such effect
- Combining these two vector control interventions should therefore be considered in context of sustainable scaling up of malaria control
- Increase in cost, hence need for good evidence of efficacy, and on cost effectiveness
- Currently there is no direct evidence of postponing resistance when using different insecticides in combined interventions

Added evidence required

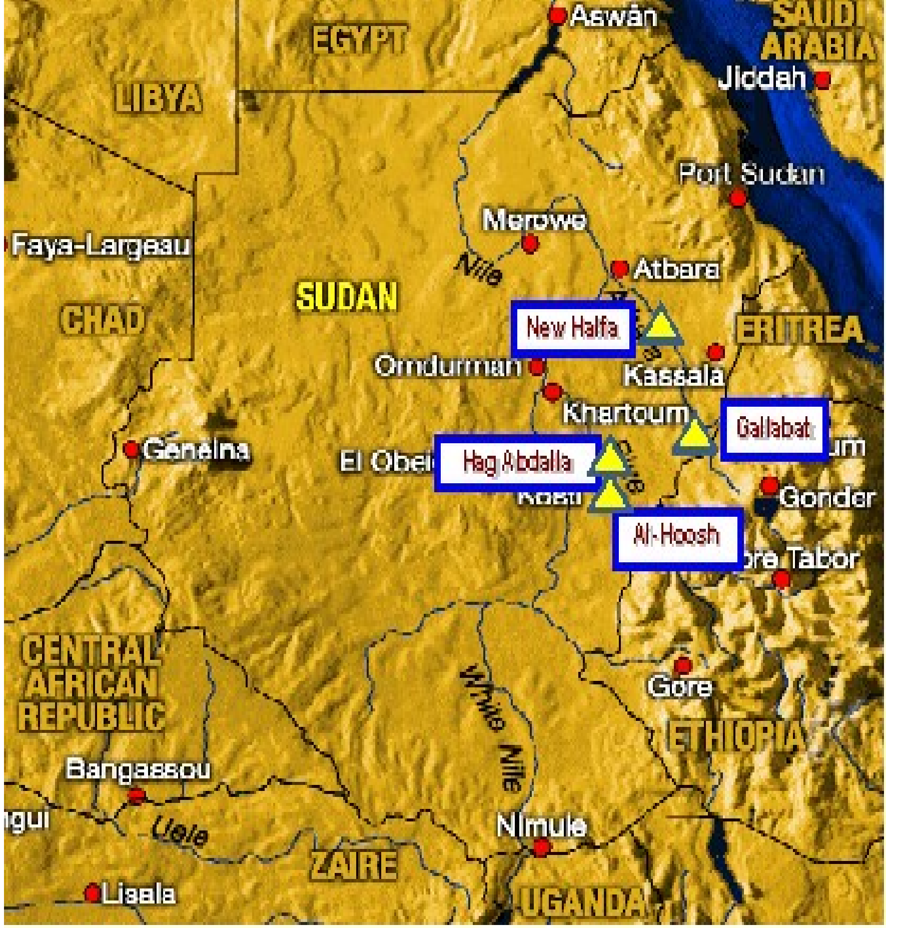
- Only CRT can measure community effects of vector control methods, free from confounding effects
- Require evidence from randomised trials with standardised end-points
- To obtain sufficient power, need to be able to pool results of trials in meta analysis
- Essential to assess combined effect of IRS+ITN when both are at high coverage
- Effect may depend on mode of action of insecticide, hence entomological measures must be included
- Presence (and possible effect of) insecticide resistance should be assessed simultaneously

CRTs on IRS+ITN versus one

- Gambia (2 arm ITN vs ITN+IRS)
- Sudan (3 arm ITN, IRS vs ITN+IRS)
- Iran (Bashargard) (3 arm)

Sudan study

- Funded by Global Environmental Facility (GEF) via UNEP/WHO-EMRO
- 5 year project implemented by National Malaria Control Programme of Sudan, with support from LSHTM and LSTM
- 4 study sites:
  1. El Hoosh (Gezira)
  2. Hag Abdallah (Gezira)
  3. Galabat (Gedaref)
  4. New Halfa (Kassala)



Three Arm Cluster Randomised

- Three intervention arms: IRS only, LLIN only, IRS+LLIN
- Clusters formed by grouping villages into clusters of approximately 2500 persons (~ 500 houses) each and separated from any neighbouring cluster by at least 3 km
- Outcome measure malaria incidence by active case detection
- Clusters be stratified by study area and village type
- Insecticide resistance estimated in each cluster

Power in each area separate and all areas combined

1. In each area the study will have 80% power to detect a difference if incidence in IRS+LLIN arm is lower than incidence in single intervention arm corresponding to relative risk of 0.6
2. For all areas combined study will have 80% to detect a difference corresponding to a RR of 0.77 (or bigger difference)

	El Hoosh (South Gezira)	Hag Abdallah (South Gezira)	Galabat (Gadaref)	New Halfa (Kassala)	Totals
Main current vector control	IRS with Bendiocarb	IRS with Bendiocarb	ITN	IRS with Deltamethrin	
Known ins. resist.	Pyr + DDT	Pyr.	-	DDT + OP	
<u>Study arms (1):</u>					
ITN	X	X	X		3
IRS	X (Bend)	X (Bend)		X (Pyr)	3
IRS+ITN Insecticide classes	X (Pyr + Bend)	X (Pyr + Bend)	X (Pyr +Pyr)	X (2) 1.(Pyr + Pyr) 2.(Pyr + Bend)	5
<5 cohort/ cluster	200	200	200	200	
Clusters (N)	39	39	26	39	143
Cohort size	7,800	7,800	5,200	7,800	**28,600**