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

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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

  – child mortality: 17%
  
  – uncomplicated malaria episodes:
    - 50% (areas of stable malaria);
    - 62% (areas of unstable malaria)
  
  – severe malaria: 45%
  
  – parasite prevalence: 13%

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1Lengeler 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”
- Extensive evidence of effectiveness from programme evaluations, mostly ‘after versus before comparisons’

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

Protective efficacy = 26% reduction in risk of infection per spray round (relative risk 0.74 per spray year)

Bioko: All cause under 5 mortality by year

Pre-intervention period

Intervention period

Relative risk=0.34 [0.23–0.49]

~Protective efficacy 66%
IRS+ITN

- If one is good on its own, are the two together even 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country and time period</th>
<th>Outcome measure used</th>
<th>Effect of nets/ITNs combined with IRS versus IRS only†</th>
<th>Nets untreated, treated or both</th>
<th>ITN use by survey, by number distributed, or not at all</th>
<th>IRS coverage by survey, sprayer data, quantity used, or not at all</th>
<th>IRS/ITN known for individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yadav (1998)</td>
<td>India, mid 1990s</td>
<td>Incidence and prevalence (all ages)</td>
<td>Significant reduction</td>
<td>Both</td>
<td>Not measured</td>
<td>Not measured</td>
<td>No</td>
</tr>
<tr>
<td>Protopopoff (2007a)</td>
<td>Burundi, 2002-05</td>
<td>Vector density and infectivity</td>
<td>a) Vector density: -56%</td>
<td>Treated household</td>
<td>Sprayer data</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b) Infectivity: no effect</td>
<td></td>
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</tr>
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<td>Protopopoff (2008)</td>
<td>Burundi, 2002-05</td>
<td>Prevalence, 1-9 years</td>
<td>Prevalence OR=0.88[0.60-1.31]</td>
<td>Treated household</td>
<td>Sprayer data</td>
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<tr>
<td>Protopopoff (2007b)</td>
<td>Burundi, 2000 (epidemic)</td>
<td>Prevalence (all ages); vector density</td>
<td>a) Prevalence: OR=0.36[0.15-0.88]*</td>
<td>Treated household</td>
<td>Household survey</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b) Vector density: no effect</td>
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<tr>
<td>Nyarango (2006)</td>
<td>Eritrea, 2000-2004</td>
<td>Incidence of cases; mortality</td>
<td>No effect (in multivariable analysis)</td>
<td>Both</td>
<td>household</td>
<td>Quantity insecticide used</td>
<td>No</td>
</tr>
<tr>
<td>Graves (2008)</td>
<td>Eritrea, 1999-03</td>
<td>Incidence of cases</td>
<td>“Significant reduction”</td>
<td>Treated</td>
<td>Number distributed</td>
<td>Quantity insecticide used</td>
<td>No</td>
</tr>
<tr>
<td>Kleinschmidt (2007) + new data§</td>
<td>Equatorial Guinea, 2006-2008</td>
<td>Prevalence, 1 to 15 years</td>
<td>Prevalence OR=0.71[0.59-0.86]</td>
<td>Both</td>
<td>household</td>
<td>Household survey</td>
<td>Yes</td>
</tr>
<tr>
<td>Previously unpublished</td>
<td>Mozambique, 2006-2007</td>
<td>Prevalence, 1 to 15 years</td>
<td>Prevalence OR=0.63[0.50-0.79]</td>
<td>Both</td>
<td>household</td>
<td>Household survey</td>
<td>Yes</td>
</tr>
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• 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 (2007), and Zambezia unpublished)
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
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
Prevalence of infection in children 2 to <15 years from recent household surveys in Bioko, Equatorial Guinea and Zambezia, Mozambique

<table>
<thead>
<tr>
<th>Region</th>
<th>Un-protected</th>
<th>IRS only</th>
<th>Net only</th>
<th>IRS + Net</th>
<th>Odds Ratio: IRS + Net versus IRS only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioko, Equatorial Guinea, 2006/7/8</td>
<td>33 [20-31]</td>
<td>25 [19-33]</td>
<td>30 [26-36]</td>
<td>19 [15-24]</td>
<td>0.71 [0.59-0.86], p=0.001</td>
</tr>
<tr>
<td>Zambezia, Mozambique, 2006/7/8</td>
<td>61 [49-72]</td>
<td>46 [38-55]</td>
<td>59 [43-74]</td>
<td>34 [26-43]</td>
<td>0.60 [0.49-0.72]</td>
</tr>
</tbody>
</table>
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)
<table>
<thead>
<tr>
<th></th>
<th>Prevalence of infection in children&lt;5 years by vector control protection, % <a href="N">95% CI</a></th>
<th>Odds Ratio: IRS + ITN versus IRS only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No protection</td>
<td>IRS only</td>
</tr>
<tr>
<td></td>
<td>65 [40-84] (105)</td>
<td>52 [34-70] (169)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 [51-59] (63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38 [25-54] (175)</td>
</tr>
<tr>
<td>2009 and 2010</td>
<td>0.57 [0.27-1.19]</td>
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</tr>
</tbody>
</table>
## Overall vector control coverage and combining IRS & Nets (Bioko)

<table>
<thead>
<tr>
<th>Year</th>
<th>IRS</th>
<th>Net use</th>
<th>IRS AND Net use</th>
<th>IRS OR Net use</th>
</tr>
</thead>
</table>

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