Responding to pyrethroid resistance:

Sustaining malaria control using alternative insecticides

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KCMC Moshi and NIMR Muheza in Tanzania, and CREC in Benin
Themes

• Impact of pyrethroid resistance on ITNs and IRS
• Responding to resistance
  - Alternative insecticides on nets and IRS
  - Reformulation
  - Combinations
An. gambiae and resistance

- Benin

- M form, Pyrethroid susceptible

- M form, Pyrethroid resistant, kdr+oxidases
• Does pyrethroid resistance reduce the effectiveness of ITN and IRS?

• Comparison of ITNs and IRS in areas of
  – pyrethroid resistance
  – pyrethroid susceptibility

• Experimental hut trials
What do experimental huts measure?

Insecticide performance under realistic, controlled conditions

Personal protection
- Reduction in blood-feeding
- Deterred mosquito entry

Transmission control potential
- Mosquito mortality
# Contrasting impact of pyrethroid ITN in N and S Benin (nets with 6 holes)

## N Benin

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<thead>
<tr>
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<th>% Deterred</th>
<th>% Mortality</th>
<th>% Blood-fed</th>
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<tbody>
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<td>Untreated</td>
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<tr>
<td>Lambda</td>
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## S. Benin

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**Personal protection**

- An gambiae M form (susceptible)
- An gambiae M form (kdr+oxidases)
Contrasting impact of pyrethroid IRS in N and S Benin

**N Benin**

Transmission control

- Untreated
  - GST transferase: 1.4
- lambda-cyhalothrin: 72%
- DDT: 42%

**S Benin**

Transmission control lost?

- Untreated
  - GST transferase: 12%
- lambda-cyhalothrin: 31%
- DDT: 50%

Pyrethroid susceptible, DDT resistant

GST transferase

Pyrethroid and DDT resistant

Kdr + oxidases
Responding to resistance

- **Alternative insecticides**
  - New active ingredients
    - 10y between discovery and practical use
  - Repurposed insecticides
    - Agricultural origin
    - Ingestion and contact action
    - Short lived
    - Slow acting

- **Combination products**
  - Two-in-one ITNs
  - Mixtures of AI on ITNs or IRS

- **Reduce insecticide usage**
  - IVM (cf Integrated Pest Management)
  - Non chemical control
  - Spatial repellents
Repurposed insecticides

- Indoxacarb (oxadiazine)
- Chlorfenapyr (pyrrole)
- Chlorpyrifos methyl (OP)
- Pirimiphos methyl (OP)
- Others
Chlorpyrifos methyl (Reldan CS)

- **OP from Dow AgroSciences**

- **Microencapsulated formulation**
  - Prolonged activity as IRS

- **Hut trial (IRS) comparing**
  - Chlorpyrifos methyl
  - DDT
  - Lambdacyhalothrin
Indoor Residual Spraying

An. gambiae M form (pyrethroid resistant) in S. Benin

An. gambiae control restored with chlorpyrifos methyl
Residual activity of on cement walled huts

[Graph showing the residual activity of different chemicals over time]

- Chlor methyl
- DDT
- Unsprayed hut
- Lambdacyh.
- Chlor. methyl
- DDT
• DDT perhaps not so residual, long lasting alternatives are feasible
• Reformulation pragmatic way to repurpose agro-pesticides - quick wins
Chlorfenapyr

- Pyrrole insecticide
- BASF
- Non neurotoxic
- METI: disrupts energy transfer in mitochondria
- No cross resistance to pyrethroids or OP/carb
- Low mammalian toxicity
Trials of chlorfenapyr ITN against resistant *An gambiae* in S Benin

**Mortality**

- Chlorfenapyr
- Lambda-cyhalothrin
- Untreated

**Blood-feeding**

- Chlorfenapyr
- Lambda-cyhalothrin
- Untreated
Loss (decay/abrasion) of chlorfenapyr on ITN during the hut trial against An gambiae

![Graph showing mortality and bloodfed response over weeks after treatment](image)
Indoor Residual Spraying with chlorfenapyr SC

Pyrethroid resistant *An. gambiae* in S. Benin

*An. gambiae* control restored with chlorfenapyr
Decay of chlorfenapyr IRS during the hut trial against An. gambiae

![Graph showing the decay of chlorfenapyr IRS during the hut trial against An. gambiae. The x-axis represents weeks after treatment, ranging from 0 to 8 weeks, and the y-axis shows the percentage response. The graph includes bars for control IRS and IRS treated groups, with a line graph indicating the mortality and bloodfed response by weeks.]
Chlorfenapyr

• AI has potential in vector control
  - IRS
  - LLIN in combination with pyrethroid

• Reformulation
Pirimiphos methyl - Actellic CS

- Organophosphate, produced by Syngenta
- Trials supported by IVCC
- Microencapsulated formulation
  - Prolonged residual activity
Treatments and application rates in experimental huts in S. Benin on mud and cement walls

1. **Actellic CS Type 1**: 0.5g/m²
2. **Actellic CS Type 2**: 0.5g/m²
3. **Actellic CS Type 1**: 1g/m²
4. **Actellic CS Type 2**: 1g/m²
5. **Actellic EC**: 1g/m²
6. **Icon CS**: 0.03g/m²
7. **Untreated control hut**
Efficacy against pyrethroid resistant *An. gambiae* in cement huts

- **Actellic CS** at 0.5 and 1g/m² kill >80% after 8 months
- Loss of activity with **Actellic EC** and **Icon CS** after short time
Efficacy against free-flying *An. gambiae* in mud huts

- Lower mortality on mud than on cement with the lower dosage
- Mortality ≥ 80% after 7 months
Efficacy against free-flying *Cx. quinquefaasciatus* in huts

- High mortality against Culex for >6 months
Combination products

• Analogous to combination drugs (ACTs)
• AI with complementary properties
  - Pyrethroid fast acting, potent against susceptible forms
  - Slow acting AI or synergist to kill resistant forms
• Combination LLINs
  - Mixtures or two-in-one formats
  - Synergists (PermaNet 3.0 with PBO)
  - Repurposed agro-pesticides
• Combination IRS
  - Alternations in time
  - Mixtures?
Conclusions and needs

- Pyrethroid resistance major threat
- Alternative insecticides exist: some old, some new, both drawn from agropesticides
- Reformulate for LLINs or IRS to improve residuuality or wash resistance
- Accelerate development and evaluation of combination products
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Indoxacarb

Oxadiazine from Dupont

Acts on Na\(^+\) channels

No cross resistance to pyrethroids or OPs
Indoxacarb activity on netting

Slow acting

More active than permethrin against resistant An. gambiae