Recent research on resistance in West Africa

Mark Rowland
Themes

What resistance is out there in Africa and is it important?

Does pyrethroid resistance undermine the effectiveness of ITN & IRS in W. Africa?

What can be done about it – are there alternative insecticides?
Distribution of resistance in *Anopheles gambiae*

Absence mutation *kdr*

Presence *kdr*

Presence *Ace.1*

Oxidase based pyrethroid resistance in *A. funestus*

Oxidase based permethrin/DDT resistance in *A. gambiae* and *A. arabiensis*
Evaluation of resistance

- Evaluation of operational impact of resistant vectors in experimental huts

- Trials of interventions against resistant populations
  - Vector population indicators
  - Disease control indicators
West African experimental huts
Principle of verandah huts
What do experimental huts measure?

- Insecticide performance under realistic, controlled conditions
  - Personal protection
    - prevention of blood-feeding
    - Deterrency – stops entry of mosquitoes into huts
  - Mosquito mortality – transmission control
  - Survival of resistant mosquitoes - operational importance
Deliberately holed net
Experimental hut studies – does pyrethroid resistance reduce ITN and IRS effectiveness?

Comparison of:
Insecticide Treated Nets (ITN)
Indoor Residual Spraying (IRS)

In areas of:
pyrethroid resistance
pyrethroid susceptibility

In:
Ivory Coast
Benin
Benin

Equatorial

Savannah

Malanville – pyrethroid susceptible

Cotonou – pyrethroid resistant
ITN against *A. gambiae* in N. Benin

Susceptible mosquitoes – ITN fully effective

Transmission control

Personal protection
ITN vs *A. gambiae* in Ivory Coast

Kdr pyrethroid resistant – little or no loss of efficacy due to resistance

Transmission control

Personal protection
ITN vs *A. gambiae* in S. Benin
loss of efficacy due to pyrethroid resistance

Transmission control lost

Personal protection lost
ITN vs A. gambiae in S. Benin

loss of efficacy of *permethrin* due to pyrethroid resistance

Transmission control lost

Personal protection partially lost
Indoor residual spraying vs *A. gambiae* in S. Benin

loss of efficacy due to pyrethroid resistance

Transmission control lost
Malaria control trial in Ivory Coast (Henri et al. 2005)

- Kdr frequency = 0.90
- 4 pairs of villages
- Lambdacyhalothrin ITN distributed to 4 villages and re-treated after 6 months
- 50 children per village (0-5 years old) followed up
- 1 year of follow up at 6 week intervals
### Summary of trial of ITN in Ivory Coast (Henry et al. 2005)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ITN</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Pre intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence %</td>
<td>84</td>
<td>80</td>
<td>ns</td>
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<tr>
<td>Parasite density</td>
<td>199</td>
<td>143</td>
<td>ns</td>
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<tr>
<td>Incidence</td>
<td>2.3</td>
<td>2.9</td>
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<tr>
<td><strong>Post intervention</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevalence %</td>
<td>68</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parasite density</td>
<td>69</td>
<td>29</td>
<td>&lt;0.001</td>
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<tr>
<td>Incidence</td>
<td>1.8</td>
<td>0.8</td>
<td>&lt;0.01</td>
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<tr>
<td>Rate ratio</td>
<td></td>
<td>0.43</td>
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<tr>
<td>Protective efficacy</td>
<td></td>
<td>56%</td>
<td>(25-75)</td>
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</table>
Bioko IRS campaign:
limited impact of pyrethroid IRS
carbamate IRS effective

Pre spraying: 36% M form, 50% kdr genotypes
Post spraying: 80% M form, 78% kdr genotypes
## Summary of W. Africa field studies on An. gambiae

<table>
<thead>
<tr>
<th>Intervention</th>
<th>ITN</th>
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<th>ITN</th>
<th>ITN</th>
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<tr>
<td>Molecular form</td>
<td>S</td>
<td>S</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M/S</td>
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<tr>
<td>Location</td>
<td>N.Benin</td>
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<td>S.Benin</td>
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<td>Bioko</td>
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<tr>
<td>Insecticide</td>
<td>Lambda</td>
<td>Lambda</td>
<td>Lambda</td>
<td>Permethrin</td>
<td>Lambda</td>
<td>Delta Alpha</td>
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<tr>
<td>Hut Deterrence</td>
<td>√√√</td>
<td>√√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>-</td>
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<tr>
<td>Hut Mortality</td>
<td>√√√</td>
<td>√√</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
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<tr>
<td>Hut Bloodfeeding inhibition</td>
<td>√√√</td>
<td>√√</td>
<td>0</td>
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<tr>
<td>Trial Malaria control</td>
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<td>?</td>
<td>?</td>
<td>0</td>
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Cause of resistance in Benin

- Mechanisms detected
  - kdr
  - higher oxidase and esterase activity

- But bioassays on A. gambiae show same level of resistance as laboratory kdr strain
  - Is metabolic resistance important?
  - Does ‘behavioural resistance’ increase blood-feeding rates
  - Role of M form?

- Investigate metabolic resistance
- Investigate behaviour
- Disease control trial with pyrethroid in S. Benin
Conclusions of recent ITN / IRS experimental hut studies

- Loss of efficacy of IRS and ITN owing to pyrethroid resistance (*kdr* + metabolism or behaviour) in M form

- *Kdr* in S form has no operational significance

- IRS selects pyrethroid resistance but so do ITNs in An. gambiae *kdr* M form

- Operational impact & disease control trials urgent

- Need alternative insecticides to supplement the pyrethroids
Ideal characteristics of an alternative to pyrethroids

Essential:
- Low human toxicity
- No cross resistance to pyrethroids
- Long residual activity

Desirable:
- Toxic to mosquitoes at low concentrations
- Rapid action
- Repellent

How do the alternatives measure up?
New insecticides may be more effective than pyrethroids or DDT

IRS South Benin: % mortality in DDT/pyrethroid resistant area ($kdr$)
**ITN in pyrethroid resistant area in Benin**

*A. gambiae* control restored with chlorfenapyr

<table>
<thead>
<tr>
<th>% DETERED</th>
<th>Untreated net</th>
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<tbody>
<tr>
<td>Permethrin 500mg/m²</td>
<td>0</td>
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<tr>
<td>Chlorfenapyr 100mg/m²</td>
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<table>
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<th>% MORTALITY</th>
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<td>Permethrin 500mg/m²</td>
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<td>Chlorfenapyr 100mg/m²</td>
<td>57</td>
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<table>
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<tr>
<th>% BLOOD-FED</th>
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<td>Permethrin 500mg/m²</td>
<td>45</td>
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<td>Chlorfenapyr 100mg/m²</td>
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- Good mortality but low personal protection
IRS in pyrethroid resistant area in Benin

An. gambiae control restored with chlorpyrifos-methyl
Chlorfenapyr ITN in huts vs An. arabiensis in Tanzania

- Chlorfenapyr equivalent mortality to deltamethrin when susceptible
- Deltamethrin better deterreny
The Innovative Vector Control Consortium

- Five year programme started Nov 2005
- Funded by a major award from the Gates Foundation
- Consortium Members
  1. Colorado State University
  2. Liverpool School of Tropical Medicine
  3. London School of Hygiene and Tropical Medicine
  4. Medical Research Council, South Africa
  5. University of California Davis
Two Thematic Areas

- **Objective 1.** Development of new products (e.g. insecticides and formulations)
- **Objective 2.** Development of better tools to facilitate malaria and dengue vector control
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