Antimalarial Drug Combinations

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WHO/TDR
A bit of History

- Failing drugs + liberal practice + inappropriate test
- Mono-therapies deployed in sequence
  - Parasite resistance
  - Effects underestimated: over-reliance
  - Excess morbidity & mortality
- Theory & trials in support of combinations
  - Evidence of efficacy/safety & effectiveness
  - Evidence on appropriate methodology
- Interaction: research-policy
- Informed policy decision
Why combining drugs?

- Mutual protection against resistance - best if:
  - Independent mode of action (different targets)
  - Complementary pharmacodynamic effects
  - Comparable concentration/time profiles
- Prolong useful therapeutic life-span
- Broader spectrum - best if:
  - Younger and more mature asexual forms
  - Gametocytes; liver stages; ...
- Long-time practice in other disciplines
**Current combinations**

**Artemisinin:**
- Very rapid killing
- Short-lived
- Residual parasites
- Act on rings + more mature asexual parasites + young gametocytes
- Virtually no selective window
- No resistance (so far)? (slower clearance in Cambodia?)

**Companion drug:**
- Rapid killing (quinolines)
- Longer residence
- Killing residual parasites
- Act on mature asexual forms
- Variable selective window
- Variable (cross) resistance
Driver of change: parasite resistance to traditional antimalarial drugs

→ evidence-based policy recommendation
Evidence of efficacy

ACTs →

Accelerate therapeutic response

↑cure rates

(↓transmissibility)

Adjuik et al, Lancet 2004

Companion Drug Study AS3 Placebo O-E V(O-E)
CQ Burkina 74/145 115/142 -21.49 16.19
C.Ivoire 115/124 129/134 -2.27 3.32
Saotome 85/181 154/175 -36.51 19.69
Subtotal 274/450 398/451 -60.27 39.19
AQ Gabon 14/94 28/98 -6.56 8.24
Ken_AMRF 57/180 108/183 -24.82 22.56
Senegal 29/159 33/156 -2.30 12.49
Subtotal 100/433 169/437 -33.68 43.29
SP Gambia 6/187 20/193 -6.79 6.07
Ken_KMRI 89/192 121/189 -16.83 23.62
Malawi 41/134 99/129 -30.33 16.43
Peru 2/97 4/93 -1.06 1.46
Uganda 48/116 89/144 -13.12 16.08
Subtotal 186/726 333/748 -68.14 63.66
MQ Thai2 1/180 46/169 -23.24 10.19
Thai3 9/179 57/181 -23.82 13.51
Subtotal 10/359 103/350 -47.06 23.70
Total 570/1968 1004/1987 -209.41 169.91

<table>
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<tr>
<th>Background drug</th>
<th>OR</th>
<th>99% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>CQ</td>
<td>0.19</td>
<td>0.12, 0.30</td>
<td>&lt;0.0001</td>
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<tr>
<td>AQ</td>
<td>0.45</td>
<td>0.30, 0.68</td>
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<tr>
<td>SP</td>
<td>0.33</td>
<td>0.24, 0.46</td>
<td>&lt;0.0001</td>
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<tr>
<td>MQ</td>
<td>0.07</td>
<td>0.03, 0.17</td>
<td>&lt;0.0001</td>
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<tr>
<td>Overall</td>
<td>0.27</td>
<td>0.23, 0.32</td>
<td>&lt;0.0001</td>
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Evidence of effects

Kwazulu-Natal, South Africa

Thai-Myanmar borders

Casamance, Senegal

Zanzibar
What have we learnt?

- Deploying effective drugs reduces morbidity & mortality
- Combining effective interventions (ACTs + insecticide-treated nets, residual spraying) works - evidence from areas of low and moderate transmission
- Fixed combinations for improved adherence
- Adapted dosage forms & dosing schedules needed to avoid
  - underdosing (failure, resistance)
  - & overdosing (toxicity; non-compliance, resistance)
The Challenges Ahead

- Drug pressure: companion drugs = few chemical families & modes of action; compromised by (cross)resistance
- The pipeline: lacks novelty in the medium term; no immediate replacement for classical artemisinin derivatives
- Deployment & practice: misuse; coverage
- Looming resistance?
- P. vivax, mixed infections
- Multiple first-line therapies to dilute pressure?