Effective Radical Cure: The Challenge

Bali, Indonesia
9th-12th October, 2017
**Why Bother?**

**P. vivax relapses:**

- Occur frequently
- Are usually very frequent
- Are often asymptomatic
- Cause a cumulative risk of anaemia, morbidity and mortality
- Are a major source of transmission

**Radical Cure is vital for the control and elimination of P. vivax**
Are we prescribing radical cure for *P. vivax*?

*Is the radical cure we are providing effective?*

*If not how can we do it better?*
Antimalarial Efficacy

- **Efficacy** - the performance of an intervention under ideal and controlled circumstances

**Drug Factors**
- Pharmacodynamics: Potency, Stage specificity
- Pharmacokinetics: ADME, Interactions
- Dosing strategy
- Tolerability
- Drug quality and formulations

**Parasite Factors**
- Biomass
- Sequestration
- Mixed Species
- Staging
- Resistance

**Host Factors**
- Innate and Acquired Immunity
- Comordities: coinfection, GI
- Nutrition
- Pharmacogenomics: CYP2d6
- Treatment seeking behaviour
- Adherence
Efficacy 14 day Primaquine Regimens

Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of *Plasmodium vivax* infection in Ethiopia: A randomized controlled trial.

Randomized trial of primaquine hypnozoitocidal efficacy when administered with artemisinin-combined blood schizontocides for radical cure of *Plasmodium vivax* in Indonesia.

- **ACT plus Low Dose 14d PQ**
- **ACT plus High Dose Pq**
Effectiveness - the extent to which a drug regimen achieves its intended effect in the real world

= Efficacy Plus...

Host Factors
- Treatment seeking behaviour
- Access to healthcare
- Education and information
- Severity of disease / Perception of need
- Patient adherence
- Cost to the patient and carers

Drug Factors
- Tolerability
- Complexity of regimen
- Concomitant treatments
- Formulation / packaging

Health Systems
- Policy adherence
- Perception of need
- Concerns over safety
- Cost to providers
- Drug quality
- Supply chain and capacity
Unsupervised Primaquine Doesn’t Work So Well

**CQ**

- HR = 3.5 [1.4-8.9], p=0.008
- 87% efficacy
- 63% efficacy

**CQ + Pq**

- 84% efficacy

**AL**

- HR = 3.9 [1.3-11.4]; p=0.014
- 84% efficacy
- 52% efficacy

**AL + Pq**

- 84% efficacy
Primaquine Effectiveness - Papua

Unsupervised primaquine for the treatment of *Plasmodium vivax* malaria relapses in southern Papua: A hospital-based cohort study

*Plos Med 2017*

**Risk of P. vivax Recurrence**

- No PQ
- Low dose
- High dose

**Drug Use**

- n=46,221 High dose Pq

**AHR 95% CI P**

<table>
<thead>
<tr>
<th></th>
<th>AHR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Overall</td>
<td>0.90</td>
<td>0.86-0.95</td>
<td>&lt;0.001</td>
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<tr>
<td>1 to &lt;5yrs</td>
<td>0.85</td>
<td>0.79-0.90</td>
<td>&lt;0.001</td>
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<tr>
<td>5 to &lt;15yrs</td>
<td>0.98</td>
<td>0.86-1.12</td>
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<td>&gt;=15yrs</td>
<td>0.99</td>
<td>0.91-1.08</td>
<td>0.876</td>
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<tr>
<td>2007</td>
<td>0.91</td>
<td>0.85-0.97</td>
<td>0.003</td>
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<tr>
<td>Outpatients</td>
<td>0.89</td>
<td>0.84-0.93</td>
<td>&lt;0.001</td>
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Controlling for: Age, Gender, Admission status, Ethnicity, Year
Improving Treatment Regimens

IMPROV - Efficacy Study
IMproving Primaquine Radical Cure Of Vivax

Schizonticidal treatment: Cq or DHA-Pip
Plus
Control Arm vs Pq 7days vs Pq 14 days

N=2,400
9 Sites, 4 countries
New Drugs

Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study


Tafenoquine
Single dose radical cure
The Long And The Short Of It….

Adherence Issues

Tafenoquine
Single Dose

Primaquine...
HD-7days    HD-14days
LD-7 Days    LD-14 days
HD-21 days   Weekly x8

Need for G6PD Testing
Improving the Effectiveness of Radical Cure

- Is it a problem?
- Why is it a problem?
- What can we do about it?
- Is it a priority?
- How can we measure it?
- How can we provide evidence to support appropriate interventions?