Return of chloroquine-sensitive falciparum malaria in Malawi

U01AI44824:
Clinical trials of chloroquine combinations in Malawi
What happens when you stop using chloroquine?
Malaria treatment in Malawi

- CQ resistance > 80% in 1990
  - Clinical efficacy < 50%
- Malawi changed from CQ to SP in 1993
- Strong effort to convince health workers and population to stop using CQ
  - SP made widely and freely available
  - CQ available by prescription only
Molecular marker for chloroquine resistant falciparum malaria: \textit{pfcrt} K76T

- \textit{Plasmodium falciparum} chloroquine resistance transporter (\textit{pfcrt})
- Lysine→Threonine mutation at codon 76
- Linked to in vitro resistance phenotype
- Strongly associated with clinical failure
CQ resistance mutation

CQ → SP

A

% of infections

Year
39 22 24 46 75

pfcr K76T

B

% of infections

Year
38 22 21 150 34
38 22 20 231 33

dhfr N51I
dhfr C59R

SP resistance mutations
Prevalence of PfCRT 76T in Blantyre

- 2001 0%
- 2002 0%
- 2003 0%
- 2004 0%
- 2005 0%
Next step: Uncontrolled trials of treatment of asymptomatic infections

<table>
<thead>
<tr>
<th></th>
<th>Parasite-free days 3-7</th>
<th>Parasite-free day 14</th>
<th>Parasite-free day 28</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blantyre adults</td>
<td>63/63</td>
<td>55/55</td>
<td>42/42</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>at day 28</td>
</tr>
<tr>
<td>Salima children</td>
<td>51/52</td>
<td>47/51</td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>at day 14</td>
</tr>
</tbody>
</table>

Kublin et al. 2003, Mita et al. 2003
Next step:

Randomized clinical trial of chloroquine vs. sulfadoxine-pyrimethamine treatment of uncomplicated falciparum malaria in children
Phil Thesing and the BMP team

Miriam Laufer
Assistant Professor of Pediatrics
University of Maryland
Study participants

- **Inclusion criteria**
  - Age 6 months to 12 years
  - Symptoms of malaria
  - Parasite density 2,000-200,000/mm³
  - Informed consent

- **Exclusion criteria**
  - Danger signs or severe disease
  - Concurrent bacterial illness
  - Chronic antibacterial medication
Treatment allocation

- Randomized to receive either:
  - Sulfadoxine-pyrimethamine
    - 1.25 mg/kg sulfadoxine and 25 mg/kg pyrimethamine
    - Single dose
    - Still first-line antimalarial treatment drug in Malawi
  - Chloroquine
    - 10 mg/kg on days 0 and 1
    - 5 mg/kg on day 2
Outcomes

- Adequate clinical and parasitologic response
- Treatment failure
  - Early treatment failure (days 0-3)
  - Late clinical failure (days 4-28)
  - Late parasitologic failure (day 28)
Continuous observation phase

• First 30 participants in each group observed continuously at research clinic until:
  - 2 consecutive negative malaria smears
  - 12 consecutive hours afebrile
## Results: Characteristics at enrollment

<table>
<thead>
<tr>
<th></th>
<th>Chloroquine (N=105)</th>
<th>Sulfadoxine-pyrimethamine (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (95% confidence interval)</td>
<td>2.6 (2.2-3.0)</td>
<td>2.9 (2.5-3.4)</td>
</tr>
<tr>
<td>Number female (%)</td>
<td>57 (54)</td>
<td>51 (49)</td>
</tr>
<tr>
<td>Mean hemoglobin in mg/dL (95% CI)</td>
<td>9.5 (9.1-9.8)</td>
<td>9.2 (8.8-9.6)</td>
</tr>
<tr>
<td>Geometric mean parasite density in mm$^3$ (95% CI)</td>
<td>19,379 (15163-24768)</td>
<td>18,856 (12245-23322)</td>
</tr>
<tr>
<td>No. reporting antimalarial drug use in preceding week (%)</td>
<td>13 (12)</td>
<td>13 (12)</td>
</tr>
</tbody>
</table>
Results: follow up

- **80** completed follow up in CQ arm
  - 13 moved from study area
  - 6 vomited the study drug
  - 5 withdrew consent
  - 1 administered antimalarial drug during follow up period

- **87** completed follow up in SP arm
  - 11 withdrew consent
  - 4 moved from study area
  - 2 not found
  - 1 excluded due to pneumonia
Results: CQ outcomes

• 1 treatment failure in the CQ arm
  - Parasite density on day 2 (8,880 parasites/mm³) greater than day 0 (6,480 parasites/mm³)

• 28-day treatment success rate: 99% (93-100)
Results: SP efficacy

- 71 treatment failures in the SP arm
  - Early treatment failure (n=31)
  - Late clinical failure (n=22)
  - Late parasitologic failure (n=18)
- 28-day treatment success rate: 21% (13-30)
Time to treatment failure

hazard ratio 112.4; 95% CI 15.5-833.3; P<0.001
Worst-case scenario: time to treatment failure assuming all CQ losses are failure

CQ 28 day efficacy 80% (95% CI 70-86)
hazard ratio 5.4; 95 % CI 3.2-9.1; P<0.001
Results: parasite clearance time

Mean parasite clearance time:

CQ: 2.6 days (2.5-2.8)
SP: 8.8 days (6.3-11.2)

P<.001
Results: fever clearance time

Mean fever clearance time:

CQ: 10.3 hours (8.1-12.6)
SP: 47.7 hours (37.7-57.7)

P<.001
Results: Genotyping

- All infections, including the treatment failure, have wild-type ("sensitive") pfcr K76
Competition and fitness

- Expansion of wild-type *pfcrt*, not back-mutation of T76 to K76 (Mita et al., 2004)
- Survival advantage of chloroquine-sensitive parasites in the absence of drug pressure
  - More efficient replication?
  - Evades host immune system?
  - More readily transmitted (human-vector or vector-human)?
- In the absence of drug pressure susceptible organisms out-compete resistant organisms
Experience in other countries

• Africa
  - Not applicable: No other country has eliminated chloroquine use

• Asia
  - Vietnam
    • 15 years after switch for CQ to SP: 67% pfcrt 76T
  - Thailand
    • pfcrt 76T fixed in population at 100%
  - China
    • 1979 to 2001: 90% to 54% pfcrt 76T

Why did this occur in Malawi and not in Asia?

- Extent of chloroquine use
  - Chloroquine is used for treatment of *P. vivax* in Asia
    - Widely available in clinics, markets (F. Nosten, personal communication)
  - Chloroquine use was not reported in a study of 1,000 children in 2000 in the same township as our study (Holtz et al. 2003)
Why did this occur in Malawi and not in Asia?

- **Low transmission (Asia, S. America)**
  - Single-clone infections
  - Limited opportunity for competition between sensitive and resistant parasites

- **High intensity transmission (Africa)**
  - Polyclonal infections
  - Direct competition between sensitive and resistant parasites
Should Malawi start using chloroquine again?

• No.

• Chloroquine resistant malaria surrounds Malawi
  - Mozambique and Zambia
  - It may even surround Blantyre

• Very low level CQ resistance may exist
  - Current study limited to 28-day follow-up
Next steps

• Recommend complete withdrawal of chloroquine from Africa
• Longitudinal trial of CQ combination therapy
  - Identify characteristics of the best partner drugs to prevent reemergence of resistance
Protecting drugs

![Graph showing concentration vs. time with peak at CQ]
Protecting drugs

Concentration vs. Time

ART CQ
Protecting drugs

Concentration vs. Time

New infections
Protecting drugs

[Graph showing concentration over time with IC100-CQR and IC100-CQS levels indicated.]
Protecting drugs

Window of selection

Concentration

Time

IC100-CQR

IC100-CQS
Protecting drugs

Window of selection

Concentration

Time

IC100-CQR

IC100-CQS
Protecting drugs

Window of selection

IC100-CQR

IC100-CQS

Concentration

Time
Protecting drugs

Window of selection

Concentration

Time

IC100-CQR

IC100-CQS
Protecting drugs

Window of selection

IC100-CQR

IC100-CQS
Protecting drugs

Window of selection

IC100-CQR

IC100-CQS

Concentration

Time
Longitudinal clinical trial of chloroquine combinations

- Children with malaria randomized to same treatment for all malaria episodes for 1 year
  - Chloroquine monotherapy
  - Chloroquine + artesunate
  - Chloroquine + azithromycin
  - Chloroquine + atovaquone/proguanil

- Goal: Identify optimal PK/PD characteristics of partner drugs to prolong useful life of combination therapy in this setting
The future

- Chloroquine for intermittent preventive therapy in pregnancy, infants, children?
- Chloroquine combination therapy?
- What will happen if SP is effectively withdrawn from Africa?
Thanks to:

**Maryland**
Miriam Laufer
Phillip Thesing
Nicole Eddington
Shannon Takala
Jean-Claude Akpa

**Malawi**
Terrie Taylor
Fraction Dzinjalamala
Rhoda Masonga
Osward Nyirenda
Maganizo Chagomerana

NIH R01AI44824, K01TW000014, U01AI44824, K23AI49203