Antimalarial drug resistance in *P. falciparum* malaria in Tanzania: Current status and challenges

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Commonly used antimalarials

- Chloroquine (CQ) – up to 2001
- Sulphadoxine-pyrimethamine (SP) up to 2006
- Artemisinin-based combinations (ACTs) – currently
CQ resistance

**Pfcrt**

<table>
<thead>
<tr>
<th>72</th>
<th>73</th>
<th>74</th>
<th>75</th>
<th>76</th>
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<tbody>
<tr>
<td>C</td>
<td>V</td>
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<td>K</td>
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Common in South-East Asia/South America

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<td>C</td>
<td>V</td>
<td>I</td>
<td>E</td>
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Common in East Africa

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<td>V</td>
<td>M</td>
<td>N</td>
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**Pfcrt 76T** – strong predictor of CQ resistance
SP resistance

**dhfr**

\[
\begin{array}{cccccc}
50 & 51 & 59 & 108 & 164 \\
C & N & C & S & I \\
50 & 51 & 59 & 108 & 164 \\
C & I & R & N & I
\end{array}
\]

*Dhfr triple mutation*

High Pyrimethamine resistance

**dhps**

\[
\begin{array}{cccccc}
436 & 437 & 540 & 581 & 613 \\
S & A & K & A & A \\
436 & 437 & 540 & 581 & 613 \\
S & G & E & A & A
\end{array}
\]

*Dhps double mutation*

High sulphadoxine resistance

\[
\begin{array}{cccccc}
50 & 51 & 59 & 108 & 164 \\
C & I & R & N & I \\
50 & 51 & 59 & 108 & 164 \\
S & G & E & A & A
\end{array}
\]

\[
C & I & R & N & I + S & G & E & A & A
\]

= **Quintuple - High SP resistance**
540E – a strong predictor of treatment failure

581G mutation, SP super-resistance
ACT resistance

- Pfmdr1 Mutations

**Pfmdr1**

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<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>Y</strong></td>
<td><strong>S</strong></td>
<td><strong>N</strong></td>
<td><strong>D</strong></td>
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**QN resistance but ↑ susceptibility to MQ, HF, ACT**

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<td><strong>?</strong></td>
<td><strong>C</strong></td>
<td><strong>D</strong></td>
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**↓ CQ effectiveness**

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**↓ AS-AQ effectiveness**

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**↓ ALu effectiveness**

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<td><strong>F</strong></td>
<td><strong>?</strong></td>
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<td><strong>D</strong></td>
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**↓ parasite clearance rate by ALu**
Replacement of CQ in 2001

- Was complete
- CQ use was banned
  - It remained for prophylaxis and treatment of malaria in sickle cell

- SP was first line
- However SP was already in use before
  - SP policy = transient,
  - Replace by ACTs in December 2006
- SP continued in IPTp and IPTi programmes

- IPTp and IPTi, very effective in reduction of malaria, reduction of maternal and infant mortality

- In 2010 WHO (2010) recommended application of IPT where dhps 540E is < 50%
<table>
<thead>
<tr>
<th>Country</th>
<th>Author/year</th>
<th>Mutation (K540E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanzania (Morogoro)</td>
<td>(2006) Malisa et al., 2011</td>
<td>70%</td>
</tr>
<tr>
<td>Tanzania (Mbeya)</td>
<td>(2005) Schonfeld et al., 2007</td>
<td>77.4%</td>
</tr>
<tr>
<td>Tanzania (Korogwe)</td>
<td>(2006) Gesase et al., 2009</td>
<td>94.3%</td>
</tr>
<tr>
<td>Rwanda</td>
<td>(2005) Karema et al., 2010</td>
<td>84% → 97%</td>
</tr>
<tr>
<td>Kenya</td>
<td>(2006-2007) Bonizzoni et al., 2009</td>
<td>74% → 99%</td>
</tr>
<tr>
<td>Uganda</td>
<td>(2002-2004) Lynch et al., 2008</td>
<td>98% → 100%</td>
</tr>
<tr>
<td>Mali</td>
<td>(2006) Dicko et al., 2010</td>
<td>1.6%</td>
</tr>
<tr>
<td>Senegal</td>
<td>(2009-2010) Wurtz et al., 2012</td>
<td>0%</td>
</tr>
</tbody>
</table>
Where are we currently?
# CQ resistance surveillance in Tanzania 2010 - 2011

Table 1: Distribution of *Pfcr* K76T resistance marker in 6 regions of Tanzania

<table>
<thead>
<tr>
<th>Region</th>
<th>Frequency of K76T</th>
<th>Prevalence of K76</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K76 (%)</td>
<td>76T (%)</td>
</tr>
<tr>
<td>Tanga</td>
<td>108 (94.7)</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Coastal</td>
<td>130 (93.5)</td>
<td>9 (6.5)</td>
</tr>
<tr>
<td>Mtwara</td>
<td>66 (97.1)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Kagera</td>
<td>82 (92.1)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td>Mwanza</td>
<td>150 (93.2)</td>
<td>11 (6.8)</td>
</tr>
<tr>
<td>Mbeya</td>
<td>136 (95.1)</td>
<td>7 (4.9)</td>
</tr>
<tr>
<td>Overall</td>
<td>672 (94.3)</td>
<td>42 (5.7)</td>
</tr>
</tbody>
</table>

(χ²=7.88, p=0.163)
CQ resistance trends

- Coastal: 90%
- Mtwara: 80%
- Tanga: 70%
- Mbeya: 60%
- Mwanza: 50%
SP- resistance

dhfr

Matondo et al, 2014
Pfdhps 581G

- Super resistance to Sp
- IPTP failure (Minja DT et al 2013)

Dhps 581G
Tanga – 55%
Kagera – 20%

Kavishe et al, in preparation
ACT resistance

• NFD polymorphisms in Tanzania
NFD - ($\chi^2 = 2.3$, $p = 0.512$, exc Mbeya)

N = 687

Kavishe RA et al 2014
Conclusions

• CQ resistance down to app 5%
  – Well implemented ban
  – Possible return of CQ in treatment,
  – Increase restriction on CQ importation and use for few more years? A decade?

• ACT resistance, though not confirmed in East Africa, rise in ALu associated polymorphisms = alarm for intensified pharmacovigilance studies
  – K13 propeller – a matter of time to enter African shores
• High SP resistance an alarm for SP-IPT programmes

• WHO (2012)
  • IPTp should continue even if quintuple mutations are >90%

• The emergence and spread of dhps 581 – threat

• WHO 2013 recommendations:
  - Need more data on dhps 581 for informed decisions

• Current observations in Tanzania
  • Urgent need to find alternative to SP for IPTp in E. Africa
  • In west Africa – situation is different
  • However, resistance levels also growing
Acknowledgements

• Mr. Sungwa Matondo – KCMC
• Mr. Abdul Chambo – KCMC
• Dr. Hugh Reyburn – KCMC
• Prof. F. Mosha – KCMC
• Asia Mohamed
• Petro Paulo - KCMUCo
• All other co-authors of the published articles

Others:

• Mr. Akili Kalinga – NIMR, Tukuyu
• Ms. Jackline Mosha, Mwanza/NIMR
• MR. Dominic Mosha
• Dr. Cally Roper – LSHTM
• Dr. Michael Alifrangis – CMP
• Dr. A. Manjurano

• Wellcometrust
• THRiVE consortium