Drug quality & Antimalarial Efficacy

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Worldwide Antimalarial Resistance Network
WWARN
Chloroquine & SP spread of resistance
Chloroquine & SP spread of resistance
Mefloquine resistance

1990
Revisiting history

Response to the first waves of resistance
  – Slow
  – Inadequate assessment of risk – cost
  – Millions of deaths
Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tamming, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hongsatatpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotiranich, Ph.D., Pharah Lim, M.D., Trent Hedman, Ph.D., Sen-Sam An, Shummay Yeung, Ph.D., Pratap Singhhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.
Artemisinin resistance
What next? Spread, emergence
Preventing the global spread of antimalarial resistance: can we subvert evolution?

• Have we done everything to prevent or delay the “evolution”?

• Translating science into public health action
  – Improve the value of existing data
  – Preserve efficacy of drugs in current use
  – Detect and manage resistance spread/emergence
  – Ensuring efficacy of new drugs
WWARN Collaboration: >250 partners

100,000 clinical trial patient data

Over two thirds of all ACT clinical data published since 2000

Data pooled and analysed to identify failure risks
Policy - Data – Funding – Change?
Trans-discipline approach

PV programs

NMCPs

MRA Programs

Clinical

Modelling

PK

Drug quality

Safety

Molecular

In vitro

WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK

WWARN
Preventing the Global Spread of antimalarial Resistance: Can We Subvert Evolution?

• Resistance is NOT

• Maintaining the Useful Life of ACTs
  1. Identify underlying factors promoting resistance
  2. Optimising regimen
     • Efficacy & Safety
  3. Targeting interventions
     • Time & Place
Understanding risk factors driving resistance

- Young children & Pregnant Women
- Adherence
- Poor Quality
- Drug interactions
- Comorbidities: e.g. Malnutrition, HIV

Comorbidities:
e.g. Malnutrition, HIV
Is the risk higher for antimalarials?

- Over 50% of antimalarials are sold in the private market
  - No need of prescription, limited diagnostic capacity
- Non malaria cases receiving antimalarials
- Highest proportion of poor quality antimalarials in countries with highest transmission
- WHO report
  - Of 46 sub-Saharan countries 30% did not have an MRA and about 63% (had) minimal capacities
  - Only 4 countries have WHO pre-qualified medicine analysis laboratories in malarious Africa
AQ Scientific Group objectives

Reduce impact of poor quality antimalarials - particularly ACTs - on the spread of drug resistance and on harm to public health

- Increase information availability
- Identify gaps in the current evidence
- Advocate for more public health attention
Antimalarial quality

- Intentional fraudulent production
- Result from negligent factory error
- Leave factory good quality but degrade due to heat, humidity

Relative sizes of circles unknown!
Antimalarial Quality Surveyor Database

• Collating: systematic review of > 404
  – English, French and Spanish
  – From 1946 up to present
  – Reports from malaria endemic country authors
  – Newspaper articles using MRA data
  – Alerts about counterfeit antimalarials

• Standardizing Data

• Mapping to identify trends
www.wwarn.org/aqsurveyor

Review of all published reports on antimalarial drug quality

We would be grateful for any additional information, corrections or comments from users and authors. Visit the AQ Surveyor web page for information on Methodology, External resources, Acknowledgements, and the User guide.
Review of all published reports on antimalarial drug quality

> 30% of antimalarials tested over 67 years did not meet the criteria of good quality
Review of all published reports on an antimalarial drug quality

8 Random surveys!
Where?
Poor antimalarial and efficacy

Malaria

- Good Quality
- Falsified No Active Ingredient
- Sub-standard Or Degraded
Drug concentration

Underdosing

Parasites

Selective window

MIC

WEEKS

0 1 2 3 4 5 6 7 8

$10^{12}$

$10^8$

$10^4$
Treatment failure is more likely in hyperparasitemic individuals.
Poor antimalarial and efficacy

Malaria

- Good Quality → Cure
  - • Death
  - • Severe form = hyperparasitemia = Higher chance of selection
    → Resistance

- Falsified No Active Ingredient

- Sub-standard Or Degraded
  - • Underdosing
    → Resistance
Can we test the hypothesis?

• Good quality vs Poor quality
  – Ethical concerns
  – Real life: Confounding factors
• Using proxy of poor quality medicines
  – Underdosed drugs
AS-AQ Dose impact study group sites

- 49 published studies (n=11,768) & 8 unpublished studies (n=1,505)
- 9,106 patients between 1999–2012
## Baseline characteristics

| Variable                                                                 | Asia  
|--------------------------------------------------------------------------|------|
|                                                                           | n=434 (4.8%) | Africa  
|                                                                           | n=8,635 (94.8%) | South America  
|                                                                           | n=37 (0.4%) |
| Geometric mean parasitaemia [95% CI] in parasites/µl                     | 8,504 [7,409-9,761] | 19,508 [18,944-20,089] | 80 [55-116] |
| Median Age [IQR, Range] in years                                        | 17 [8-28,0.6-80] | 3 [1.7-5,0-80] | 20 [16-25,8-58] |
| Drug Formulation                                                         |            |            |            |
| Fixed Dose Combination (FDC)                                             | 78.6% | 44% | 0% |
| Co-blistered non-fixed dose combination (co-blistered NFDC)              | 0% | 14.6% | 0% |
| Non-fixed dose combination: Target dose 25 mg/kg (Loose NFDC-25)        | 0% | 15% | 0% |
| Non-fixed dose combination : Target dose 30 mg/kg (Loose NFDC-30)       | 21.4% | 26.5% | 100% |
Total mg/kg administered

- Artesunate
- Amodiaquine
Underdosing and efficacy

- PCR-Corrected cumulative risk of recrudescence

<table>
<thead>
<tr>
<th>Combination</th>
<th>Day 28 [95% CI]</th>
<th>Day 42 [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDC</td>
<td>98.1% [97.8-98.6%]</td>
<td>96.1% [95.4-97.6%]</td>
</tr>
<tr>
<td>Co-blistered NFDC</td>
<td>97.9% [97.6-99.4%]</td>
<td>-</td>
</tr>
<tr>
<td>Loose NFDC 25</td>
<td><strong>93.4% [91.9 – 94.9]</strong></td>
<td>-</td>
</tr>
<tr>
<td>Loose NFDC 30</td>
<td>95.0% [94.1-95.9%]</td>
<td>92.1% [89.8.1-94.4%]</td>
</tr>
</tbody>
</table>

Underdosing will result in lower efficacy & facilitate emergence of resistance.
Random survey of antimalarial quality 2003-2012

- Study availability and quality of antimalarials
  - Private sector in Lao PDR
  - Covert sampling (180 outlets in 2003, 144 in 2012)
- Dramatic reduction in availability of oral artesunate monotherapy (14% vs 5% in 2012)
- No evidence for falsification in 2012 vs 88%, 2003
- Poorly manufactured drugs, ineffective medicines still common
  - 25.4% (37) outside pharmacopeial limits in 2012
  - 7% of samples were chloroquine
  - Parenteral chloroquine still made as an antimalarial?
Interpretations and lessons

- Improvement because of policy change in national policy and Global Fund support for ACTs
- Substandard medicines common – great risk for drug resistance
- Inappropriate sale of old antimalarials – needs more MRAs and NMCPs actions
- No reports of falsified ACTs in SE Asia – recent history suggests that this is surprising – who is looking?
- No reports of falsified iv/im artesunate – who is looking?
All health programs are threatened:

- 1.4 Million Coartem®
  Angola, Cameroon, DRC, Benin, Nigeria, at least
No one is immune

In October 2004 a doctor working for Médecins Sans Frontières (MSF) in Darfur reported that a local donation of Ringer’s lactate infusions was contaminated with a fungal growth. Subsequent investigations revealed that weaknesses in the bottling and quality control procedure during manufacture led to the contamination. The product then passed through three intermediates, including one UN agency, before being offered to relief agencies in Darfur, only one of which reported the problem. The World Health Organization (WHO) and the supplier jointly issued a recall of the contaminated batches. Six months after the recall, however, less than 15% (2200 of 15 000 bottles) of the contaminated product had been located.

Caudron et al. TMIH 2008
1. Cost of inaction - Resistance

Scenario where 30% ACTs failed and treatment for severe cases of malaria is reverted to quinine

- Each year increase of > than 116,000 deaths
- Excess of $32 M in healthcare costs
- >$385 M productivity losses due to extended patient illness

Lubell et al. Mal J 2014

Artemisinin & Insecticide resistance emergence
2. Cost of inaction - Drug quality

- Estimated median number of children <5 malaria deaths associated with consumption of poor-quality antimalarials in 39 countries
  - 122,350 deaths (IQR: 91,577–154,736)

Renschler et al. AJTMH 2015
Vast gaps and poor quality data

- Only 8 published random surveys!
- First guidelines on medicine quality surveys - 2009 – advocated random and LQAS surveys
  - WHO guidelines in preparation
- Quality assured drugs for clinical trials!
“The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge”
Daniel J. Boorstin (1985)
The Discoverers: A History of Man's Search to Know His World and Himself

Call for action!
Policy - Data – Funding – Change
Thank you!

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