ACCELERATE TO ZERO: STRATEGIES TO ELIMINATE MALARIA
THREE POTENTIAL FUTURE TRAJECTORIES FOR MALARIA...
WHY ERADICATION IS THE ONLY SUSTAINABLE FUTURE

Resurgence of malaria predictability occurs when current control efforts fail

Cohen, J., et. al., Malaria Resurgence. Malar J. 2012 Apr 24;11:122
MALARIA ERADICATION: AN AUDACIOUS GOAL

“Any goal short of eradicating malaria is accepting malaria; it’s making peace with malaria; it’s rich countries saying: ‘We don’t need to eradicate malaria around the world as long as we’ve eliminated malaria in our own countries.’ That's just unacceptable.”

Melinda Gates, 2007
ACCELERATE TO ZERO

We can accelerate the trajectory to malaria eradication by **concurrently** achieving three goals: 1) Identifying the human reservoir of infection in asymptomatic persons + 2) Eliminating the human reservoir + 3) combined with geographically and temporally targeted transmission prevention and strengthened surveillance and response.

**Complete Detection:** Detect the human parasite reservoir

**Complete Cure:** Eliminate the human parasite reservoir

**Complete Prevention:** Effective transmission prevention

**Eradication**

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**Mobilize for Action**
ACCELERATE TO ZERO

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2. **Complete Cure:**
   Eliminate the human parasite reservoir

3. **Complete Prevention:**
   Effective transmission prevention

**Eradication**

Mobilize for Action
MALARIA ERADICATION IS THE ELIMINATION OF PLASMODIUM PARASITES FROM THE HUMAN POPULATION

Malaria Eradication as defined in 1963 by WHO:

“Malaria eradication is to extirpate the roots of the infection – the parasites – from a given population so that the mosquitoes will find none to transmit.”

Emilio Pampana,
A Textbook of Malaria Eradication.
Oxford University Press. 1963
CLINICAL (INCOMPLETE) CURE VERSUS PARASITOLOGICAL (COMPLETE) CURE

**CLINICAL CURE**

Resolution of symptoms and prevention of severe disease and death.

- Clinical cure with an ACT only targets asexual stage parasites.
- Mature sexual stage 5 *P. falciparum* gametocytes in peripheral blood are not affected by ACTs.

**COMPLETE CURE**

Resolution of symptoms and prevention of severe disease and death plus complete parasitological cure.

- Clinical cure with an ACT for asexual stage parasites + single dose primaquine for sexual stage 5 *P. falciparum* gametocytes
MIND THE GAP: STAGE 5 P. FALCIPARUM GAMETOCYTES

4AQ = 4 aminoquinolines such as chloroquine only effective on stage 1 and 2 Pf gametocytes

Artemisinins = Artesunate, Dihydroartemisinin effective on stage 1 - 4 Pf gametocytes

8AQ = 8 aminoquinolines. Primaquine and tafenoquine are effective on stage 5 gametocytes
NEW DRUG DEVELOPMENT: COMPLETE CURE

- Understand the effect of drug candidates across the life cycle.
- Interrupt transmission is a key objective
- Combination Treatment
- Growth inhibition versus cell death
SERCAP – SINGLE EXPOSURE RADICAL CURE AND PROPHYLAXIS

Product Characteristics:

• Single fixed dose combination tablet
• Radical cure of Pf and Pv malaria species infecting humans
• Affordable
• Long duration/ post-treatment prophylaxis
• Transmission blocking
• All lifecycle stages
• High barrier to resistance
TARGETING THE RESERVOIR OF PARASITES IN ASYMPTOMATIC PEOPLE MAY BE NECESSARY

**Symptomatic** persons seeking care are the tip of the iceberg

- Higher parasitemias
  - Microscopy and RDT (+)

**Asymptomatic** persons who do not seek care are the majority of people in malaria endemic areas.

- Lower Parasitemias
  - Below the limit of detection of microscopy or current RDTs

**Not Infected**

- True Negative

**Infected**
The Future Message….
Complete Cure of the asymptomatic father and mother to save the life of the child?
ACCELERATE TO ZERO

We can accelerate the trajectory to malaria eradication by **concurrently** achieving three goals: 1) Identifying the human reservoir of infection in asymptomatic persons + 2) Eliminating the human reservoir + 3) combined with geographically and temporally targeted transmission prevention and strengthened surveillance and response.

<table>
<thead>
<tr>
<th>1</th>
<th>Complete Detection: Detect the human parasite reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Complete Cure: Eliminate the human parasite reservoir</td>
</tr>
<tr>
<td>3</td>
<td>Complete Prevention: Effective transmission prevention</td>
</tr>
</tbody>
</table>

**Eradication**

Mobilize for Action
**PREVENT TRANSMISSION**
Develop and deploy interventions to prevent transmission by breaking the transmission cycle

- Vector Control
- Vaccines
- Drugs
ACCELERATE TO ZERO

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1. **Complete Detection:** Detect the human parasite reservoir
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3. **Complete Prevention:** Effective transmission prevention

= Eradication

Mobilize for Action
CONCURRENT DEPLOYMENT OF DRUGS AND PREVENT TRANSMISSION INTERVENTIONS

In some parts of the world with intense and perennial transmission, drugs must be administered on a mass basis, together with the application of residual insecticides, in order to interrupt transmission. Here, chemotherapy must form an essential weapon throughout the attack phase.

*WHO Expert Committee on Malaria Twelfth Report, 1966*

Quinine plus insecticide most certainly lowered the sick rate much faster than quinine alone, an observation which has been repeated over and over and over again.

*Park Ross 1936*
Entomological inoculation rate ranged from 142·5 infected bites per person per year in 1990 to 482·6 in 2000, and 7·6 in 2012.

Parasite prevalence in children declined from 87% in 1990 to 0·3% in 2012. In adults, it declined from 58% to 0·3%.

The greatest changes were associated with the replacement of chloroquine with ACTs and the introduction of LLINs.

Current tools and strategies (control) are very effective.

Rapid decline of clinical immunity allows rapid detection and treatment of novel infections and thus has a key role in sustaining effectiveness of combining artemisinin-based combination therapy and ITNs despite increasing pyrethroid resistance in An. gambiae.
EMERGING RESISTANCE: OUR WITS VERSUS THEIR GENES

- Malaria interventions should be chosen, tested, and implemented to minimize a detrimental evolutionary response (resistance).
- Natural selection of resistance genes is favored by genetic diversity, extended time and large population size.
- A selective pressure will reliably select out variants that survive in the new environment.
ANTI-MALARIAL DRUGS FOR THE NEXT DECADE

• **Issues**
  • Countering emerging resistance

• **Solutions**
  • New drug discovery & development
    • Single Encounter Radical Cure and Prophylaxis (SERCaP)
    • Complete Cure
  • Strategies to protect therapies from the threat of resistance
    • Current: Using current drugs better
      - New regimens: Extended dosing & triple therapy
      - Use good drugs: Ban oAMT & substandard drugs
  ▪ Future: New strategies
    • Going on Offense
RED QUEEN DYNAMICS: THE EVOLUTIONARY ARMS RACE

“Well, in your country," said Alice panting a little, "you'd generally get to somewhere else - if you ran very fast for a long time, as we have been doing."

"A slow sort of country!" said the Red Queen. "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

Lewis Carroll,
Through the Looking Glass
DRUG RESISTANCE IS A TRACTABLE TARGET FOR DRUG DISCOVERY

- Resistance pathways can be identified through human or
USE CURRENT DRUGS BETTER AND WISER: TRIPLE THERAPY

- The curse of recrudescence (or persistence?)
- The goal is complete cure
- Use “balancing” combinations
  - Artemether-lumefantrine and amodiaquine
  - Dihydroartemisinin-piperaquine and mefloquine
  - Artesunate-atovaquone-proguanil

NEW STRATEGIES: GOING ON OFFENSE

<table>
<thead>
<tr>
<th>Transmission Intensity</th>
<th>T3 Test, Treat, Track</th>
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<tbody>
<tr>
<td>EIR &gt; 10</td>
<td>universal LLINs + ACTs ± MDA</td>
</tr>
<tr>
<td>PR &gt; 10%</td>
<td></td>
</tr>
<tr>
<td>incidence &gt; 7400/1000</td>
<td></td>
</tr>
<tr>
<td>seroconversion &gt; 0.19</td>
<td></td>
</tr>
<tr>
<td>1 &lt; EIR &lt; 10</td>
<td>universal LLINs + ACTs ± IRS ± MSAT (using PCR)</td>
</tr>
<tr>
<td>1% &lt; PR &lt; 10% (PCR ≈ 40%)</td>
<td></td>
</tr>
<tr>
<td>incidence &gt; 7400/1000</td>
<td></td>
</tr>
<tr>
<td>seroconversion &gt; 0.19</td>
<td></td>
</tr>
<tr>
<td>0.1 &lt; EIR &lt; 10</td>
<td>universal LLINs + ACTs ± IRS ± FSAT/HIFSAT (using PCR or RDT)</td>
</tr>
<tr>
<td>1% &lt; PR &lt; 5% (PCR ≈ 10%)</td>
<td></td>
</tr>
<tr>
<td>incidence &gt; 10/1000</td>
<td></td>
</tr>
<tr>
<td>seroconversion &gt; 0.03</td>
<td></td>
</tr>
<tr>
<td>PR ≈ 0.1% (1% &lt; PCR &lt; 5%)</td>
<td></td>
</tr>
<tr>
<td>incidence &gt; 10/1000</td>
<td></td>
</tr>
<tr>
<td>seroconversion &gt; 0.01</td>
<td></td>
</tr>
<tr>
<td>incidence = 0/1000</td>
<td>targeted VCM + ACTs ± IRS ± HIFSAT (using RDT)</td>
</tr>
<tr>
<td>seroconversion &gt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

ACT, artemisinin-based combination therapy; EIR, entomological inoculation rate; FSAT, focused screening and treatment; HIFSAT, highly focused screening and treatment; IRS, indoor residual spraying; LLIN, long-lasting insecticidal net; MDA, mass drug administration; MSAT, mass screening and treatment; PCR, polymerase chain reaction; PR, parasite rate; RDT, rapid diagnostic test; VCM, vector control management.\(^3\)
EMERGING RESISTANCE: 2015

Lots of parasites

- Treat sick people
- Multiple times
- Treat during transmission season
- Greatest genetic diversity
- Greatest population, 1% parasitemia = $10^{11}$ parasites

Not enough drug

- Bad Drugs
- Poor compliance
- Multiple doses
- No DOT
- Under dose kids and pregnant women
- Poor GI absorption
COUNTERING EMERGING RESISTANCE

- Treat well people
- Treat during dry season
- Genetic diversity bottleneck
- Population size bottleneck, $10^4 - 10^6$ parasites

Enough drug

- Good Drugs
- SERCaP
- Directly observed Rx
- Properly dose kids and pregnant women
- Improved GI absorption
LET’S FINISH THE JOB

• Eradication is Saving lives now, Saving lives forever
• Eradication is biologically possible and the only sustainable goal
• Eradication will require new concepts, new tools, and new strategies.
• The next decade will be a period of intense experimentation and learning, leading to a rapidly evolving policy environment for new tools and technologies.
• An end of one-size-fits-all approach.
GLOBAL IMPACT WILL REQUIRE TAILORED LOCAL PROBLEM SOLVING

“Before DDT, malariologists were trained as problem solvers, after DDT malariologists were trained as solution implementers”.

José Antonio Nájera
Our vision
A world free of malaria