ACCELERATE TO ZERO
MALARIA ERADICATION STRATEGIES AT THE BILL AND MELINDA GATES FOUNDATION

Institute of Medicine Forum on Microbial Threats
Vector Borne Diseases: Exploring the Environmental, Ecological, and Health Connections
16-17 September 2014, Washington DC, USA

Alan Magill MD
Director, Malaria
Boundaries of Malaria Transmission By Country

1990

Transmission
No transmission

Source: Malaria Elimination Initiative (2011) UCSF Global Health Group
WHAT A DIFFERENCE 15 YEARS MAKES

1998
• 500 million acute malaria cases
• 2 million deaths
• No Long Lasting Insecticide treated Nets (LLINs).
• No Indoor Residual Spray (IRS)
• Widespread chloroquine and sulfadoxine-pyrimethamine (SP) resistance and no ACTs.
• Limited diagnostic testing available.
• No IPTp or SMC
• Limited new product pipeline.
• No Global Fund and PMI.
• Limited political will and financial resources.

2013
• 207 million acute cases
• 627,000 deaths
• 136 million new LLINs distributed
• 135 million people protected by IRS.
• 331 million ACT courses were procured by the public and private sectors in endemic countries.
• mRDTs and Test, Treat, and Track (T3) policy.
• Targeted interventions for highest risk populations: IPTp, SMC
• Promising pipeline of diagnostics, drugs, vaccines, delivery strategies and innovative vector control tools.
• The Global Fund and the President’s Malaria Initiative disburse > $1 Billion/Year

Mortality rates decreased by 45% globally: 3.3M lives saved, 90% in under 5 in Africa
Today’s Malaria Eradication Goals and Planning was enabled by the Success of the Past Decade
### THE CURRENT MALARIA CONTROL TOOLBOX

<table>
<thead>
<tr>
<th>CURRENT TOOLS</th>
<th>CURRENT STRATEGIES</th>
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<tbody>
<tr>
<td>Pyrethroid only LLINs</td>
<td>Universal distribution</td>
</tr>
<tr>
<td>Insecticides</td>
<td>4 classes available used in limited indoor residual spray (IRS)</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; generation mRDTs</td>
<td>Increased use enabling test, treat, and track (T3)</td>
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<tr>
<td>Artemisinin combination treatments (ACTs)</td>
<td>Treat symptomatic people seeking care</td>
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<tr>
<td>Sulfadoxine + pyrimethamine (SP)</td>
<td>Targeted to pregnant women for IPTp</td>
</tr>
<tr>
<td>Amodiaquine+ SP</td>
<td>Seasonal Malaria Chemoprophylaxis</td>
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THE CURRENT CONTROL PARADIGM

• Focus on disease burden reduction
• A limited set of Interventions must be continuously applied at high coverage and maintained indefinitely.
• Emerging and spreading resistance to drugs and insecticides threatens to set back our progress
• Projected costs to maintain these control measures are immense:
  • “An estimated US$ 5.1 billion is needed every year between 2011 and 2020 to achieve universal access to malaria interventions.”
  • World Malaria Report 2012
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
EMERGING RESISTANCE

Artemisinin Resistance in the Greater Mekong Subregion

Pyrethroid resistance in Sub Saharan Africa
IMPACT OF PYRETHROID RESISTANCE

“Our wits versus their genes”

Figure 11: Impact of pyrethroid-impregnated insecticide-treated nets in areas of Benin with An. gambiae resistant and susceptible to pyrethroids

From the Global Plan for Insecticide Resistance Management
RETROSPECTIVE ANALYSIS OF CHANGE IN INSECTICIDE USE MAY PROVIDE BEST EVIDENCE FOR IMPACT OF RESISTANCE

Kigozi et al, PLOS One, 2012
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
Resurgence in countries that successfully eliminated finds only four failures out of 50 successful programs.

Elimination may be surprisingly “sticky”

- Reinforced by loss of immunity
- Economic development and GDP only weakly predictive
- Endemic transmission in remaining hotspots is a stable reservoir that threatens to reintroduce malaria to surrounding areas
The Importance of Getting to Zero

- Resurgence in countries that successfully eliminated finds only four failures out of 50 successful programs.
- Elimination may be surprisingly “sticky”
  - Reinforced by loss of immunity
  - Economic development and GDP only weakly predictive
  - Endemic transmission in remaining hotspots is a stable reservoir that threatens to reintroduce malaria to surrounding areas

“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
THREE POTENTIAL FUTURE TRAJECTORIES FOR MALARIA...

In our strategy, we have chosen to ‘Accelerate to Zero’, which leads to three overarching goals for the period (2014-2020)

**Global annual malaria parasite incidence**

- **Eliminate Now**
- **Prepare for the Future**
- **Sustain progress**
  - Prevent resurgence and
  - Move countries closer to elimination

**GOALS**

- 1. Eliminate Now
- 2. Prepare for the Future
- 3. Sustain progress

**“Bend the Curve”**

- Accelerate to zero
- Sustain progress
- Resurgence

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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.

1. Complete Detection: Detect the human parasite reservoir
2. Complete Cure: Eliminate the human parasite reservoir
3. Complete Prevention: Effective transmission prevention

Eradication

Mobilize for Action
ACCELERATE TO ZERO

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   - Eliminate the human parasite reservoir

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**Eradication**

Mobilize for Action
### WHY PARASITES IN PEOPLE ARE IMPORTANT

<table>
<thead>
<tr>
<th></th>
<th>Mosquitoes</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifespan</strong></td>
<td>&lt; 30 days</td>
<td>&gt; 70 years</td>
</tr>
<tr>
<td><strong>Duration of parasitemia</strong></td>
<td>&lt; 5 days</td>
<td>Up to 15 years</td>
</tr>
<tr>
<td><strong>Travel distance</strong></td>
<td>1 km flight range</td>
<td>Circle the globe</td>
</tr>
<tr>
<td><strong>Parasite biomass</strong></td>
<td>&lt; 1%</td>
<td>&gt; 99%</td>
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</table>
T3: TEST, TREAT, AND TRACK

- Universal coverage.
- Every suspected malaria case is tested with a quality diagnostic.
- Every confirmed case is treated with a quality assured ACT.
- Every treated case is tracked through timely and accurate surveillance systems.
- Information to guide policy and operational decisions
OVER DIAGNOSIS OF MALARIA IN TANZANIA

- 53% of blood slides called positive in routine laboratories, only 2% were positive by expert microscopy.
- Sensitivity of routine microscopy was 71.4% and specificity was 47.3%.
- Positive and negative predictive values were 2.8% and 98.7%, respectively.
- Median parasitemia was only three parasites per 200 white blood cells (WBC) by routine microscopy compared to 1226 parasites per 200 WBC by expert microscopy.
- The sensitivity and specificity of RDTs using expert microscopy as reference were 97.0% and 96.8%.
Malar J. 2011 Nov 2;10:332.
TARGETING THE RESERVOIR OF PARASITES IN ASYMPTOMATIC PEOPLE MAY BE NECESSARY

Symptomatic persons seeking care are the tip of the iceberg

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

Higher parasitemias
Microscopy and RDT (+)

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

Infected

True Negative
• 50 to near 100% of malaria infections are symptomatic
• Error bars correspond to the 95% CI
• Hollow shapes indicate diagnosis by microscopy
• Filled shapes indicate diagnosis by PCR
• Diamonds, triangles, and squares indicate surveys conducted in Asia, Latin America, and Africa, respectively.

The Future Message....

Complete Cure of the asymptomatic father and mother to save the life of the child?
A MORE SENSITIVE DIAGNOSTIC TEST IS REQUIRED TO IDENTIFY THE ASYMPTOMATIC RESERVOIR

**Test** | **Goal of test** | **Principles of design**
--- | --- | ---
Current mRDT | Symptomatic people as part of case management | Higher sensitivity

Current Dx Test Focus | To identify true positives, i.e., the asymptomatic reservoir | Use existing RDT model as basis for design because of ease of use and scalability

Future Dx test | To confirm that malaria negative patients are true negatives | Test for HRP2 antigen because high density, species specific (for Pf), long half-life acts as proxy for transmission risk
DEVELOPMENT OF NEW RDTs REQUIRES A NUMBER OF BUILDING BLOCKS

1 Higher sensitivity RDT design
   - Need capture antibodies
   - Need HRP2 antigen to develop MAb (or PAb)

1a 2nd-generation device capabilities
   - Data
   - Reader box
   - Maps of infection

2 Specimen bank to test new RDTs
   - Need samples of malaria symptomatic, asymptomatic and negative people

3 New comparator standards
   - Need new, approved standards (qPCR and quantitative HRP2) for testing new devices

4 Independent lab verification

5 Clinical/field trials

6 Regulatory
   - FDA 510K
   - WHO PQ
   - In-country NRA

7 Policy
   - WHO MPAC
   - WHO recommendation
   - Country recommendation

8 Procurement and financing

9 Country introduction and adoption

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UNDERSTANDING CONNECTIVITY BETWEEN RESERVOIRS OF TRANSMISSION IS CRITICAL TO ACHIEVE REGIONAL ELIMINATION

How many infections are being imported?
When? From where? By who?

Where are the likely sources of imported infections?
Where are they going?
Who’s bringing them?

How can we make efficient use of connectivity data to target surveillance and control, plan an attack strategy?

Legend:
- Source
- Bridge
- Sink

Regional Stratification that takes into account connectivity between (asymptomatic) reservoirs of infection
Current Area of Interest (AOI) map, Isabel Province, Solomon Islands, 31/12/2012. Key elements of the automated map include: (i) the designation of the geographic AOI area to conduct response; (ii) the type of transmission focus the AOI is located within to guide the selection of nominated response interventions; (iii) the illustration and generation of household and population data within the AOI to support rapid resource allocation, costing, and field implementation of nominated interventions.
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**Complete Detection:**
Detect the human parasite reservoir

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

**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
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
**P. Falciparum** Single Encounter Radical Cure and Prophylaxis (SERCaP)

- **Coartem®**
  - 24 pills total
  - 6 encounters in 3 days

- **Primaquine**
  - 1 pill given once
  - 1 day

**Proof of Concept for SERCaP with OZ 439 + a new compound**

- Single fixed dose combination (FDC)
  - 2 or more drugs
  - 1 pill given once
  - 1 encounter
  - Achieves radical cure for both Pf and Pv

 Achieve radical cure with a single encounter and a single intervention and one month of “prophylaxis” following the single encounter.
**P. VIVAX** SINGLE ENCOUNTER RADICAL CURE AND PROPHYLAXIS (SERCAP)

Coartem®
- 24 pills total
- 6 encounters in 3 days

DHA - piperaquine
- 6 pills total
- 3 encounters in 3 days

Single fixed dose combination (FDC)
- 2 or more drugs
- 1 pill given once
- 1 encounter
- Achieves radical cure for both Pf and Pv

Primaquine
- 28–56 pills total
- 14 encounters over 14 days

Tafenoquine
- 1 pill given once
- 1 encounter

Registration 2018/ In Use 2020

Achieve radical cure with a single encounter and a single intervention and one month of “prophylaxis” following the single encounter

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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*
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Complete Cure: Eliminate the human parasite reservoir
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Mobilize for Action

Eradication
Why didn't Noah swat those two mosquitoes?
- Unknown
Transmission is an event
When? Where?
THE ENTOMOLOGICAL LABYRINTH: VECTOR SPECIES AND BEHAVIOR HETEROGENEITY: MYANMAR

Anthropophily

Endophily

Zoophily

Exophily

An. dirus

An. minimus

An. maculatus

Indoor LC
Outdoor LC
CDC light trap

Cow 6%
Indoor 41%
Outdoor 33%

Cow 17%
Indoor 38%
Outdoor 45%

Cow 29%
Indoor 25%
Outdoor 46%

DIRUS
MINIMUS
MACULATUS

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RESIDUAL TRANSMISSION – MIND THE GAP

(A) 6 PM - 6 AM
10 PM - 6 AM
GAP

(B) 6 PM - 6 AM
ITNs/IRS
GAP

IRS  LLINs

“Risk behaviour”

Times and places where LLINs and IRS will not prevent transmission.

- Early evening and early morning
- Outside the house + human behaviors

Species shifts

- *An. arabiensis* becomes a significant vector when *An. Gambiae* and *An. funestus* decline

Shifts within species complexes

- Mosquito biting at an earlier hour
- Biting place
- Resting place
PREVENT TRANSMISSION
Develop and deploy interventions to prevent transmission by breaking the transmission cycle

Prevent Transmission

- Vector Control
- Vaccines
- Drugs
NEW PARADIGMS

- Duo-nets: 2 plus active ingredients
- Spatial Repellents
- Attractive toxic sugar baits
- Genetically modified mosquitoes (HEGs)
- Biological control
- Novel personal protection
- Anopheline extinction with entomopathogenic fungi

RCTs establish links between entomological and epidemiological indicators to establish a new paradigm

Rapid evaluation of new products within the same product category
IVCC PUBLIC HEALTH INSECTICIDE PIPELINE
Vaccines could be critical for prevention of malaria transmission in our Accelerate to Zero strategy

**Prevent Transmission**
- Highly efficacious, **Short** duration of protection (6m-1yr)

**GAME CHANGER**
- Highly efficacious, **Long** duration of protection (>/>= 5 yr)

- Facilitate our drug-based approach by providing “Prevention” component of Single Encounter Radical Cure and Prevention (SERCaP)
- Prevent reintroduction and reduce susceptibility in areas recently cleared of malaria
- Risk mitigation tool for use where other tools are insufficient/ineffective

**Paradigm shift—rethink elimination strategy**

Vaccines are ~21% of proposed 2014-2018 strategy budget
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.
Everything about malaria is so molded and altered by local conditions that it becomes a thousand different diseases and epidemiological puzzles. Like chess, it is played with a few pieces, but is capable of an infinite variety of situations.

*Lewis Hackett 1937*
MALARIA IS COMPLEX AND HETEROGENEOUS

- Ecology
- Epidemiology
- Biology
- Geographic micro heterogeneity
- Vector heterogeneity
- Human immune response heterogeneity
- Economic and structural factors
- Political factors
- Socio-cultural factors
FROM UNIVERSAL COVERAGE TO EFFECTIVE COVERAGE

GFATM Proposal called for Universal Coverage with LLINs in all at risk areas…

However, risk was poorly defined and vector control was not efficiently targeted to places where it would have impact.

In addition, *An. albimanus*, the main vector in Haiti, is an outdoor biter and rester making LLINs a suboptimal tool for prevention.

Recent CDC case control study that found no difference in bed net use between cases and controls (L. Slutsker pers. Comm.)
“Before DDT, malariologists were trained as problem solvers, after DDT malariologists were trained as solution implementers”.

José Antonio Nájera
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.
Our vision
A world free of malaria
The introduction of cinchona into Europe... ranks not only as one of the greatest events in the history of medicine but as one of the great factors in the civilization of the world.

Sir William Osler
Regius Professor, Oxford 1892
The success or failure of quinine depends on the relative densities of the mosquito and the human population. Where there are (a) few people and few mosquitoes, or (b) few people and many mosquitoes, or (c) many people and few mosquitoes, quinine will give a strikingly successful result.

*Sir Malcom Watson 1922*