MALARIA: PAST, PRESENT, AND FUTURE

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Overview

- Malaria 101: Early history, biology, and epidemiology
- The first push for malaria eradication (1950–1970)
- Worsening of malaria control (1990s)
- New focus and scale-up success (2000–2010)
  - Is eradication possible now?
History: Major Scientific Milestones

Charles Alphonse Laveran
Demonstrated parasites in patient’s blood, 1880

Ronald Ross
Discovered *Anopheles* mosquito as vector, 1897

Giovanni Batista Grassi
Demonstrated life cycle from mosquito to man, 1898–1899
Intra-erythrocytic protozoan

Human malaria: 4 major species

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*

**P. falciparum**
- Potentially fatal severe disease
  - Red blood cell destruction → severe anemia
  - Sequestration in cerebral vessels → coma
- Multi-drug resistant
Malaria Biology: Vectors of Human Malaria

- >400 species of Anopheles mosquitoes found worldwide; ~50 transmit malaria
- Each species occupies distinct ecological niche
- Major African vectors tend to bite indoors and at night
- Biting and resting behavior affect transmission potential and control
Malaria Global Burden, 2008

- ~250 million clinical cases per year; 80% in Africa
  - Children aged <5 years and pregnant women most affected
- >800,000 deaths per year; >90% in Africa
- Disability from severe forms of the disease
- Annual economic burden
  - GDP → 1.3% loss

GDP, Gross domestic product
Prevalence of *P. falciparum* Malaria in Children Aged 2–10 Years

Events Leading up to the Global Malaria Eradication Program

- Early successes in mosquito control (Panama Canal)
- Effective interventions, chloroquine and DDT, became available after WWII
- Availability of good diagnosis with microscopy
- 8th World Health Assembly launches Global Eradication Campaign (1955)

DDT, Dichlorodiphenyltrichloroethane
Eradication Strategies 1950–1970

- “Magic bullet”: DDT indoor residual spray (IRS)

- Assumptions
  - People stay indoors at night
  - *Anopheles* mosquito bites at night, rests indoors on house walls, and receives a toxic dose of DDT

- Other major activities
  - Antimalarial drug treatment: Patients, occasionally as mass treatment
  - Surveillance to detect and eliminate any reservoirs
Malaria was eliminated in 37 countries during 1950–1978.
## What Were the Problems?

<table>
<thead>
<tr>
<th>Category</th>
<th>Problem</th>
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<tbody>
<tr>
<td>Technical</td>
<td>Insecticide and drug resistance</td>
</tr>
<tr>
<td>Logistics</td>
<td>Supply chain failures</td>
</tr>
<tr>
<td></td>
<td>Poor delivery of IRS</td>
</tr>
<tr>
<td>Strategic</td>
<td>Rigidity</td>
</tr>
<tr>
<td></td>
<td>Lack of research</td>
</tr>
<tr>
<td></td>
<td>Africa not included</td>
</tr>
<tr>
<td>Financial</td>
<td>Funds diverted elsewhere</td>
</tr>
<tr>
<td>Sociocultural</td>
<td>Lack of community buy-in and participation</td>
</tr>
<tr>
<td></td>
<td>Decreasing acceptance of IRS</td>
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</table>
Consequent Change in Strategy (1970s)

- 22nd World Health Assembly (1969)
  - “Suspended” eradication campaign
  - Goal became control to “Minimize the health damage by malaria”
    - Less ambitious
    - Strategy adapted to local context

- Shift from prevention with insecticides/DDT to antimalarial treatment

- Integrate activities into primary health care
Worsening of Malaria Control (1990s)

- Decreased funding
- Intensification and spread of chloroquine resistance
Renewed Optimism in the New Millennium

- New partnerships
- New funding
- New political leadership in endemic countries
- New tools (drugs, bed nets)
A COMMITMENT TO MALARIA CONTROL AND PREVENTION: THE FIRST STEPS TOWARDS ELIMINATION

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Chief, Program Implementation Unit
Division of Parasitic Diseases and Malaria
Center for Global Health
Centers for Disease Control and Prevention
Overview

- Roll Back Malaria and U.N. Millennium Development Goals
- President’s Malaria Initiative (PMI)
  - PMI under two presidents
  - Goals, targets, and funding
  - Focused interventions
  - CDC’s role in PMI: Strategic information

- Results achieved
  - Significant reductions in malaria transmission
Roll Back Malaria (RBM)

- Global partnership
  - Launched in 1998
  - WHO, UNICEF, UNDP, World Bank

- Global framework
  - Coordination of activities
  - Mobilization of resources
  - Establishment of technical working groups
  - Establishment of subregional networks

- Global Malaria Action Plan
  - Launched September 25, 2008, by RBM partnership
  - Scaling up for impact
  - Sustaining control over time

www.rollbackmalaria.org
UNICEF, United Nations Children’s Fund
UNDP, United Nations Development Program
Goal 4: Reduce child mortality
Goal 5: Improve maternal health
Goal 6: Combat HIV/AIDS, malaria, and other diseases
  Target 6c: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
    - Incidence and death rates associated with malaria
    - Children under 5 sleeping under insecticide-treated bednets
    - Children under 5 with fever who are treated with appropriate antimalarial drugs
International Financial Disbursements to Malaria Endemic

PMI, President’s Malaria Initiative
GF, Global Fund
President’s Malaria Initiative (PMI)

- On June 30, 2005, President Bush announced a new initiative to rapidly scale up malaria control interventions in high-burden countries in Africa
  - 5-year and $1.2B investment
- Challenged other donors to increase their funding
- PMI is led by USAID and co-implemented with CDC

Source: S. Craighead/White House (12/14/06)
PMI Goal and Targets

Goal: Reduce malaria-related mortality by 50% in 15 selected countries

Targets: Achieve 85% coverage of vulnerable groups with 4 key interventions (~270 million residents)
PMI Interventions

- Artemisinin-based combination therapies (ACTs)
- Insecticide-treated bed nets (ITNs)
- Indoor residual spraying (IRS) (where appropriate)
- Intermittent preventive treatment in pregnancy (IPTp)
# PMI Funding Levels and Coverage

<table>
<thead>
<tr>
<th>Year</th>
<th>Funding Level</th>
<th>No. Countries Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>$30 M</td>
<td>3</td>
</tr>
<tr>
<td>2007</td>
<td>$135 M</td>
<td>7</td>
</tr>
<tr>
<td>2008</td>
<td>$300 M</td>
<td>15</td>
</tr>
<tr>
<td>2009</td>
<td>$300 M</td>
<td>15</td>
</tr>
<tr>
<td>2010</td>
<td>$500 M</td>
<td>15</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$1,265 M</td>
<td>15</td>
</tr>
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</table>
President Obama signals support for global health including malaria (September 2008)

The White House launches Global Health Initiative
- U.S. Government will invest $63 billion over 6 years

PMI is now a major component of GHI

"We will not be successful in our efforts to end deaths from AIDS, malaria, and tuberculosis unless we do more to improve health systems around the world, focus our efforts on child and maternal health, and ensure that best practices drive the funding for these programs."

—President Barack Obama, May 5, 2009
CDC’s Mandate in PMI: Strategic Information

- U.S. Congress (through the Lantos-Hyde Act, 2008) charged CDC to take a leading role in strategic information
  - Monitoring and evaluation
  - Surveillance
  - Operations research

- CDC is advising the U.S. Malaria Coordinator on priorities for these activities and being a key implementer

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h5501enr.pdf
PMI Focus: 15 African Countries

Angola
Benin
Ethiopia
Ghana
Kenya
Liberia
Madagascar
Malawi
Mali
Mozambique
Rwanda
Senegal
Tanzania
Uganda
Zambia
Nigeria and the Democratic Republic of Congo account for the 23% of the world’s burden of the falciparum malaria.
Proportion of Households with at Least 1 Insecticide-Treated Bed Net (ITN) from 2 Survey Points

Data source: Demographic Health Survey, http://www.measuredhs.com
Proportion of Children Aged <5 Years Who Slept Under an ITN the Previous Night

Data source: Demographic Health Survey, http://www.measuredhs.com
Zanzibar: Intervention Coverage and Malaria control

Intervention coverage percent (IRS, ITN, ACT)

Malaria positivity rate %

2003 2004 2005 2006 2007

ITN, Insecticide-treated bed net
IRS, Indoor residual spraying
ACT, Artemisinin-based combination therapy
Declines in All-Cause Mortality in Children Aged <5 Years, 7 PMI Countries, 2003–2010

Data source: Demographic Health Survey, http://www.measuredhs.com
Reserve – A Lurking Threat

- Emergence of insecticide resistance in Africa
  - DDT, pyrethroids
- Emergence of artemisinin resistance in Southeast Asia
  - Thai-Cambodia border
Significant reductions in all-cause mortality

- Tanzania 19%
- Madagascar 22%
- Ghana 28%
- Zambia 29%
- Senegal 30%
- Rwanda 32%
- Kenya 36%

Massive scale-up of control interventions has been followed by substantial decreases in all-cause mortality in children aged <5 years.

Initiative-wide impact assessment is under way.
CDC’s SCIENTIFIC EVIDENCE BASE FOR SCALE-UP AND POSITIONING FOR MALARIA ELIMINATION

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Overview

1. Scientific evidence: Basis for current interventions
2. Global Malaria Eradication Research Agenda
3. CDC operational research priorities, 2010
1. Scientific Evidence: Basis for Current Malaria Interventions

- Artemisinin-based combination therapies (ACTs)
- Insecticide-treated bed nets (ITNs)
- Indoor residual spraying (IRS) (where appropriate)
- Intermittent preventive treatment in pregnancy (IPTp)
Efficacy of ITNs on All-Cause Child Mortality from 4 Randomized Controlled Trials in Africa

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treated nets</th>
<th>Control</th>
<th>log [Relative rate]</th>
<th>Relative rate</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>(SE)</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Controls with no nets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya (Nevill)</td>
<td>11596</td>
<td>11439</td>
<td>-0.3425 (0.157)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana (Binka)</td>
<td>18457</td>
<td>18054</td>
<td>-0.1985 (0.093)</td>
<td>0.71 [ 0.52, 0.97 ]</td>
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<tr>
<td>Burkina Faso (Habluetzel)</td>
<td>14773</td>
<td>14118</td>
<td>-0.1508 (0.1139)</td>
<td>0.82 [ 0.68, 0.98 ]</td>
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</tr>
<tr>
<td>Kenya (Phillips-Howard)</td>
<td>17833</td>
<td>18099</td>
<td>-0.1744 (0.058)</td>
<td>0.86 [ 0.69, 1.08 ]</td>
<td>0.84 [ 0.75, 0.94 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>0.83 [ 0.76, 0.90 ]</td>
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17% protective efficacy against child mortality before age of 5 years
Could save 5.5 lives for every 1,000 children protected
People without nets experienced the same benefit if they lived within 300 meters of net users – reduction in
- Parasite infection (odds ratio=0.59)
- Malaria illness (odds ratio=0.52)
- Anemia (odds ratio=0.53)
- Child mortality (hazard ratio=0.72)
Survival benefit lasted beyond 6 years

Mortality rates
- Infants: 113/1,000
- Children 1–5 years old: 28/1,000
Providing nets to 65% of older children and adults would protect even children without nets
Policy Impact of the KEMRI/ CDC ITN Trial and Follow-up Studies

Established the evidence-base for widespread scale-up and universal coverage

FROM EVIDENCE TO POLICY
Continued progress in scale-up and elimination will require improved tools for malaria control and surveillance

- Scale-up: Aims to reduce morbidity and mortality
- Elimination: Aims to reduce transmission
  - Basic reproduction number <1.0

2. Global Malaria Eradication Research Agenda

- New tools and systems to accommodate
  - Drugs
  - Vaccines
  - Diagnostics
  - Insecticides
- Strategies to manage resistance to antimalarial drugs and insecticides for public health
  - Combination treatments
  - Combined delivery systems
  - Rotational or mosaic deployment

http://malera.tropika.net
Global Malaria Eradication Research Agenda

- **Alternative vector interventions**
  - ITNs and spraying work against mosquitoes indoors
  - Some mosquitoes feed and rest outdoors
    - Larviciding
    - Spatial repellants, baited traps

- **Drug interventions for reducing transmission**
  - Mass screen and treatment
  - Transmission-blocking agents

- **Surveillance: Detecting and responding to local transmission**
3. CDC Operational Research Priorities in 2010

- Optimize current malaria control interventions
- Establish role for new and revisited interventions
  - Research and development
  - Clinical and field trials of new interventions
- Integration with other initiatives
WHO now calls for universal access to malaria diagnosis and treatment for every case of suspected malaria

Diagnostic confirmation
- Minimize the overuse of treatments
- Improves detection and treatment of other causes of illness
- Forms the basis of a reliable system for monitoring malaria and malaria control
Research and Development:
Field-Ready, High-Sensitivity Test for Malaria

- As endemic countries approach elimination, highly sensitive tests become more critical
- Current diagnostic formats will improve management of malaria illness
- Elimination may rest on molecular assays
  - Available only in reference laboratories far from remote areas

Molecular assays
Research and Development: Field-Ready, High-Sensitivity Test for Malaria

- CDC and University of Georgia
- Novel system for molecular diagnosis
- Real-time fluorescence loop-mediated amplification: Real LAMP
  - Detection of malaria parasites at very low numbers
  - Without access to reference laboratory staffing and equipment
  - Validation of the first generation prototype on specimens from Tanzania completed

Clinical and Field Trials of New Interventions

- Phase III malaria vaccine trial in Kenya
  - First candidate vaccine to reach this stage of development
  - One of 11 sites in 9 countries
  - Could reduce clinical malaria by up to 35%, severe malaria by 49%

When will we have a vaccine that can eliminate malaria?

- Current vaccine within 18–24 months
- Will reduce illness burden, not transmission
- Hundreds of other candidates in development
- Millennia of co-evolution confound development
Clinical and Field Trials of New Interventions

- **Combined impact of ITNs with indoor residual spraying**
  - Northern Ghana (starting 2011)

- **Combined impact of ITNs with insecticide-treated durable wall liners**
  - Lakeside Malawi (starting 2011)

ITN, Insecticide-treated bed net
Integration Opportunities

From Scale-up To Elimination

- Community-based control/ elimination
- Integrated case management interventions
- Integrated vector control
- Integrated surveillance, monitoring and evaluation
From Scale-Up to Elimination: the Role of Partnership

- Creative partnerships within the U.S. government
  - Within Department of Health and Human Services
  - With U.S. government partners
- Partnerships beyond our system