Whither Malaria?  
From control to eradication

Regina Rabinovich  
Harvard School of Public Health  
ASM, NE Mass Sept 2014
What is Malaria?

“The greatest misconceptions about the treatment of malaria, especially in the past, have arisen from the fact that too many considered it a single disease. Malaria is not a disease – it is a variety of diseases.”

Lowell T. Coggeshall
1901 - 1987

Coggeshall LT. The Treatment of Malaria.
What is Malaria?

“What everything about malaria is so moulded 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 W. Hackett
1902 - 1962

Plasmodium Life Cycle

From Steve Hoffman
Variation is a key element of malaria

- **Epidemiology**
  - Multiple ecologies worldwide

- **Parasite heterogeneity**
  - At least 5 species infect humans.
    - Pf, Pv, Pm, Po, Pk
  - Each species composed of multiple strains
    - 0% case fatality rate for Netherlands *P. vivax*
    - 8% case fatality rate for Madagascar *P. vivax*

- **Vector heterogeneity**
  - Several mosquito species can infect humans - *An. gambie, An. fenestus, etc.* – with different feeding behaviors.

- **Human**
  - Clinical disease – from asymptomatic to coma
  - Immune response heterogeneity
  - Multiplicity of infections

*Malaria is a complex and heterogeneous biological phenomenon*
Extent of malaria transmission: 1945

Source: Malaria Elimination: Geography, finance, and economics, presentation by Prof. Sir Richard Feachem, at ASTMH 7 Dec 2008.
FIRST DAY OF ISSUE

WASHINGTON
MAR 30
9-AM
1962
D.C.

FIRST DAY OF ISSUE

TOGETHER LET US ERADICATE DISEASE!
JOHN F. KENNEDY
INAUGURAL ADDRESS

UNITED STATES
MALARIA ERADICATION
POSTAGE STAMP

ISSUED IN COOPERATION WITH
UNITED NATIONS WORLD HEALTH
ORGANIZATION'S MALARIA ERADICATION CAMPAIGN

4¢ UNITED STATES POSTAGE

WORLD UNITED AGAINST MALARIA
Malaria Deaths

(2001, R. Carter, R. Carter, Malaria Eradication: The History of a Disease and Its Eradication, R. Carter, World Health Organization)
Plasmodium falciparum
Drug Resistance
What has changed over the past decade?

- Funding
- Scaled programs
- Disease eradication framework
  - Smallpox, Rinderpest
  - Guinea worm, Polio
- Demographic changes – Middle Income
  - Projections for countries in poverty by 2035 – as a result of overall economic development
- Impact of baseline “development” on mortality and other impact measures
Extent of malaria transmission: 2008

Hypothetical phasing scenario

Source: Malaria Elimination: Geography, finance, and economics, presentation by Prof. Sir Richard Feachem, at ASTMH 7 Dec 2008.
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
Malaria Eradication was 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
Vector Diversity Informs Intervention Choice

Layering vector species distributions identifies key behavioral differences

Anopheles mosquito resistance to insecticides: 64 countries and counting

Areas of particular concern are Sub-Saharan Africa and India due to reports of widespread resistance and high rates of malaria transmission.
Emergence of new foci

29 September 2009
Summary of proposed key responses

Control
Scalling for impact (SUFI)
Sustaining control (SC)

Pre-elimination

Elimination

Prevention of reintroduction

SERCaP / MDA

VIMT

Diagnostics +

Surveillance as an intervention

Vector Control/TPP for outdoor populations

Modeling Intervention Mixes inc. CEA

HSR

Essential R&D backbone, enabling technologies and platforms

- Continuous culture of *P. vivax*
- Biology of liver stages
- Genomic and proteomic platforms
- Approaches and tools for measuring transmission

- Framework and tool for effectiveness decay analysis and health system integration
- Harmonization of data bases, model outputs, user interface
  - Training

Single Encounter Radical Cure and Prophylaxis drug suitable for MDA

Vaccine (s) that Interrupt Malaria Transmission

New Diagnostics (individual, community/MDA)

Surveillance as an Intervention

Sustained Vectorial Capacity Reduction Tool

Predictive modeling allowing strategic and operational, including costing, assessment of combining different control and elimination strategies

Minimal Enabling Framework for Health Systems Readiness

PLoS Medicine 25 January 2011
Malaria 2012

cases and deaths by country

WHO World Malaria Report 2013
Varied Health Systems

- In Africa, malaria treatment is delivered in a variety of ways
  - Zambian health system is dominated by the public sector, while Nigeria is dominated by the private.
  - Public sector systems can be very different, from health extension workers in Ethiopia to primary health centers in Madagascar.
  - Private sector access can be for-profit, premium for-profit, or non-governmental.
  - Campaigns are often public-private partnerships.

Fraction of febrile <5s receiving drugs who received them from the private sector

Current core global malaria control interventions

World Health Organization

Global Malaria Programme
50 countries are on track to reduce malaria case incidence by 75% by 2015: these account for only 3% of total estimated cases.
Progress - Mortality

Mortality rate estimates between 2000 and 2012:

42% decline globally

48% decline in children under 5 yrs

WHO World Malaria Report
The Asymptomatic Reservoir of Parasites

- 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

Symptomatic persons seeking care are the tip of the iceberg.
Prevalence of *P. falciparum* Infection Determined by Polymerase Chain Reaction (PCR) Versus Microscopy

The dashed line denotes the expected association if both techniques were equally sensitive.

**Proportionally more submicroscopic infections are missed as transmission decreases**

**Ho:** Targeting the human transmission reservoir in asymptomatic people is necessary for successful eradication

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The risk of interrupted investment: malaria resurgences

Cohen et al. Malaria Journal 2012 11:122
The benefit of malaria elimination

- Between 1945 and 2010, 70 countries eliminated malaria and 75 (95%) remain malaria free.
- Malaria resurgence occurred in 36 of 49 (73%) countries participating in the 1955 Global Malaria Eradication Program in countries that tried, but failed, to eliminate malaria.
- Malaria elimination – if achieved - is surprisingly stable.

Distribution of Pyrethroid Resistance

- Rapid scaling up of LLINs in Africa leads to insecticide resistance and behavioral changes in malaria vectors, i.e.,
  - switch from indoor to outdoor biting
  - from nocturnal to diurnal biting preferences.

Trends in Parasitology. 2011 (27)2. 91–98
Integrated Vector Control Consortium (IVCC)
New Vector Interventions to Counter Emerging Resistance

- **Combination bed nets**
  - Chlorfenapyr plus alphacypermethrin
  - Olyset Plus (Sumitomo Chemical) is a durable polyethylene net containing 2% permethrin combined with 1% of the synergist Piperonyl butoxide (PBO)
  - Olyset DUO (Sumitomo Chemical) is a durable polyethylene net containing 2% permethrin combined with 1% of pyriproxyfen. Pyriproxyfen is a juvenile hormone analog, preventing larvae from developing into adulthood and thus rendering them unable to reproduce.

- **LLINS plus IRS for short duration campaigns**
- **Attractive Toxic Sugar Baits with “stomach poisons”**
- **Spatial Repellents**
- **Larvicides**
The malaria parasite lifecycle
A malaria vaccine is feasible

- People in endemic regions become clinically immune from severe disease
- Irradiated sporozoites protect human volunteers from malaria challenge
- Passive transfer of antibody protects human volunteers
# Global malaria vaccine pipeline

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<th>TRANSLATIONAL PROJECTS</th>
<th>Phase 2a</th>
<th>VACCINE CANDIDATES</th>
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**P. falciparum vaccines:**
- Pre-erythrocytic
- Blood-stage
- Transmission-blocking

**P. vivax vaccines:**
- Pre-erythrocytic
- Blood-stage
- Transmission-blocking

Lifecycle of the malaria parasite

- **Sporozoites**
- **Oocysts**
- **Ookinete**
- **Zygote**
- **Microgametocyte (Exflagellation)**
- **Macrogametocyte**
- **Merozoites**
- **Hypnozoite**
- **Infected Hepatocyte**
- **Schizont**
- **Erythrocyte**
- **Ring**
- **Trophozoite**
- **Gametocytes**

**Transmission to Man**
- In the mosquito
- In the human liver
- In the human blood cell

**Transmission to Mosquito**
- From infected human
- In the mosquito

**Cycle leading to clinical symptoms**
- June 2014
Proposed priority workstreams for malaria medicines (MMV)

1. Making medicines safe for all
2. Unparalleled opportunities in uncomplicated malaria
3. Transmission blocking: parallel track with vaccines
4. Picking the winners for pregnancy
5. Severe malaria: parasite reduction platform
Using networks to fingerprint compounds

Membrane feed assay
Imperial College, UK

Membrane feed assay
TropIQ, Netherlands
GSK, Tres Cantos

P. cynomolgi hypnozoite assay
BPRC, Netherlands

P. yoelii/berghei liver stage assay
GNF Novartis/ UCSD, USA

In vitro blood stage activity
Swiss TPH, Switzerland & Eskitis, Australia

Gametocyte and gamete formation assays
Griffith University Australia and Imperial College UK

Gametocyte assay
GSK Tres Cantos, Spain

Resistence risk assessment
Columbia University, USA

June 2014

Population Drug Based Strategies

• Test and treat?
  – MSAT, FSAT...

• Fire and forget (Treat and don’t test)
  – MDA, FMDA, hMDA (household MDA)

• Many strategies…

• An opportunity for operational research
New medicines for Malaria Eradication

Replacing three days ACT and 14 days primaquine with a simpler therapy

Overcoming concerns about resistance

A range of players in Malaria
Malaria – the post 2015 agenda

• Global transitions
  • World Bank – focus on extreme poverty
  • What comes after the MDGs – High Level UN Panel
  • Chronic Disease agenda –
  • Does health remain on the agenda?

– Eradication framework
  • Evolving strategy led by Alan Magill/BMGF – focus on human reservoir, strategic use of drugs in large scale programs
We have burnt the boats

Ancient Greeks
Hernan Cortes - 1519

• Evidence of progress – the numbers
• We know a lot about the hardest geographic, population and strategic areas
• Ships have been burnt for everyone – GFATM, WHO, countries
• Alternatives: failure or success
Primum non nocere
Above all, do no harm

- Critical balance between risk and innovation
- Balance of risks – failure to act (more malaria) vs. failure to innovate (promise of more impact)
- Not an absolute – a creative tension.
- Science and Leadership.
- Structure for managing risks.
Knowledge Management

“A scientist who is also a human being cannot rest while knowledge which might be used to reduce suffering rests on the shelf.”

Albert Sabin

-- that which exists
-- that which should be collected
-- major gaps: learnings in the field
Its not the stuff you don’t know that gets you into trouble – it’s the stuff you know for sure that just ain’t so.

Mark Twain
Attack the bottom of the pyramid

- Malaria thrives in the most distant, disenfranchised at risk populations
- Lesson from polio – don’t ignore the hardest places to the end, it extends the time needed to success
- At the same time, leverage what is feasible right now – need early successes
Malaria Governance

• Multiplicity of leaders and players, but malaria systems are largely inherently integrated
• Partnership structure –

  Its complex

• Do we have the right leadership commitment? Architecture? How can we achieve financing goals to sustain impact forward to elimination and eradication?
When does it get easier?

There is no point at which an eradication campaign get easier.

Don Hopkins, Carter Center
Smallpox, Guinea Worm, Oncho
The sudden appearance of an epidemic typically inspires rapid attention, panic, and action. Once the crisis subsides, public attention wanes although the threat of contagion continues, especially among the world's poor.

Compare our response to severe acute respiratory syndrome, or SARS, with the more familiar germs that plague us daily. Compare it to the dangers of smoking or getting in a car and heading out on the road. Every life is precious, but when you look at the numbers, SARS just isn't as formidable a threat as we've made it out to be. Its death rate is far lower than that for AIDS or malaria, communicable, like the one believed to cause SARS, tend to be most active in the winter and early spring.

In addition to taking the steps necessary to keep SARS at bay—washing out for new cases and isolating people who are contagious to others—we would do well to channel our energies into something more lasting: a permanent, integrated and accountable global public health system for the surveillance and prevention of the microbes that are certain to emerge in the future. Right now, worldwide accounting of disease is incomplete at best, hampered in large measure by sketchy reporting from developing countries. These gaps slowed our containment of SARS and allowed us to spread more rapidly than reliable information. When the facts are few, it's easy for fear to fill the vacuum.

Howard Markel, professor of pediatrics and communicable diseases at the University of Michigan, is author of the forthcoming "When Germs Travel."
Malaria Funding for disease control

Figure 3.1 Past and projected international funding for malaria control, 2000-2016

[Bar chart showing funding for malaria control from 2000 to 2016, categorized by source including Global Fund, PMI/USAID, DFID, World Bank, AMFm, CIDA, AusAID, and Other.]

AMFm, Affordable Medicines Facility – malaria; AusAID, Australian Agency for International Development; CIDA, Canadian International Development Agency; DFID, Department for International Development; GF, Global Fund; PMI, President’s Malaria Initiative; USAID, United States Agency for International Development; WB, World Bank

For the GF and PMI/USAID, funds from the last quarter of 2013 onwards are projected; for other agencies, funds from 2012 onwards are projected.

Source: See Box 3.1
IT ALWAYS SEEMS IMPOSSIBLE... UNTIL IT IS DONE

Nelson Mandela