The Great Malaria Debate: Elimination of Artemisinin-resistant Malaria from Southeast Asia – is it Possible?

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Malaria can be eliminated

COL John Boyd Coates, Jr., MC, USA
http://history.amedd.army.mil/booksdocs/wwii/Malaria/default.htm
100 years pre-eradication

Source:
Global malaria control and elimination
WHO 2008
Eradication era
1945 - 1977

Source:
Global malaria control and elimination
WHO 2008
Control era
1977 - 2007

Source:
Global malaria control and elimination
WHO 2008
Why are we talking about malaria eradication now?
Figure 3.2.


International financial disbursements to malaria endemic countries have increased from approximately $100 million in 2003 to nearly $1.5 billion in 2009.

Current tools:
Long-lasting insecticide-impregnated nets

WHO/S. Hollyman

C. Plowe
Mass drug administration
Song et al. Malaria J 2010
Dihydroartemisin-piperaquine + primaquine
1/3 of malaria-endemic countries eliminating malaria now

THE MALARIA ELIMINATION GROUP
The Global Health Group
UCSF Global Health Sciences
April 2009
San Francisco
Can malaria be eradicated?

Yes...

with an end to poverty and strife.

and/or

with new and better tools that can be implemented everywhere.
Eradication: What has worked for other infectious pathogens?
Eradication programs

**Failure**
- Hookworm
- Yellow fever
- Yaws
- Malaria

**Success**
- Smallpox
- Polio (Americas)
- Measles (Americas)

**Near success**
- Polio
- Guinea worm
- Rinderpest
- Rubella (Americas)

DA Henderson, malERA Zenith Week, March 2010
Eradication programs

• **Failure**
  - Hookworm
  - Yellow fever
  - Yaws
  - Malaria

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Vaccines: Principal tool

DA Henderson, malERA Zenith Week, March 2010
A Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Infants

The RTS,S Clinical Trials Partnership

- Efficacy against clinical malaria 30.1% (95% CI, 23.6 to 36.1)
- Efficacy against severe malaria 26.0% (95% CI, −7.4 to 48.6)
- Impact on transmission not reported
AMA1 polymorphism in Mali mapped on crystal structure

Takala et al. Sci Transl Med 2009
Phase 2 efficacy trial
AMA1 vaccine efficacy against clinical malaria in 400 Malian children

Overall efficacy against clinical malaria

Strain-specific efficacy

Thera et al. NEJM 2011
Seroreactivity to 263 diverse AMA1 variants among 400 Malian children immunized with FMP2.1/AS02$_A$ AMA1 malaria vaccine or rabies vaccine

Broad antibody response against diverse AMA1 variants does not translate to broad efficacy against diverse parasites

Laurens et al. PLoS ONE in press

Jason Bailey et al. unpublished
Subunit vaccines have proven poorly efficacious.

What next?
IMMUNIZATION OF MAN AGAINST FALCIPARUM AND VIVAX MALARIA BY USE OF ATTENUATED SPOROZOITES*

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Jessup State Prison, Maryland
MALARIA FIGHTER

Scientist Stephen Hoffman may be close to neutralizing one of history’s most implacable killers—and forging a new entrepreneurial model for attacking global diseases. By Michael Mysel

On a recent afternoon, in stifling 100-degree heat, eight fragile children lie in cribs covered with mosquito nets in the pediatric ward of a small hospital in Navrongo, a rural town in the West African country of Ghana. They all arrived today, burning up with malaria, a remorseless killer in this region. Their shell-shocked mothers look on as the kids shiver and moan. The nurses say business is slow; they normally admit 10 patients per day at this time of year. The kids in the ward, having survived a trek in from the bush that many malaria victims here don’t, will get medicine and are likely to survive. But that does little to brighten the outlook of Patrick Atobrah, the hospital’s sad-eyed medical superintendent. He and his few doctors are overwhelmed. “The results can be quite horrible,” he says.

The area around Navrongo has one of the highest malaria rates in the world. During the rainy season, 82 percent of the area’s children between the ages of 5 and 10 will be infected with the disease. Navrongo, in short, is a heavy contributor to malaria’s brutal global toll. Roughly 2 million people die of the disease every year. Most are children. The death count is headed upward because the drugs and pesticides used to treat malaria are increasingly ineffective. “We need help,” Atobrah says. More specifically, he needs “an
Live, aseptic, radiation-attenuated sporozoites

- High yields produced in sterile mosquitoes
- Can be frozen and thawed, maintain viability
- 8 dissectors make vaccine lots for clinical trials
- Would need ~100 dissectors to produce enough vaccine for global markets
- Genetically attenuated sporozoite vaccines under development
  - Set back by breakthrough infection in first human trial
- Whole organism approach may help overcome genetic diversity

Hoffman et al. Human Vaccines 2010
Volunteers in Baltimore and Silver Spring, Maryland

- Immunized with radiation-attenuated sporozoites
  - Intradermal or subcutaneous injection

- Challenged with bites of mosquitoes infected with the same chloroquine-sensitive strain of *P. falciparum* used to create the vaccine (homologous challenge)
First clinical trial of PfSPZ Vaccine
at University of Maryland’s Center for Vaccine Development
and US Navy Medical Research Center

Intradermal – 2 injections separated by 1 cm

Photos: Kirsten Lyke
Controlled Human Malaria Infection (CHMI)

- Volunteers hospitalized days 7-18 after challenge
- 5 infected bites assures infection
- Promptly treated with chloroquine
- Proven safe in 1000s of volunteers over 40 years

Photos: Kirsten Lyke
PfSPZ challenge trial

- **Dose 1**: 6 SC, 6 ID, 7,500 SPZ/dose
  - Only 2/16 protected in Group 2

- **Dose 2**: 10 SC, 10 ID, 30,000 SPZ/dose

- **Dose 3**: 10 SC, 10 ID, 135,000 SPZ/dose

- **Dose 4**: 10 SC, 10 ID, 135,000 SPZ/dose

Epstein, Tewari, Lyke et al. Science 2011
IV administration of PfSPZ Vaccine results in much stronger immune responses in Rhesus monkeys

Epstein, Tewari, Lyke et al. Science 2011
Protection Against Malaria by Intravenous Immunization with a Nonreplicating Sporozoite Vaccine
IV PfSPZ Vaccine had 100% protective efficacy in highest dose group

R A Seder et al. Science 2013;341:1359-1365
The logistical challenges are daunting...

Malaria elimination in Italy 1900-1962

Snowden “The Conquest of Malaria” 2006

Malaria elimination in Myanmar 2013-20??
...but a frozen live sporozoite vaccine is already being delivered in liquid nitrogen in Africa

*Theileria parva* (East Coast Fever)

International Livestock Research Institute, Kenya
Need to optimize vaccine delivery
Would an IV vaccine for malaria elimination be any harder to accept than smallpox vaccination?
Can malaria be eradicated?

Yes...
but this will be very hard with current tools, and much easier with a highly efficacious vaccine.

In the meantime, global eradication is the right aspirational goal, and elimination can **and must** be achieved in Southeast Asia to prevent spread of artemisinin resistance.

Elimination will be aided by a new molecular marker for artemisinin resistance (S7 1330 Room B)
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