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

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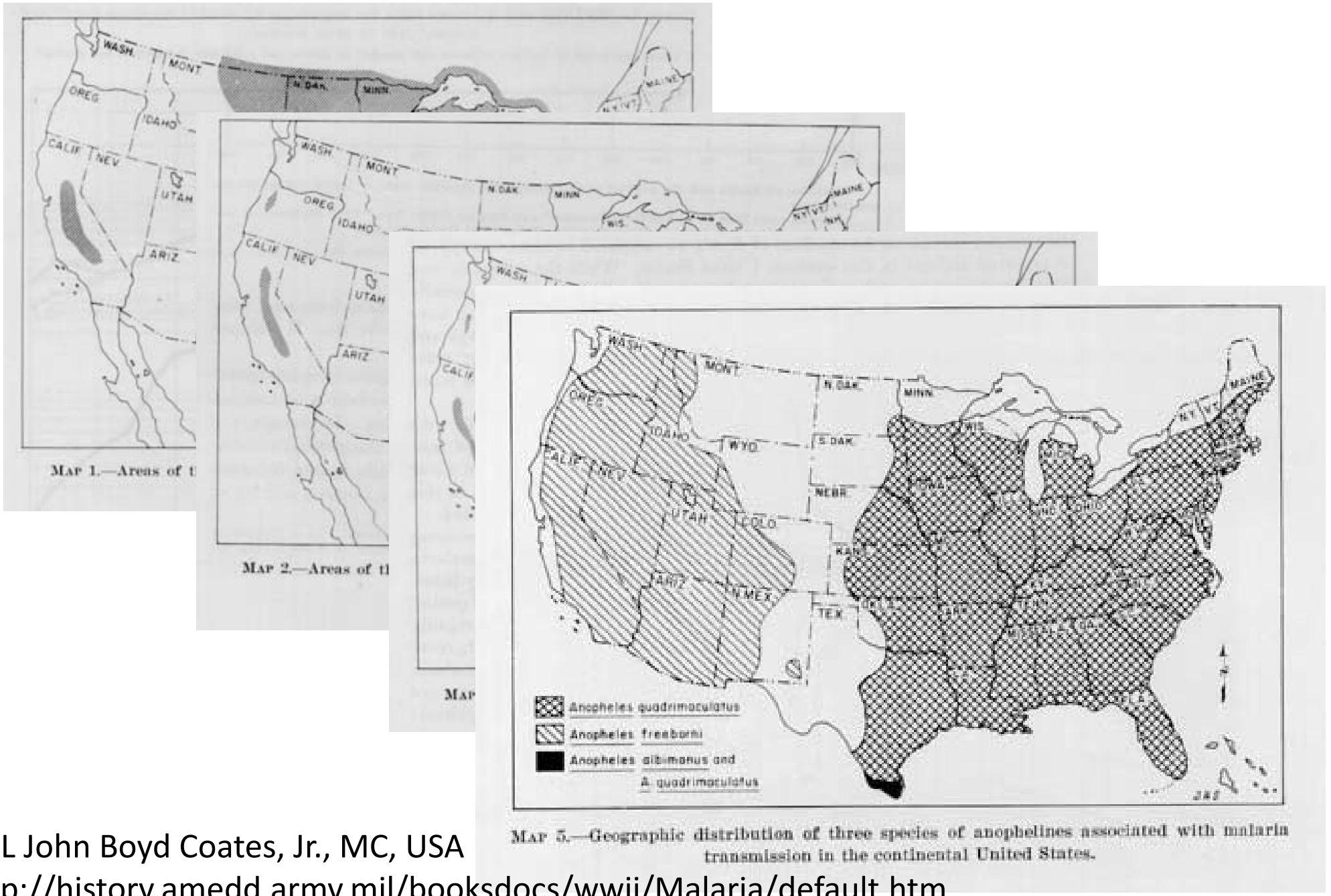
University of Maryland School of Medicine

Joint International Tropical Medicine Meeting
Bangkok, Thailand
October 20, 2013

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
CENTER FOR VACCINE DEVELOPMENT

Malaria can be eliminated



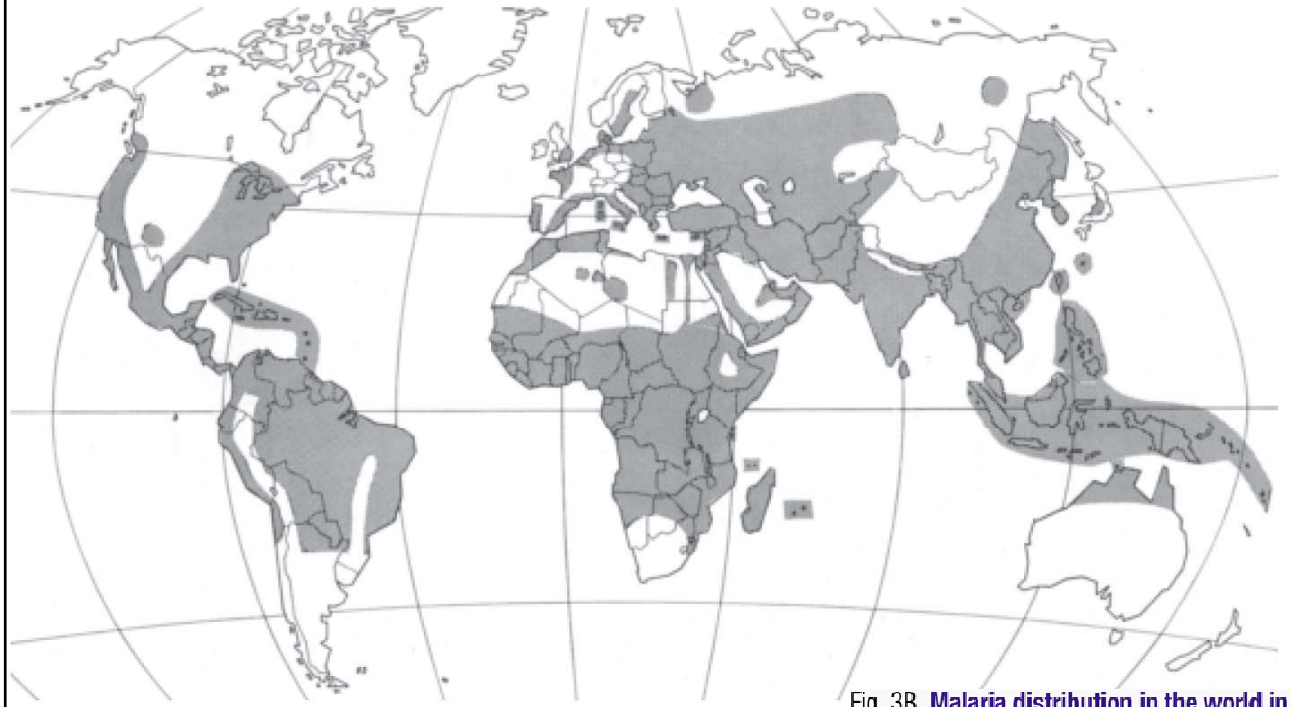
Map 1.—Areas of t

Map 2.—Areas of t

Map 5.—Geographic distribution of three species of anophelines associated with malaria transmission in the continental United States.

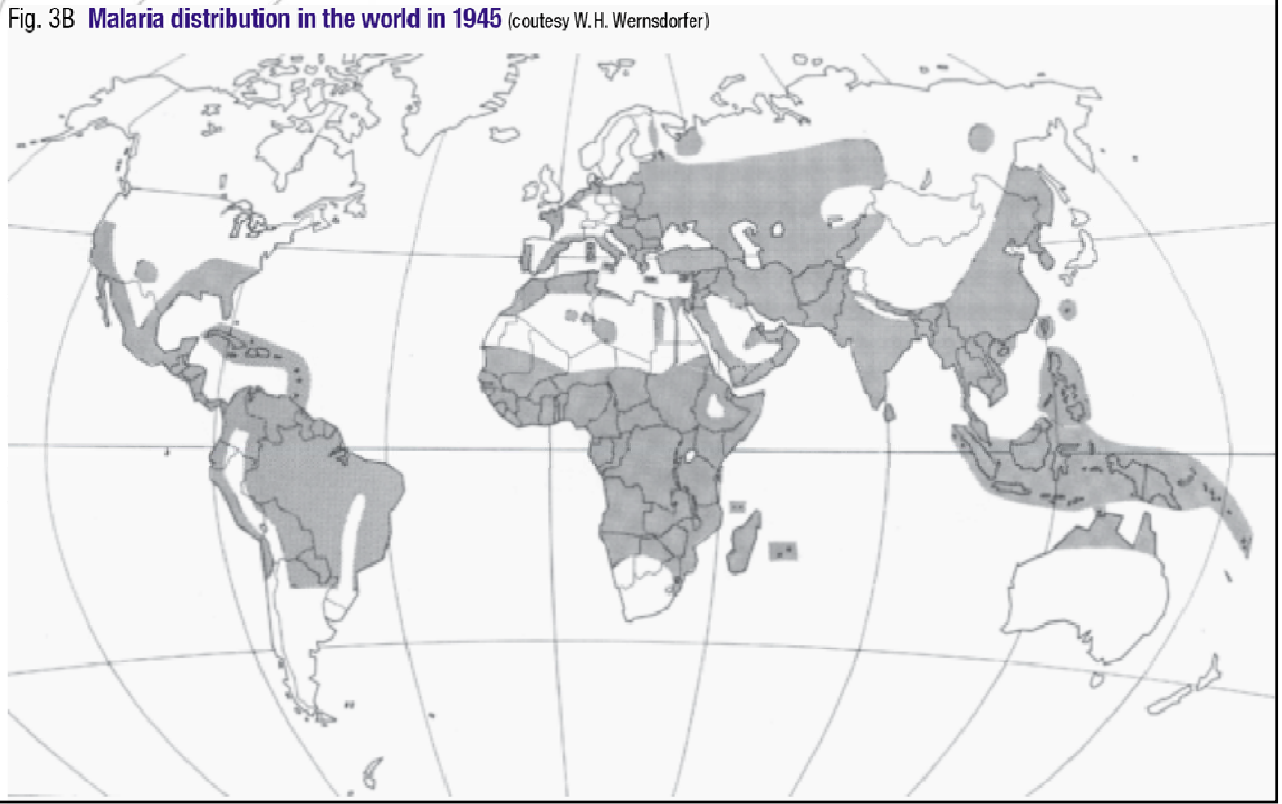
COL John Boyd Coates, Jr., MC, USA
http://history.amedd.army.mil/booksdocs/wwii/Malaria/default.htm

Fig. 3A **Malaria distribution in the world in the mid-nineteenth century** (Wernsdorfer 1980)



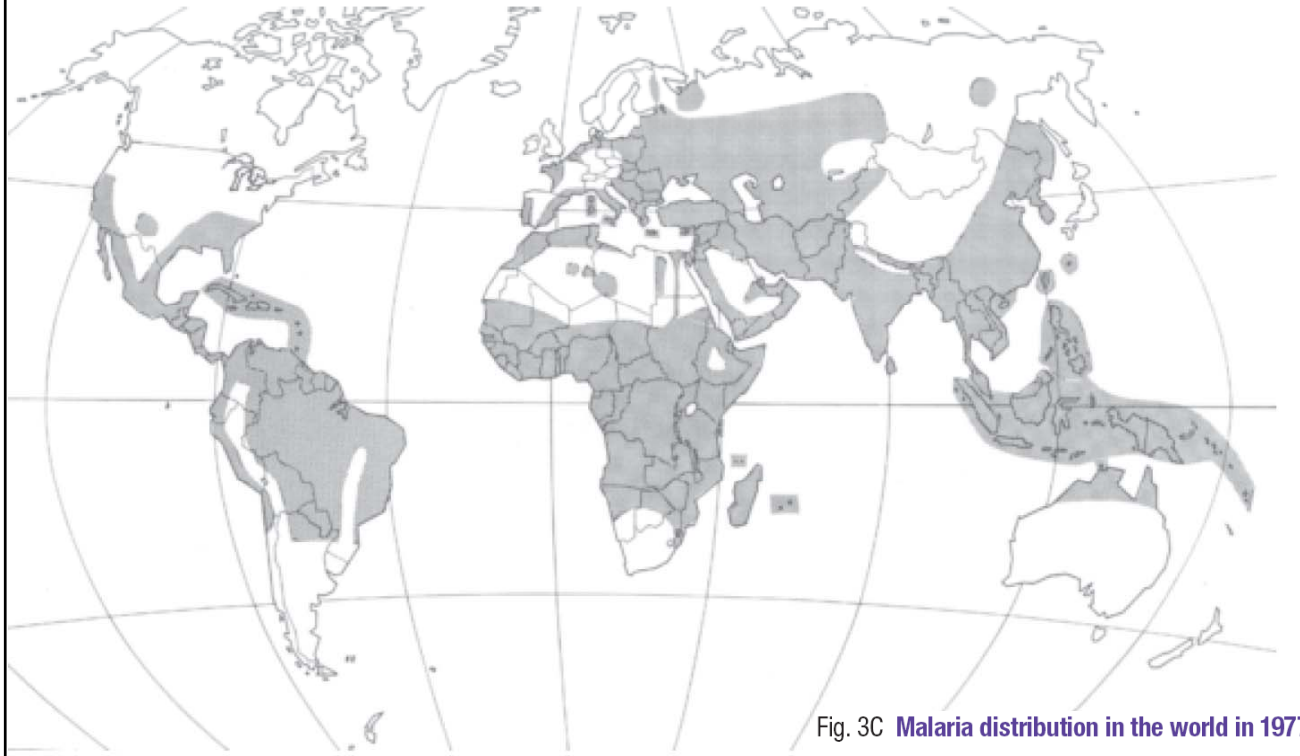
100 years pre-eradication

Fig. 3B **Malaria distribution in the world in 1945** (coutesy W. H. Wernsdorfer)



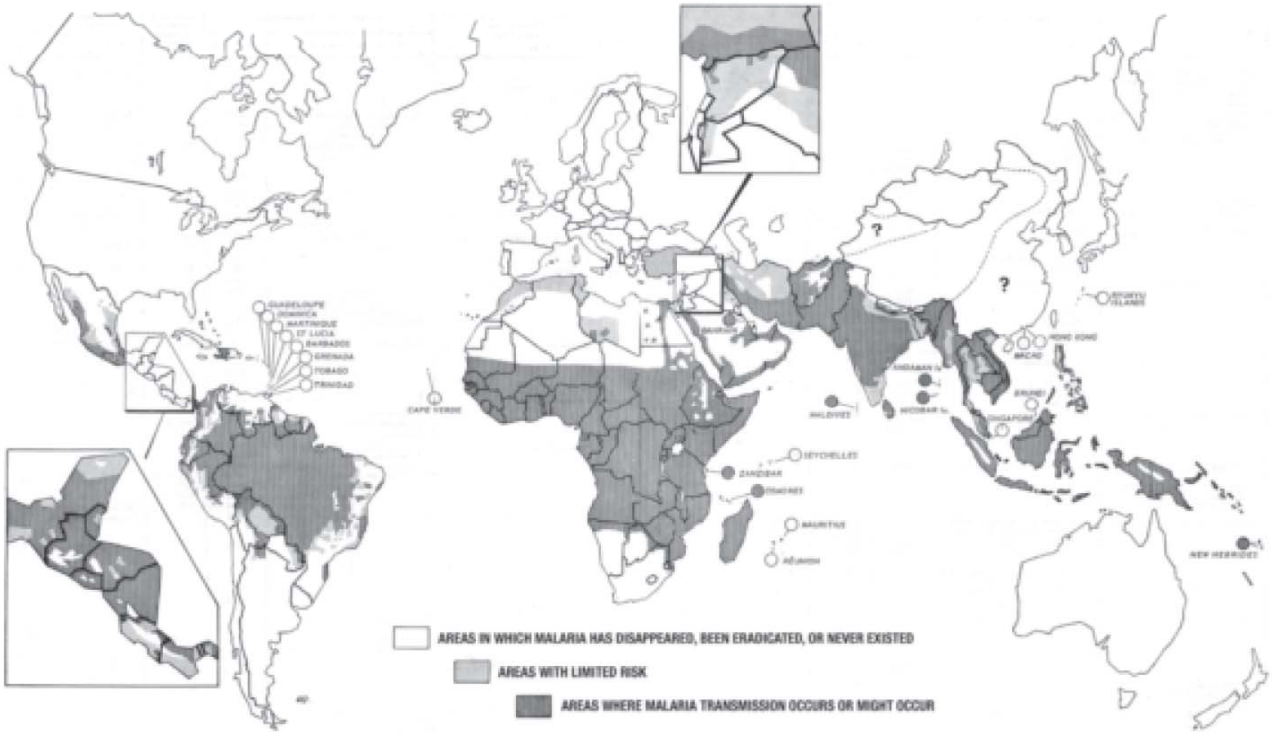
Source:
Global malaria control and elimination
WHO 2008

Fig. 3B **Malaria distribution in the world in 1945** (coutesy W.H. Wernsdorfer)



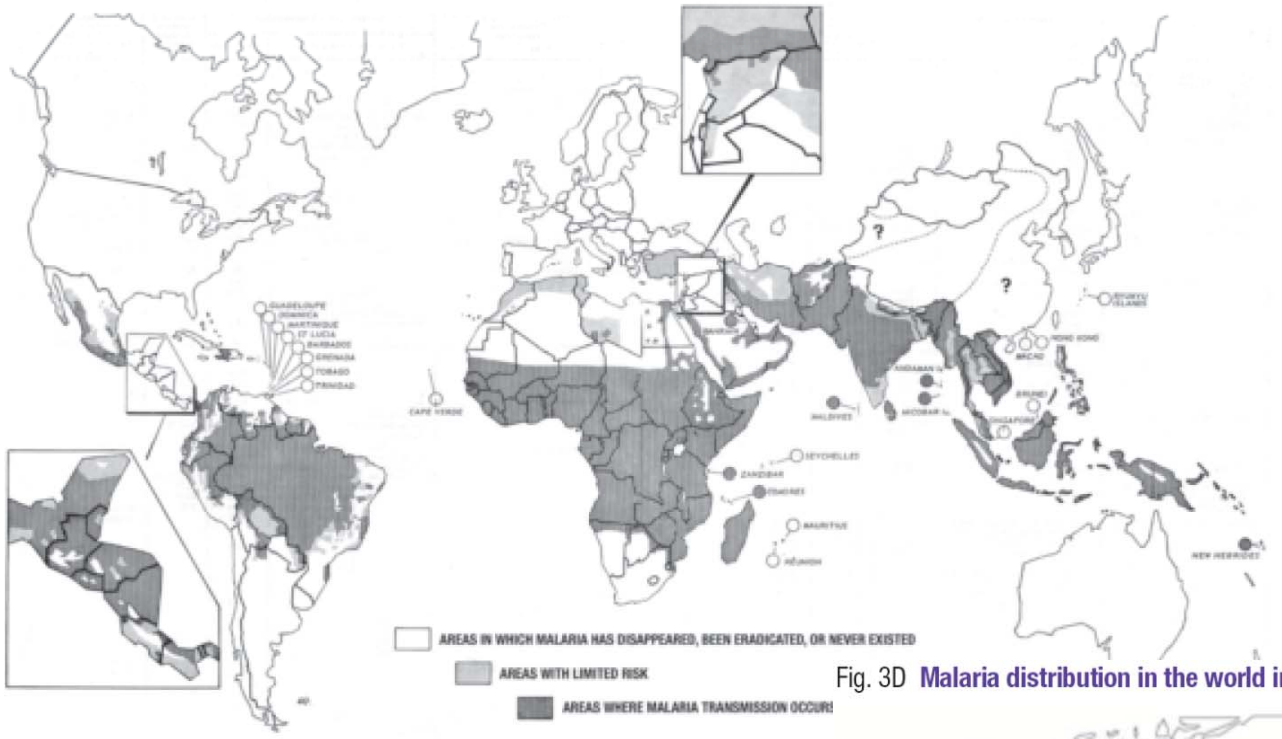
Eradication era
1945 - 1977

Fig. 3C **Malaria distribution in the world in 1977** (WER 1979)



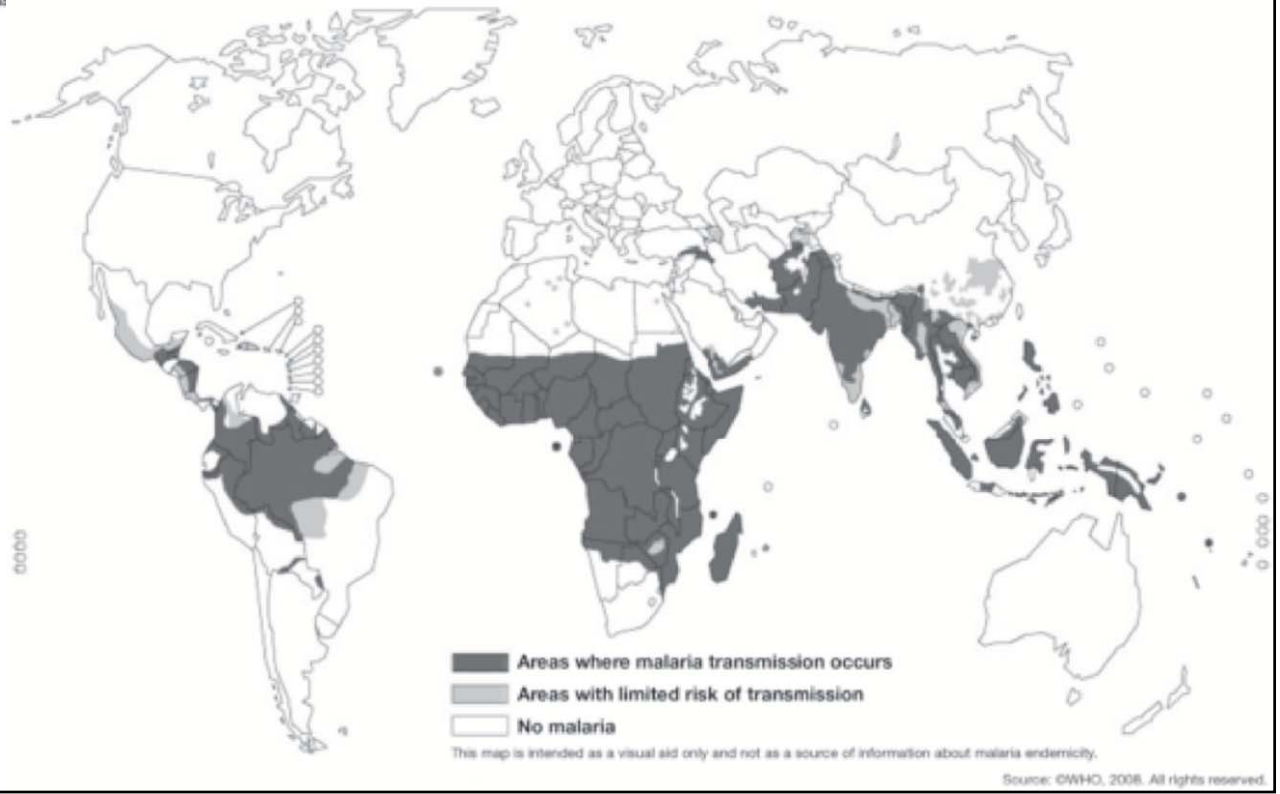
Source:
Global malaria control and elimination
WHO 2008

Fig. 3C **Malaria distribution in the world in 1977** (WER 1979)



Control era
1977 - 2007

Fig. 3D **Malaria distribution in the world in 2007** (*International Travel and Health*, WHO, 2008)



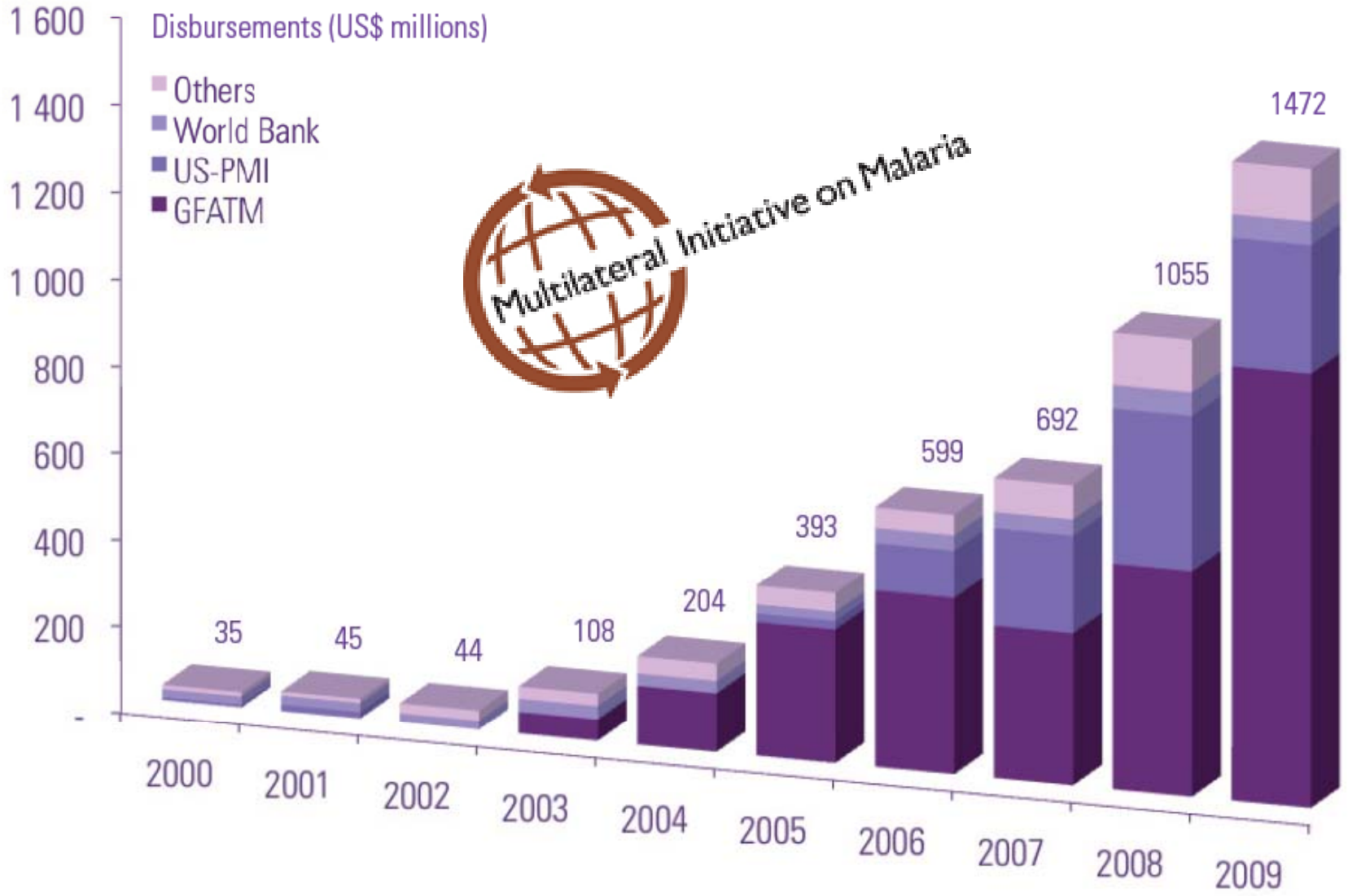
Source:
Global malaria control and elimination
WHO 2008

Why are we talking about malaria eradication now?

Figure 3.2.

International donor disbursements to malaria endemic countries, 2000–2009.

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



Source: The Global Fund, World Bank, US-PMI, OECD database (for 2008); IHME database (for 2000–2007 and 2009).

Current tools:
Long-lasting insecticide-impregnated nets

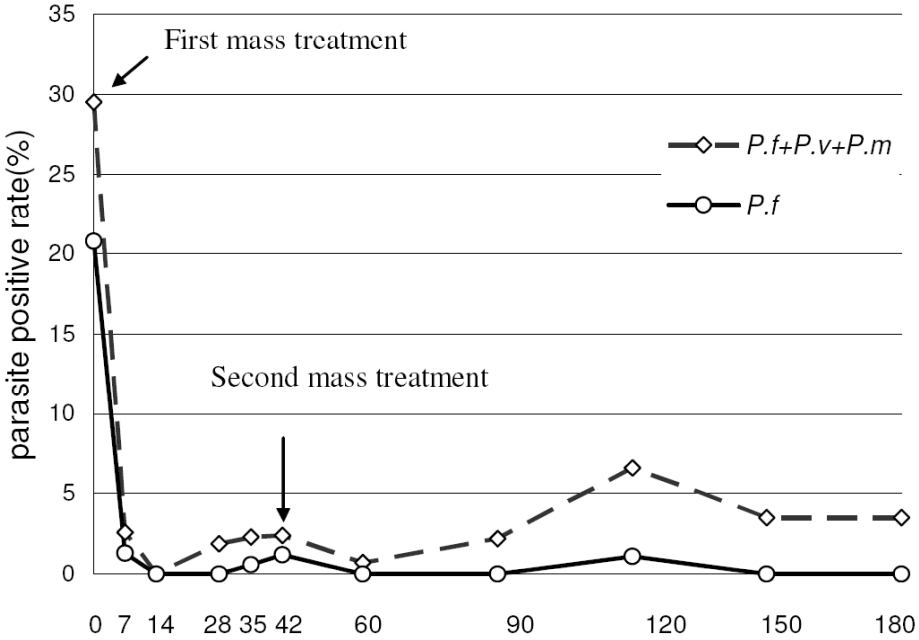
WHO/S. Hollyman

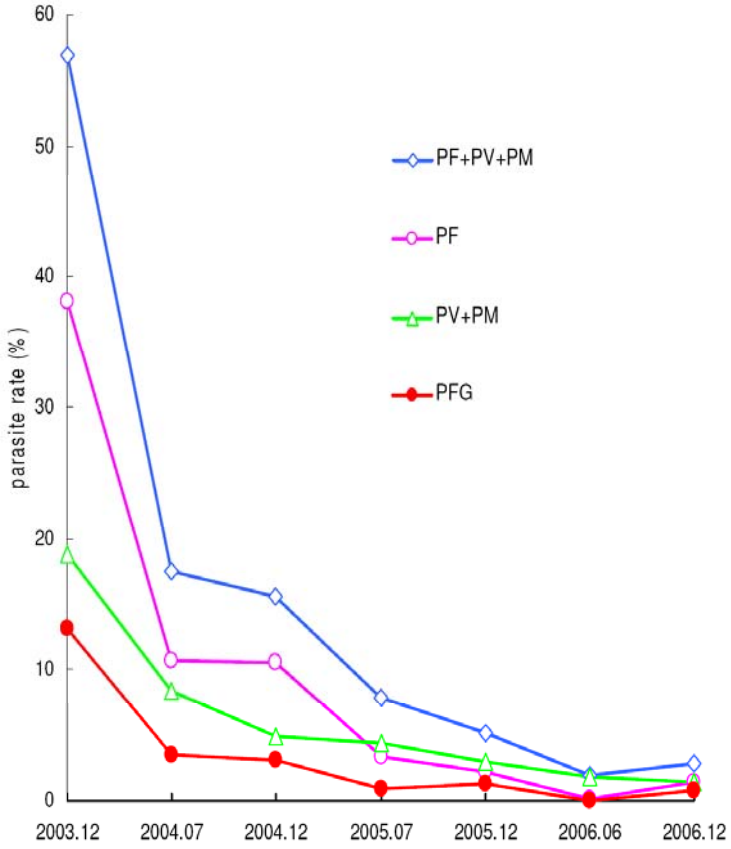
C. Plowe

Mass drug administration

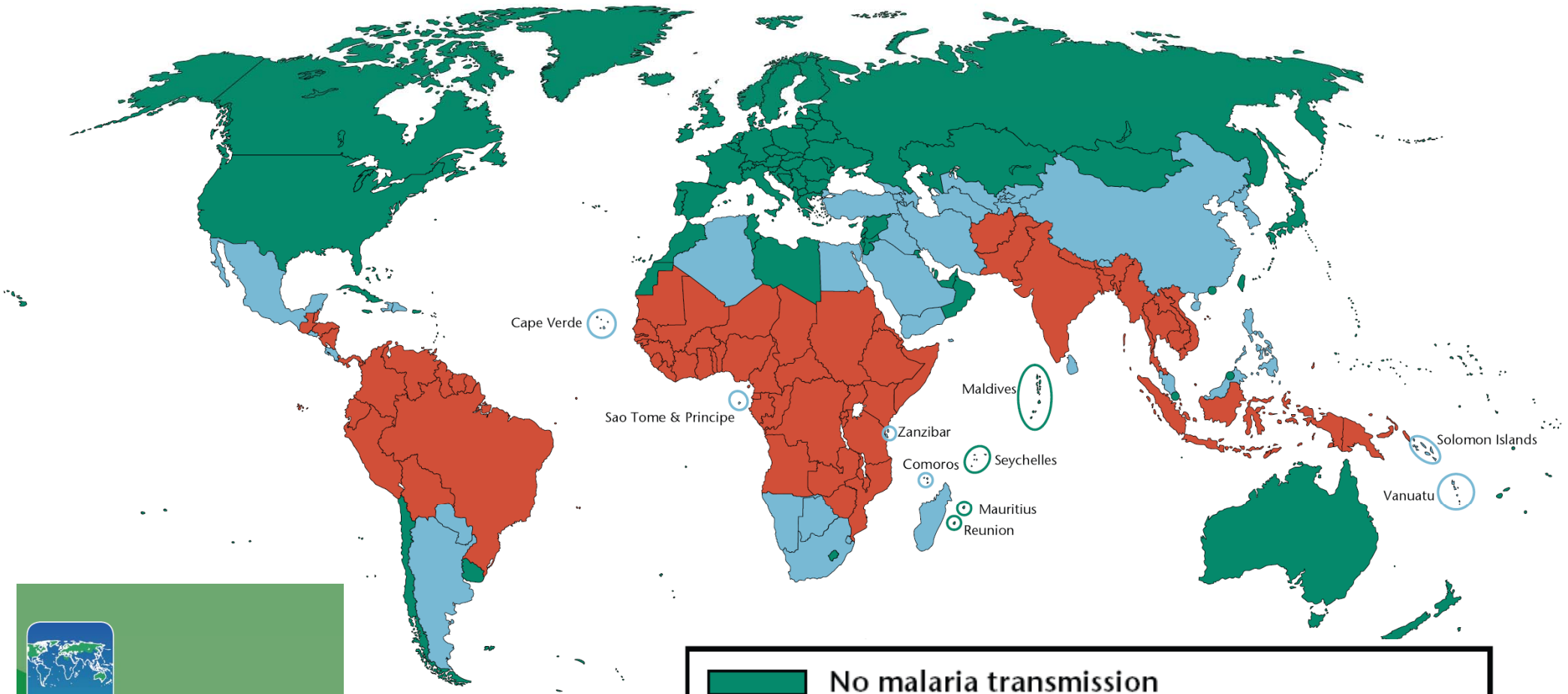
Song *et al.* Malaria J 2010

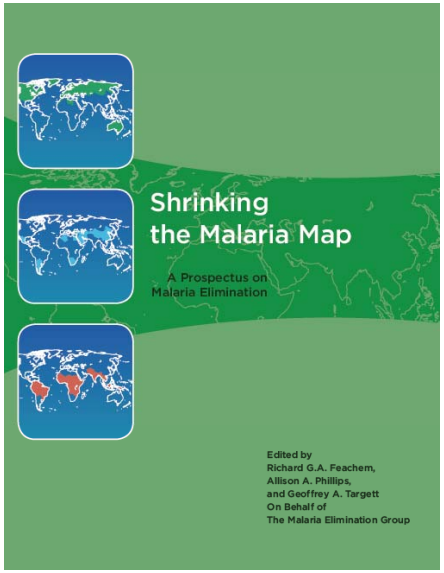
Dihydroartemisin-piperaquine + primaquine





1/3 of malaria-endemic countries eliminating malaria now





THE MALARIA ELIMINATION GROUP

The Global Health Group — April 2009

UCSF Global Health Sciences — 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

Vaccines: Principal tool

- Success
  - Smallpox
  - Polio (Americas)
  - Measles (Americas)
- Near success
  - Polio
  - Guinea worm
  - Rinderpest
  - Rubella (Americas)

DA Henderson, malERA Zenith Week, March 2010

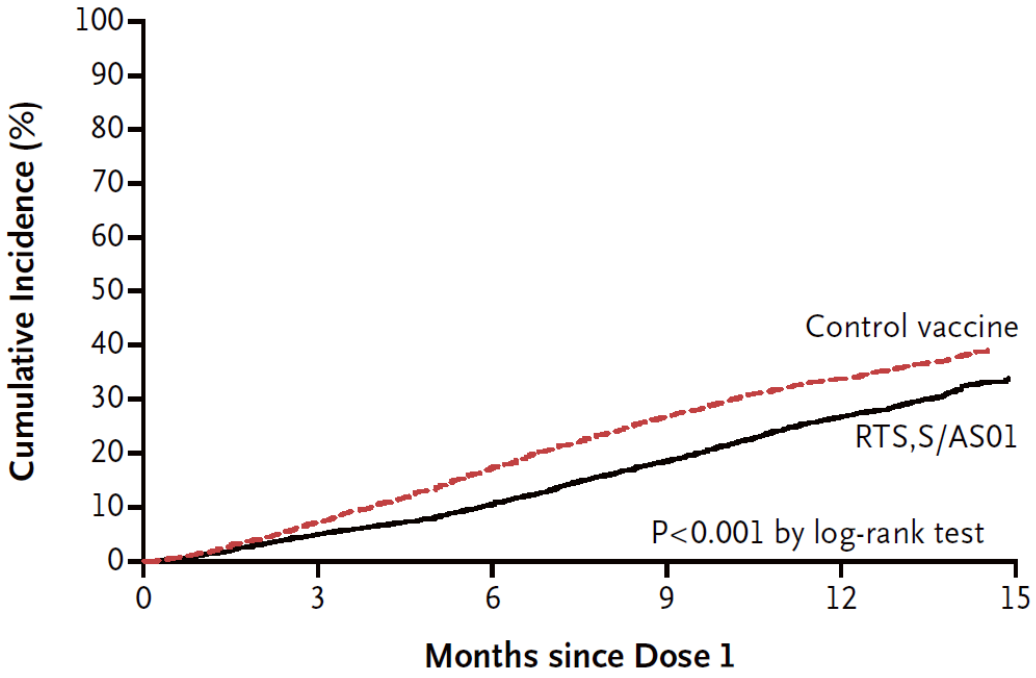
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Infants

The RTS,S Clinical Trials Partnership

B Intention-to-Treat Population



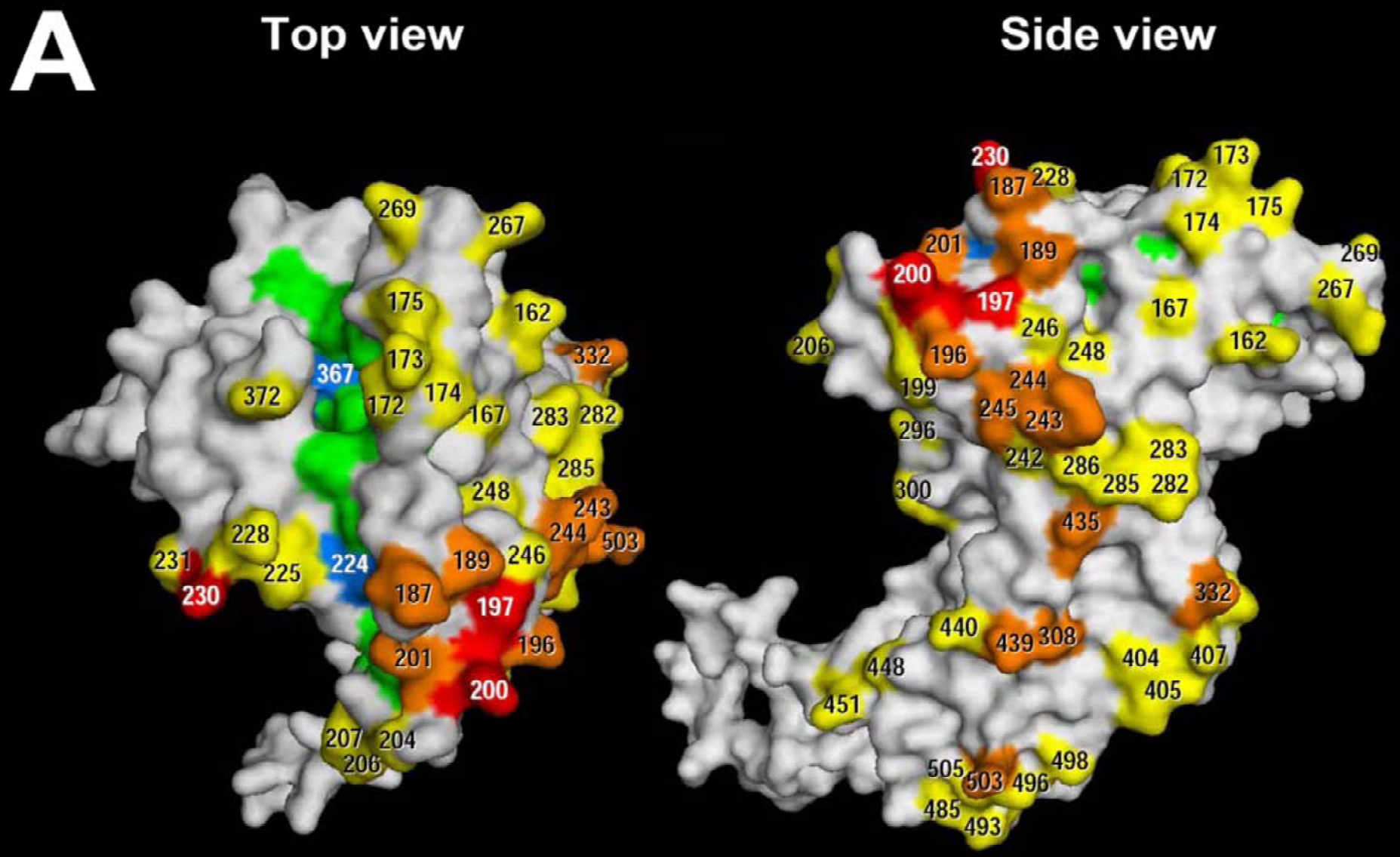
No. at Risk

RTS,S/AS01	4358	4015	3709	3322	2884	1152
Control vaccine	2179	1985	1737	1510	1325	535

Figure 2. Cumulative Incidence of a First or Only Episode of Clinical Malaria (Primary Case Definition).

- 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



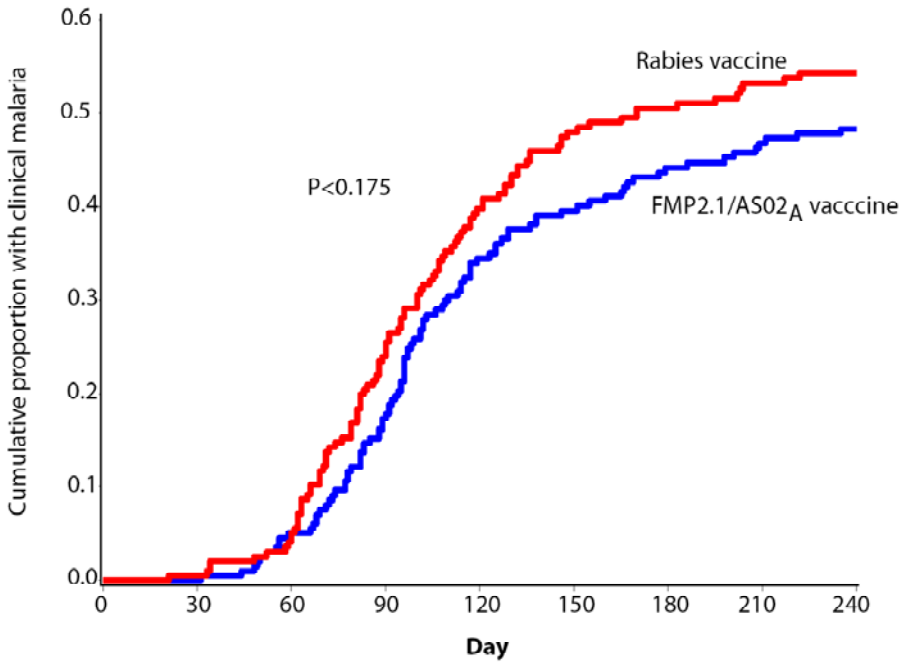
Takala *et al.* Sci Transl Med 2009

Phase 2 efficacy trial

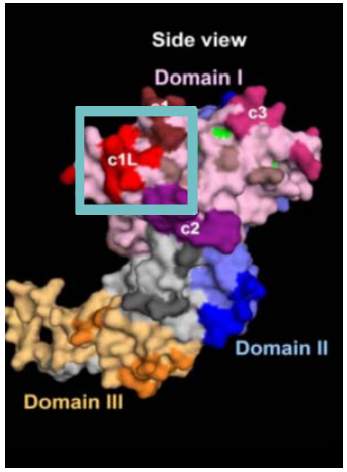
Bandiagara MALARIA PROJECT

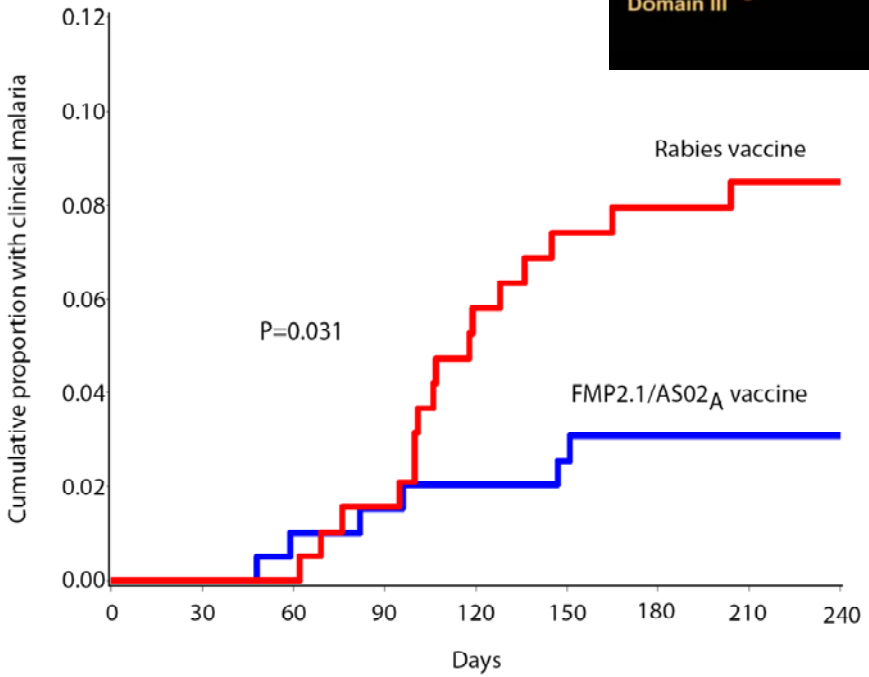
AMA1 vaccine efficacy against clinical malaria in 400 Malian children

Overall efficacy against clinical malaria



Strain-specific efficacy

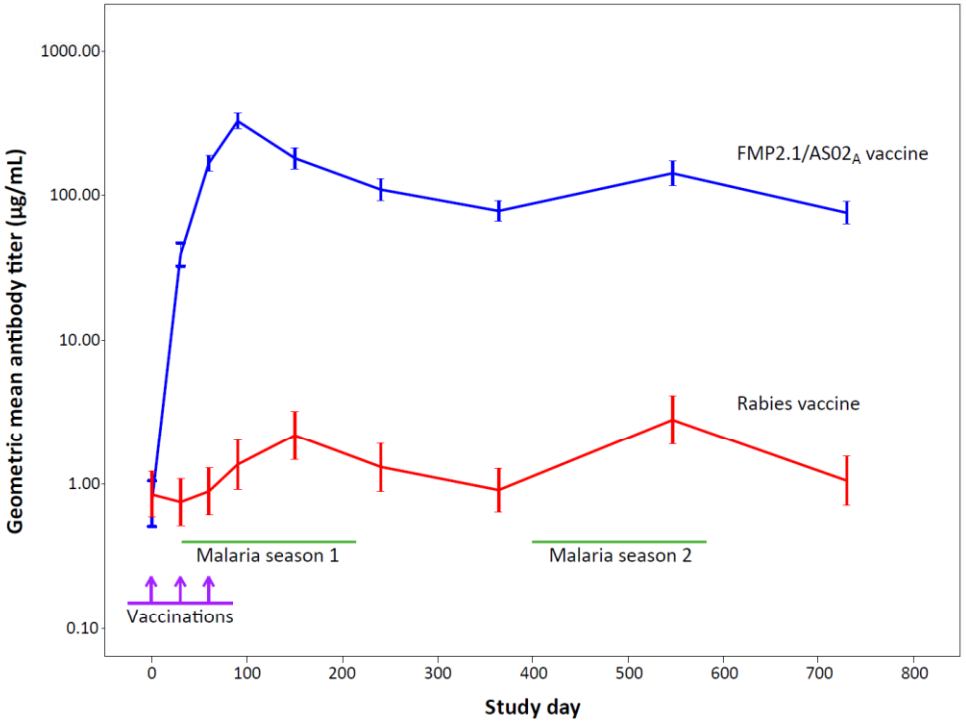




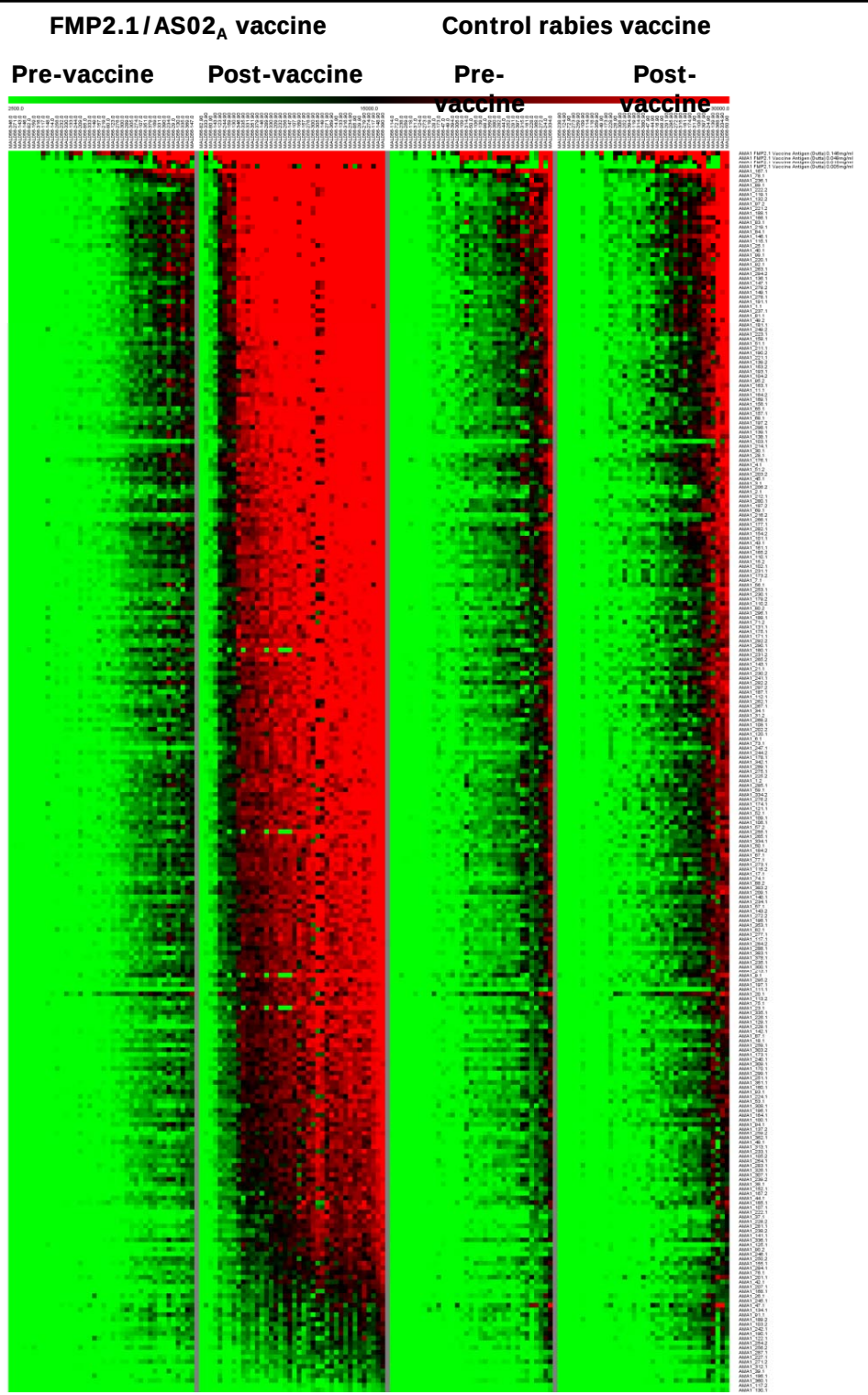
Thera *et al.* NEJM 2011

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?

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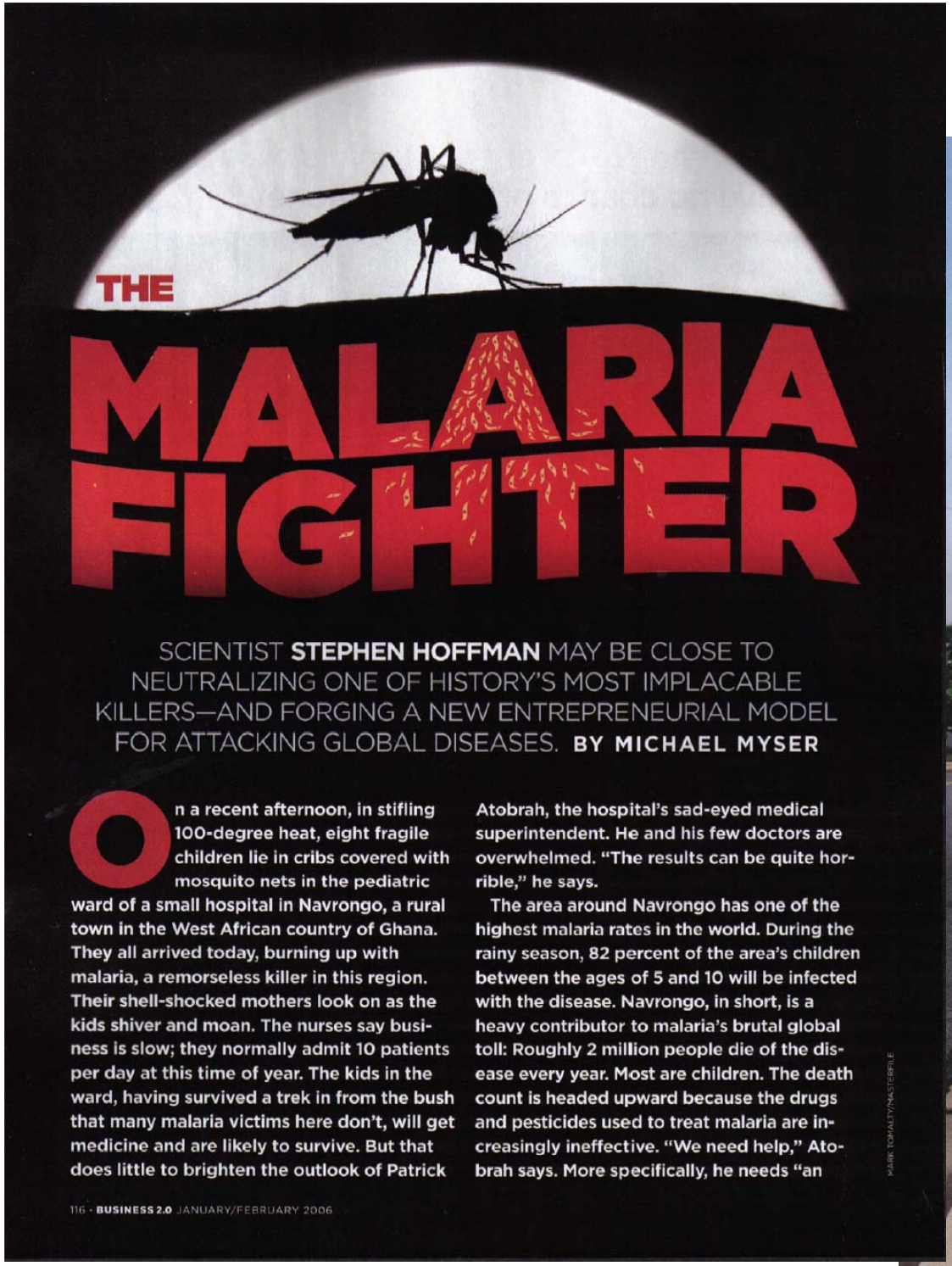
IMMUNIZATION OF MAN AGAINST FALCIPARUM AND VIVAX MALARIA BY USE OF ATTENUATED SPOROZOITES*

DAVID F. CLYDE, VINCENT C. McCARTHY,
ROGER M. MILLER, AND WILLIAM E. WOODWARD
University of Maryland School of Medicine, Baltimore, Maryland 21201

Jessup State Prison, Maryland



THE 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 MYSER**

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

MARK TOMALTY/MASTERFILE

BUGGED Anger at witnessing countless deaths from mosquito-borne malaria fuels Hoffman's crusade to create a vaccine against the disease.

PHOTOGRAPHS BY CHRIS MUELLER/REDUX

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

Live Attenuated Malaria Vaccine Designed to Protect Through Hepatic CD8$^+$ T Cell Immunity

J. E. Epstein,[1*] K. Tewari,[2*] K. E. Lyke,[3*] B. K. L. Sim,[4,5] P. F. Billingsley,[4] M. B. Laurens,[3,6] A. Gunasekera,[4] S. Chakravarty,[4] E. R. James,[4] M. Sedegah,[1] A. Richman,[4] S. Velmurugan,[4] S. Reyes,[1] M. Li,[5] K. Tucker,[7] A. Ahumada,[4,5] A. J. Ruben,[4] T. Li,[4] R. Stafford,[4,5] A. G. Eappen,[4] C. Tamminga,[1] J. W. Bennett,[8] C. F. Ockenhouse,[8] J. R. Murphy,[8] J. Komisar,[8] N. Thomas,[1] M. Loyevsky,[4] A. Birkett,[9] C. V. Plowe,[3,6] C. Loucq,[9] R. Edelman,[3] T. L. Richie,[1] R. A. Seder,[2]†‡ S. L. Hoffman[4,5]†‡

with reduced or no virulence (*13*), our vaccine consisted of ~1 × 10 μm metabolically active, nonreplicating, purified, aseptic, cryopreserved, whole parasites (*14*) (figs. S1 to S3 and table S1). Thus, there were no precedents for method, route and site of administration, or dosage.

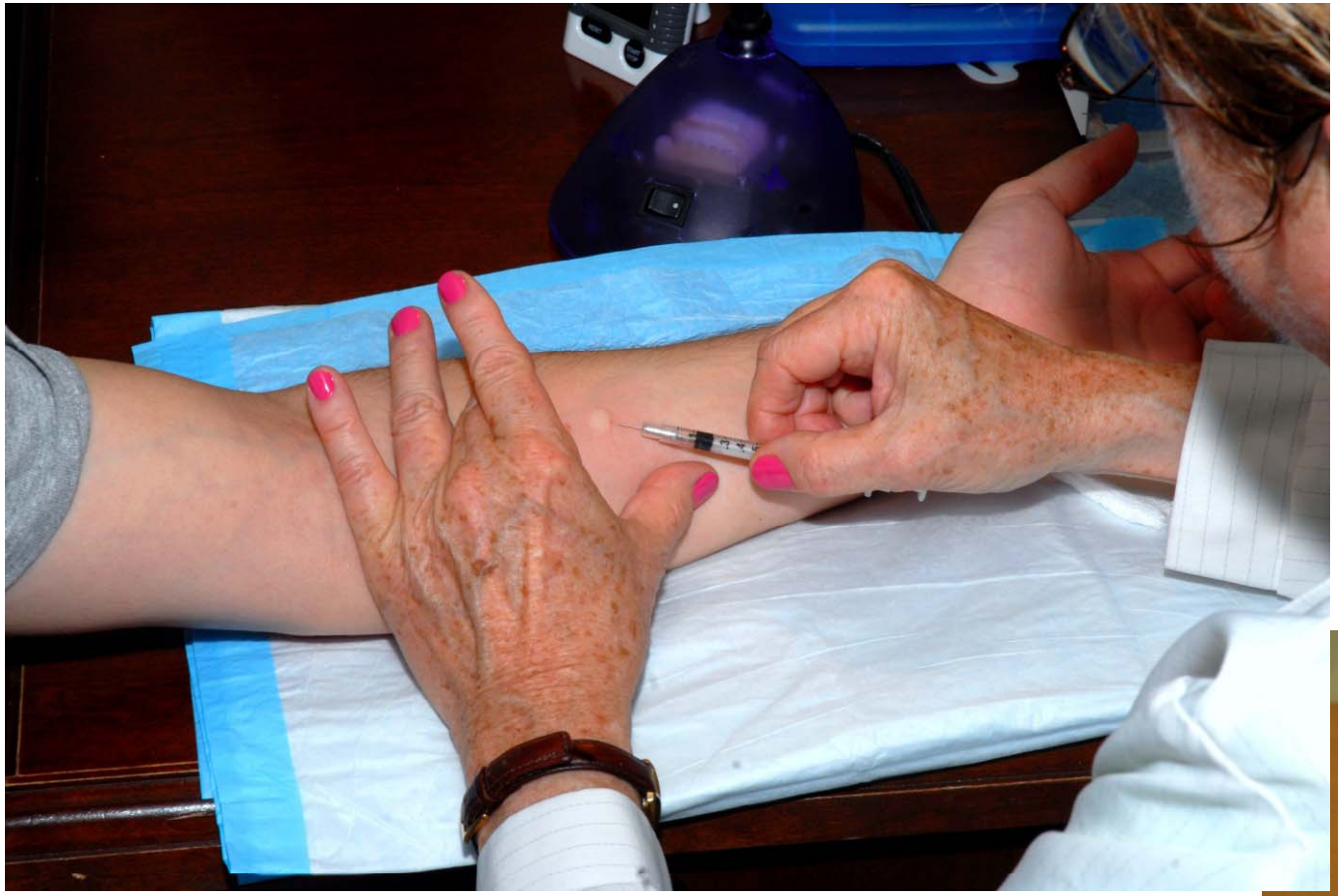
The only human data were obtained from volunteers immunized by bite of irradiated, PfSPZ-infected mosquitoes. In those studies, volunteers were generally exposed to several hundred mosquitoes simultaneously in a surface area of ~56 cm^2 of skin, and each mosquito inoculated PfSPZ in <0.5 μl of saliva (*15*). Undoubtedly some SPZ were inoculated directly into blood vessels, but it has been shown in mice that mosquitoes deposit many SPZ in the dermis and some in subcutane-

www.sciencemag.org SCIENCE VOL 334 28 OCTOBER 2011

- 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

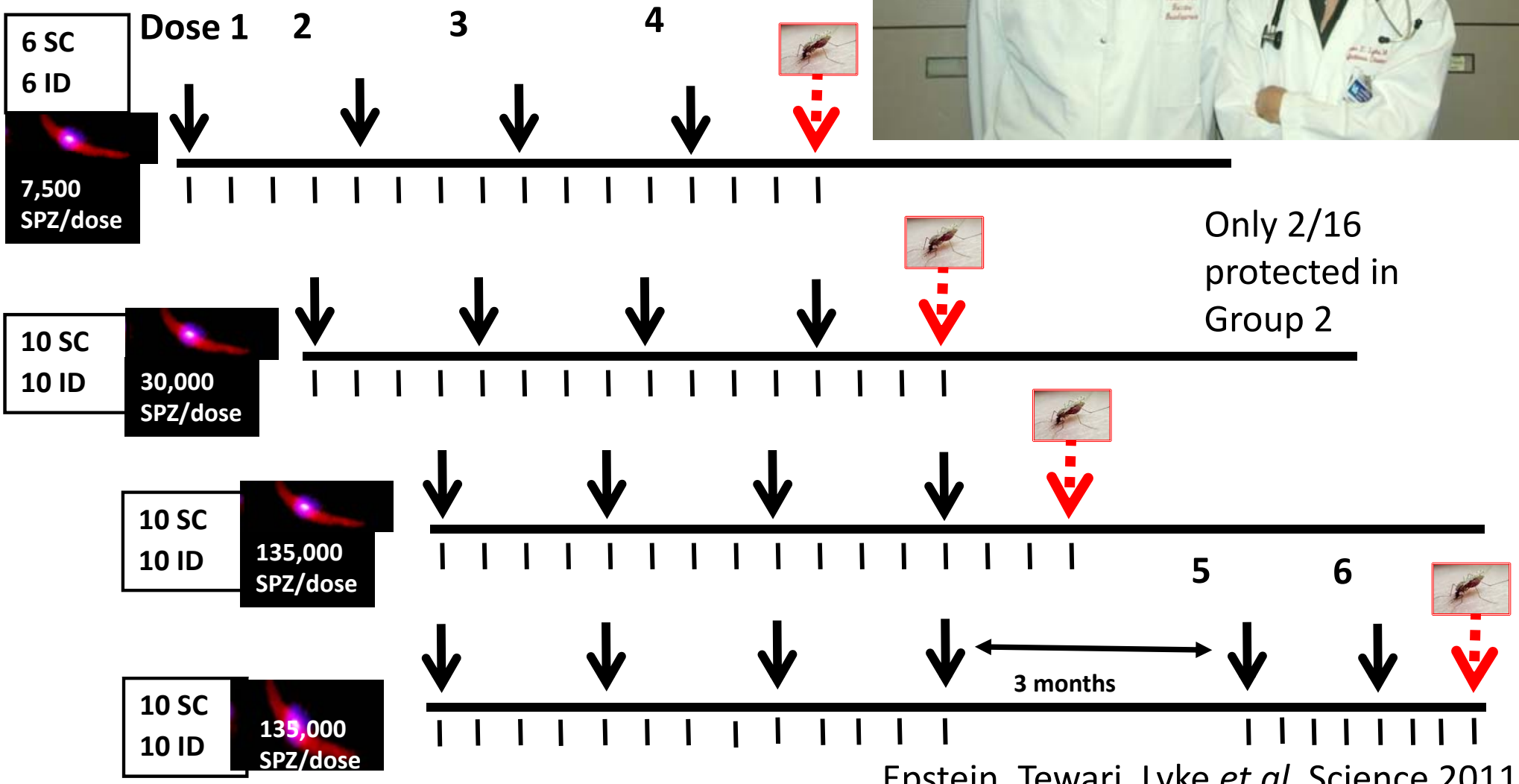
Photos: Kirsten Lyke

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

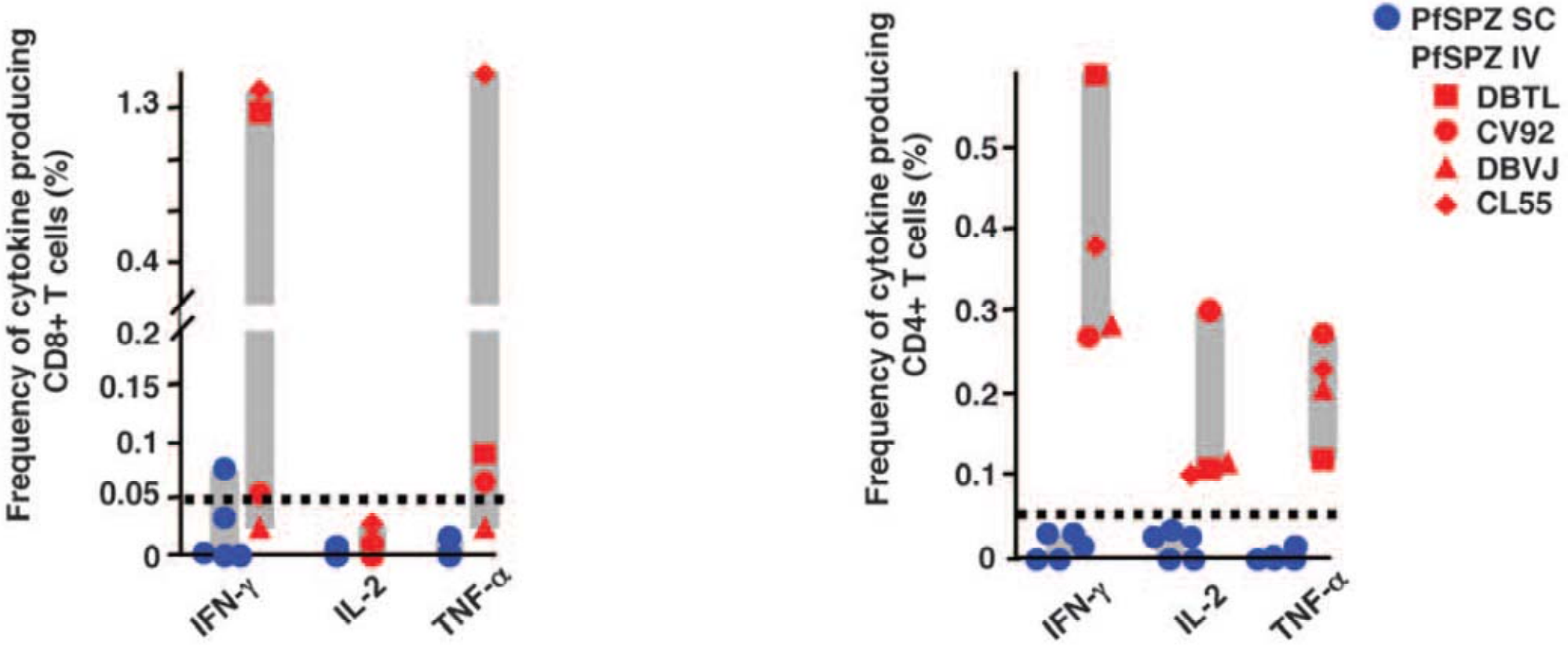
Photos: Kirsten Lyke

PfSPZ challenge trial



Epstein, Tewari, Lyke *et al.* Science 2011

IV administration of PfSPZ Vaccine results in much stronger immune responses in Rhesus monkeys

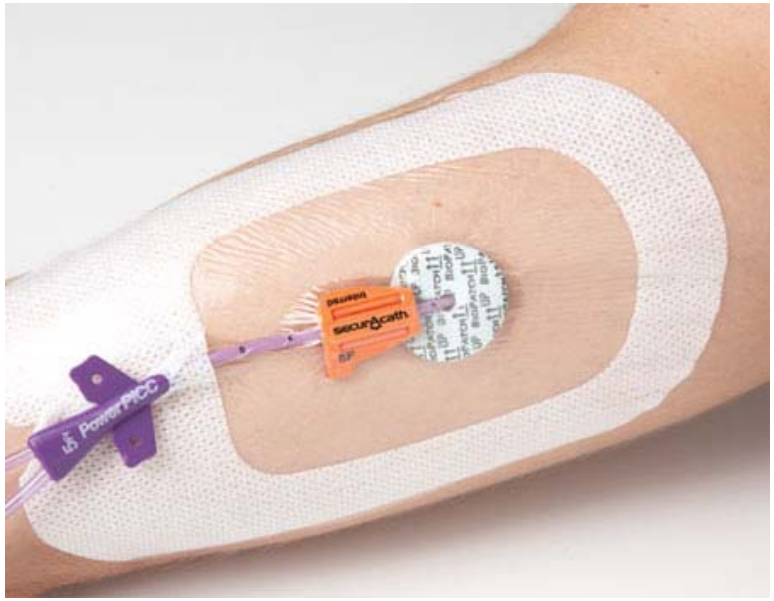


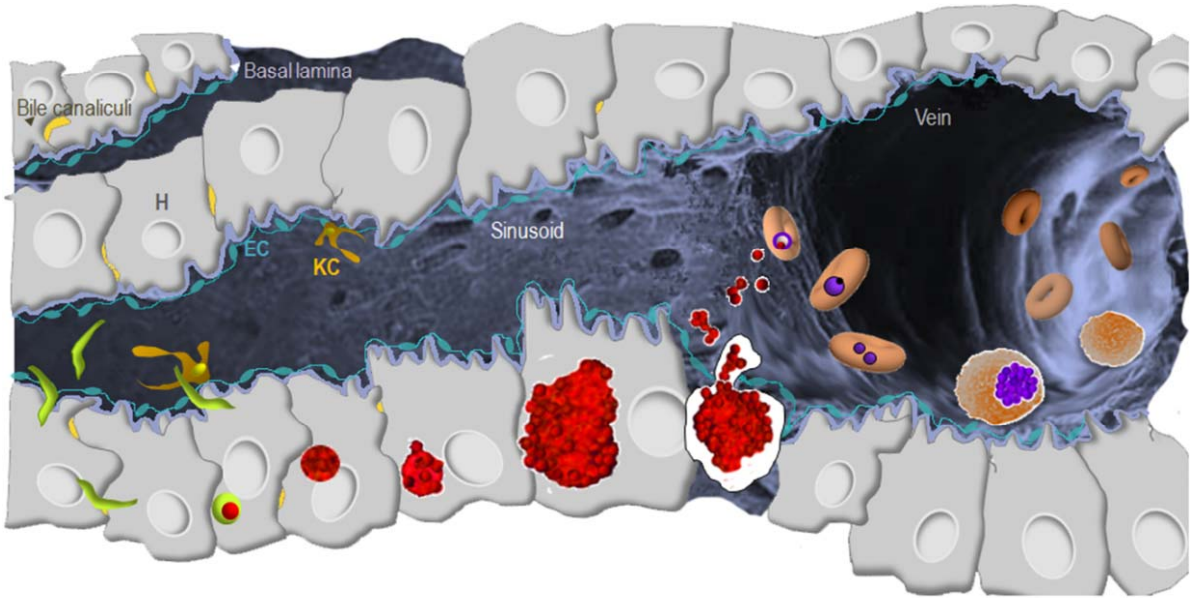
Epstein, Tewari, Lyke *et al.* Science 2011

RESEARCH ARTICLE

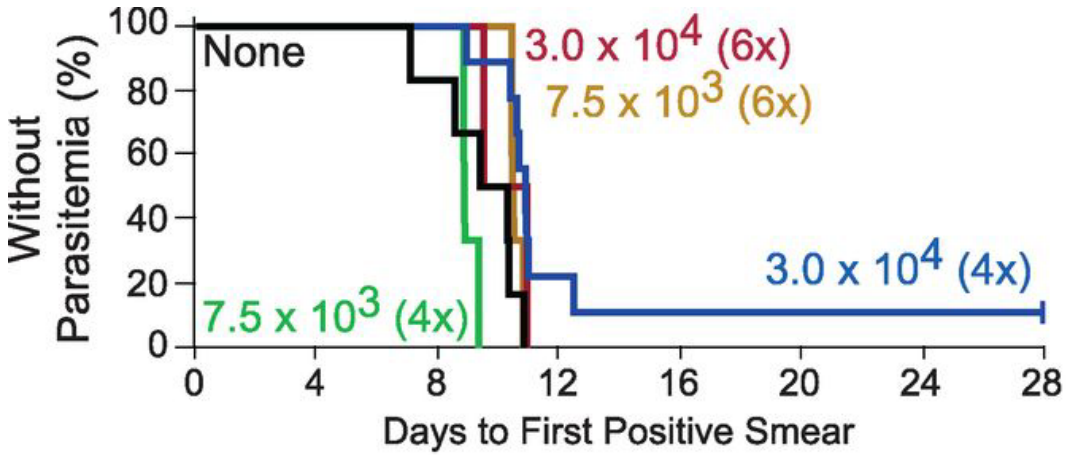
Protection Against Malaria by Intravenous Immunization with a Nonreplicating Sporozoite Vaccine

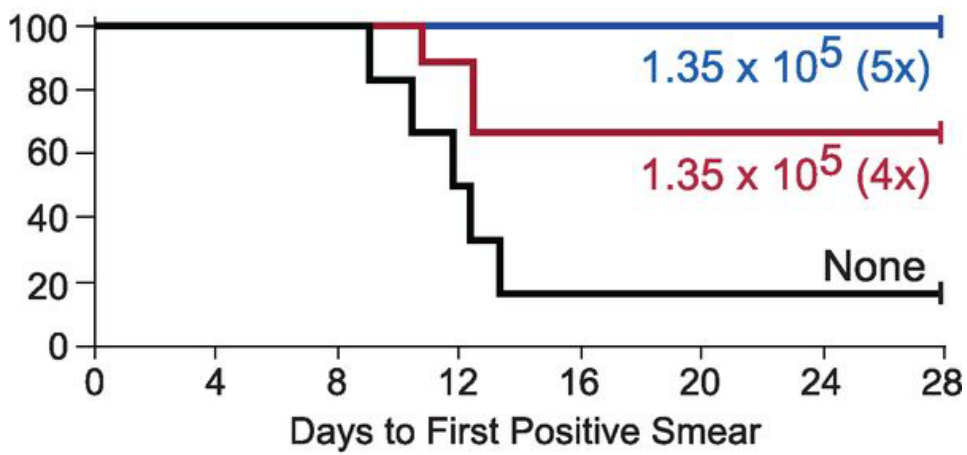
www.sciencemag.org SCIENCE VOL 341 20 SEPTEMBER 2013





IV PfSPZ Vaccine had 100% protective efficacy in highest dose group





Vaccination Dose	# Inj.	CHMI Parasite*	# of Subjects	Parasite Free	Vaccine Efficacy
None		NF54	6	0	
7.5×10^3	4	NF54	3	0	0%
7.5×10^3	6	NF54	3	0	0%
3.0×10^4	4	NF54	9	1	11%
3.0×10^4	6	NF54	2	0	0%

Vaccination Dose	# Inj.	CHMI Parasite*	# of Subjects	Parasite Free	Vaccine Efficacy
None		3D7	6	1	
1.35×10^5	4	3D7	9	6	60%
1.35×10^5	5	3D7	6	6	100%

R A Seder *et al*. Science 2013;341:1359-1365

Published by AAAS

The logistical challenges are daunting…

Malaria elimination in Italy 1900-1962

Malaria elimination in Myanmar 2013-20??

Snowden "*The Conquest of Malaria*" 2006

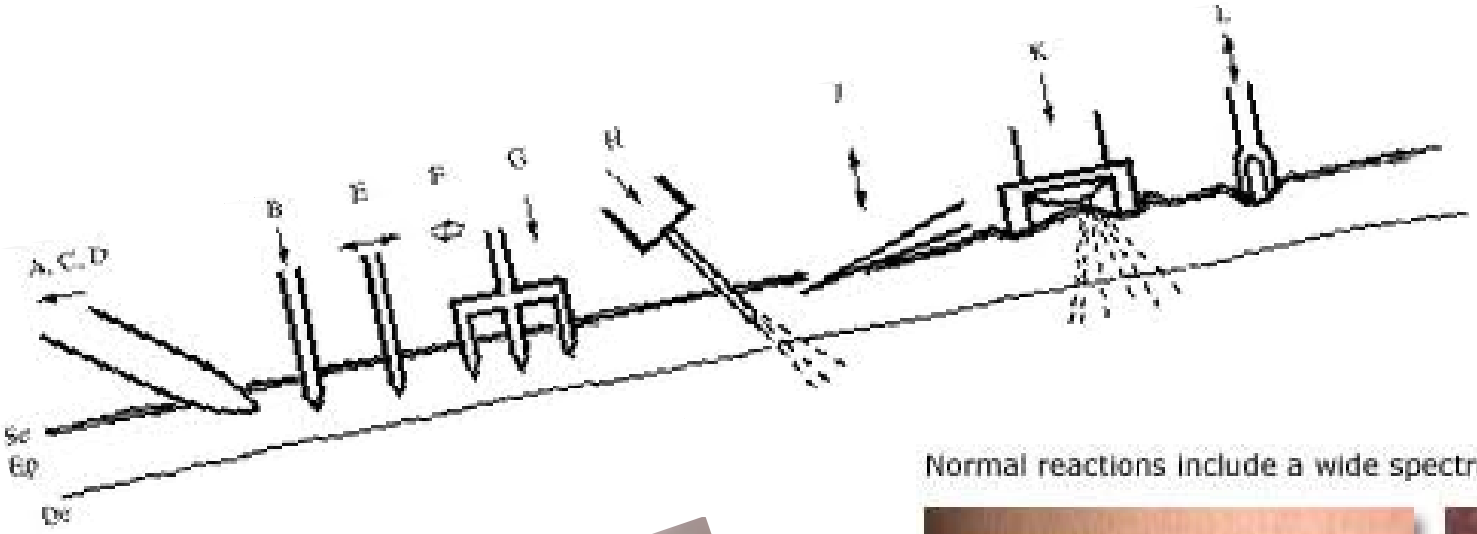
…but a frozen live sporozoite vaccine is already being delivered in liquid nitrogen in Africa

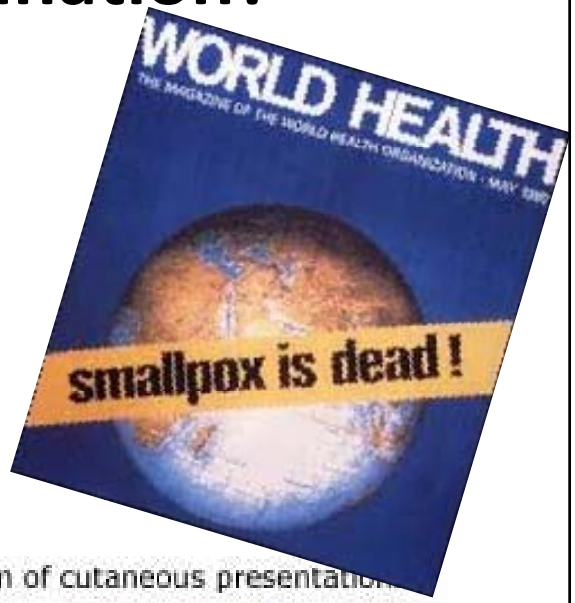
Theileria parva (East Coast Fever)

International Livestock Research Institute, Kenya

Need to optimize vaccine delivery

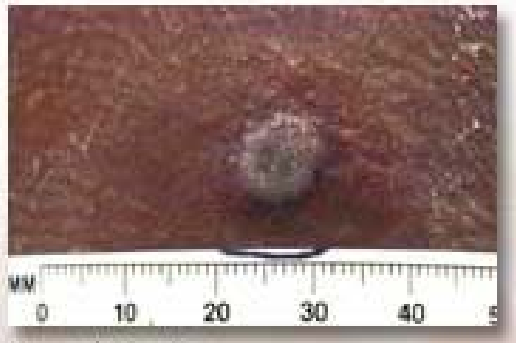
Would an IV vaccine for malaria elimination be any harder to accept than smallpox vaccination?





Normal reactions include a wide spectrum of cutaneous presentation

Normal Reaction



Normal Reaction


Normal with Lymphangitis

Normal with Satellite Lesions

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)

Thanks to:

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Karen Ball

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Drissa Coulibaly
Abdoulaye Djimde
Dapa Diallo
Abdouyale Kone
Ando Guindo
Karim Traore
The BMP team

WRAIR
Ann Stewart
Brent House
Evelina Angov
Elke Bergmann-Leitner
David Lanar
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Sanaria
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Peter Billingsley
Eric James
Adam Richman
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Anusha Gunasekera
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UC Irvine
Phil Felgner
Jozlyn Pablo

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