

**EDCTP 5<sup>th</sup> Annual Forum**  
**October 12 – 14, Arusha**  
**Tanzania**

# Recent Advances in Malaria

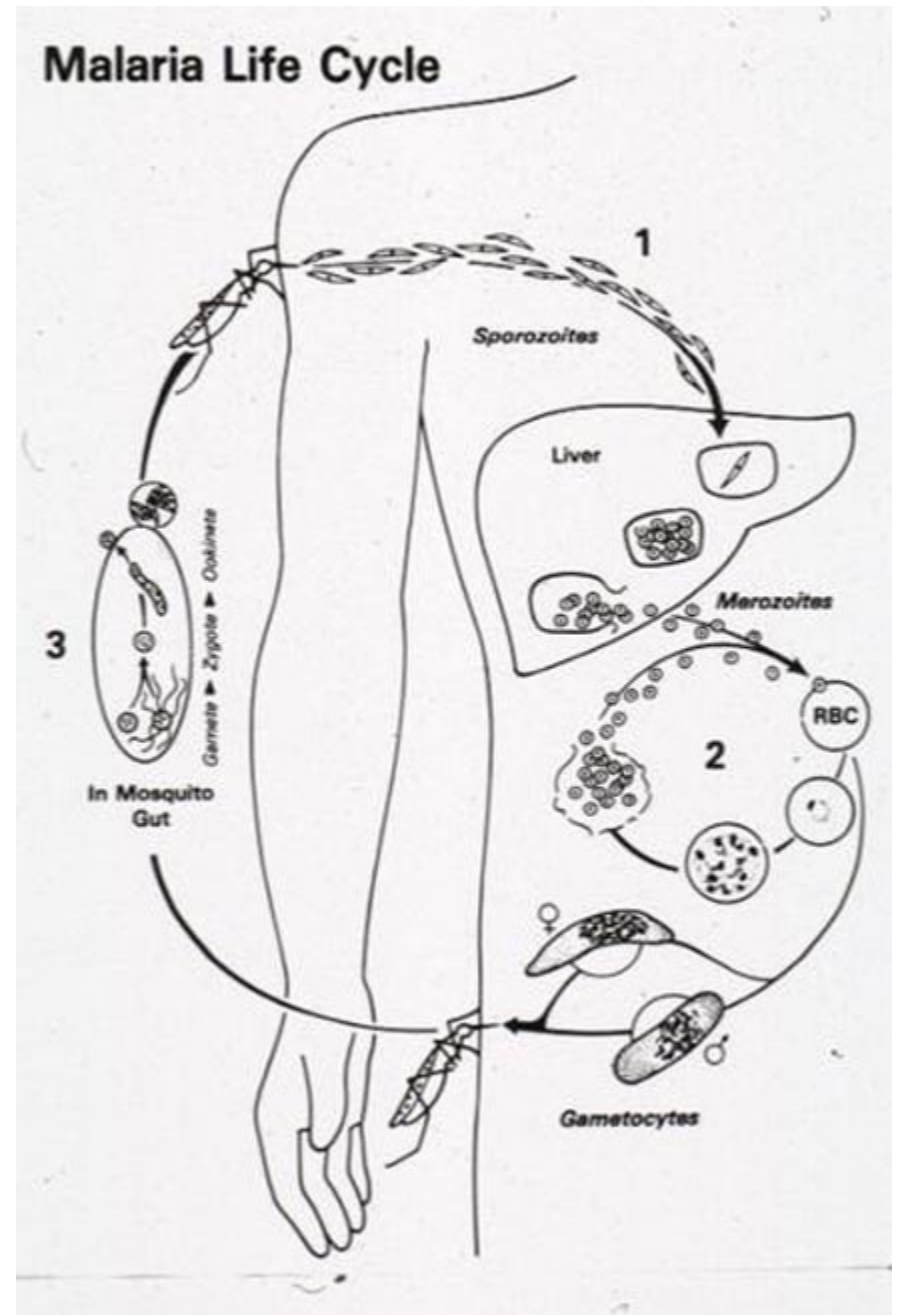
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MRTC – University of Bamako  
Mali

# Introduction

- Malaria is a complex parasitic disease that has shaped mankind
- Once a worldwide problem, malaria is confined to developing tropical world.
- Malaria is re-emerging in places where it had been eliminated
- Increasing mobilization of resources for research & control
- Where are we today and where are we heading?

# PLAN

- Brief historical prospective
- Current status
- Looking forward



# Vector side



# DDT era

- DDT => high expectation for the elimination of the malaria vector.
- Resistance and environmental concerns lead to the dismays of DDT.
- Environmental activists groups have even called for the total ban of DDT production.
- Development of new classes of insecticides

# Pyrethroids

- ITN = environmentally friendly vector control
- ITN = major component of malaria control in the field.
- New methods of incorporating the insecticide: long lasting nets (LLN) that resist several washes.

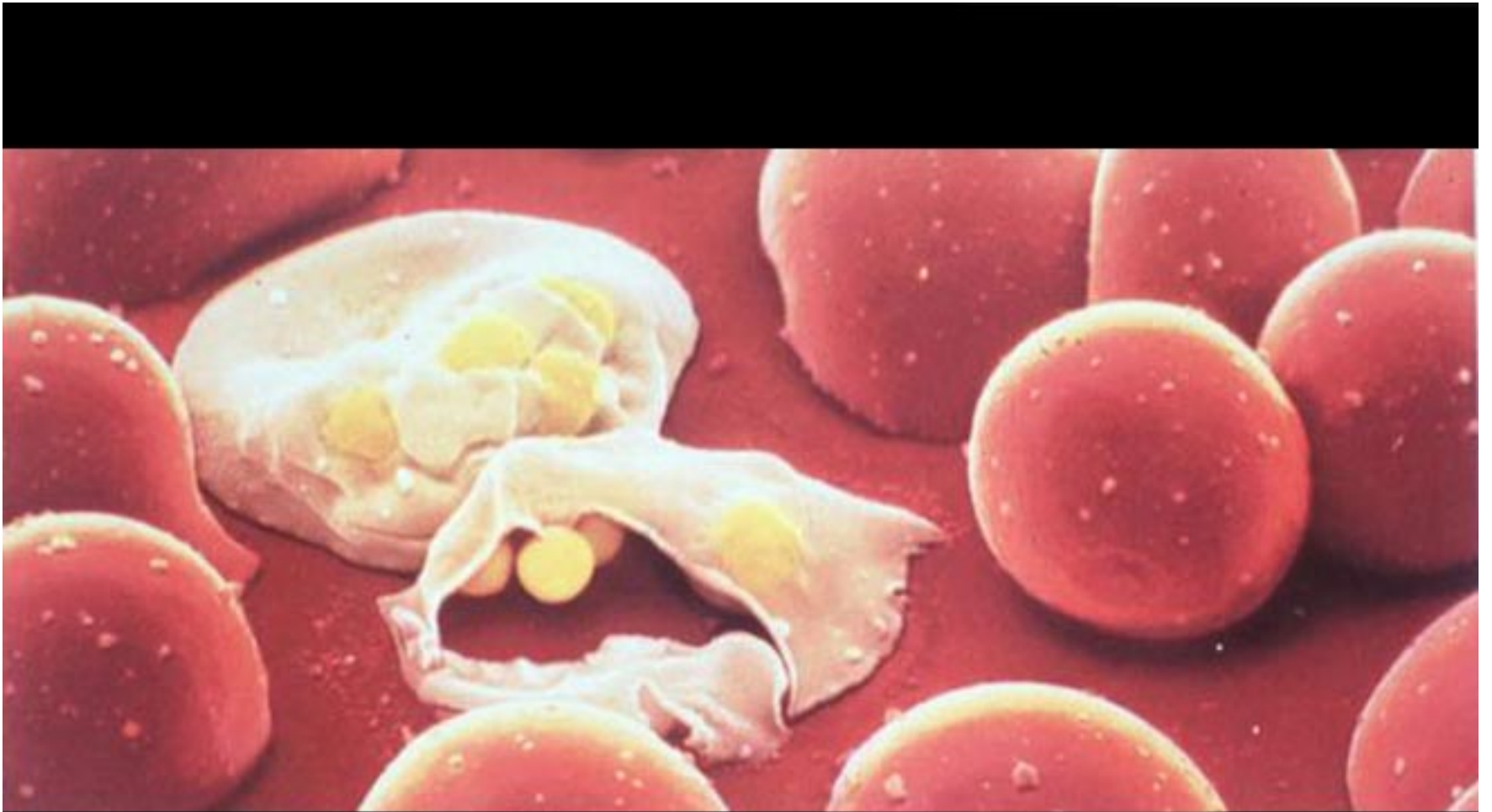
# IRS rediscovered

- Indoor residual spraying has been rediscovered
- This IRS is an important addition to the battery of vector control measures
- Other methods:
  - larvicides, bacteria
  - Plants
  - Environmental interventions

# New vector control measures

- Sterilize with radiations & release male mosquitoes
- Recent scientific breakthrough demonstrated the feasibility of genetic modification of the malaria vector.
- It is now possible to genetically engineer mosquitoes that may be refractory to the parasite, thus decreasing sharply their vector capacity.
- The implications of the release of such genetically modified mosquitoes in the environment are poorly understood.
- Age-specific anti-mosquito agents are being investigated in the lab

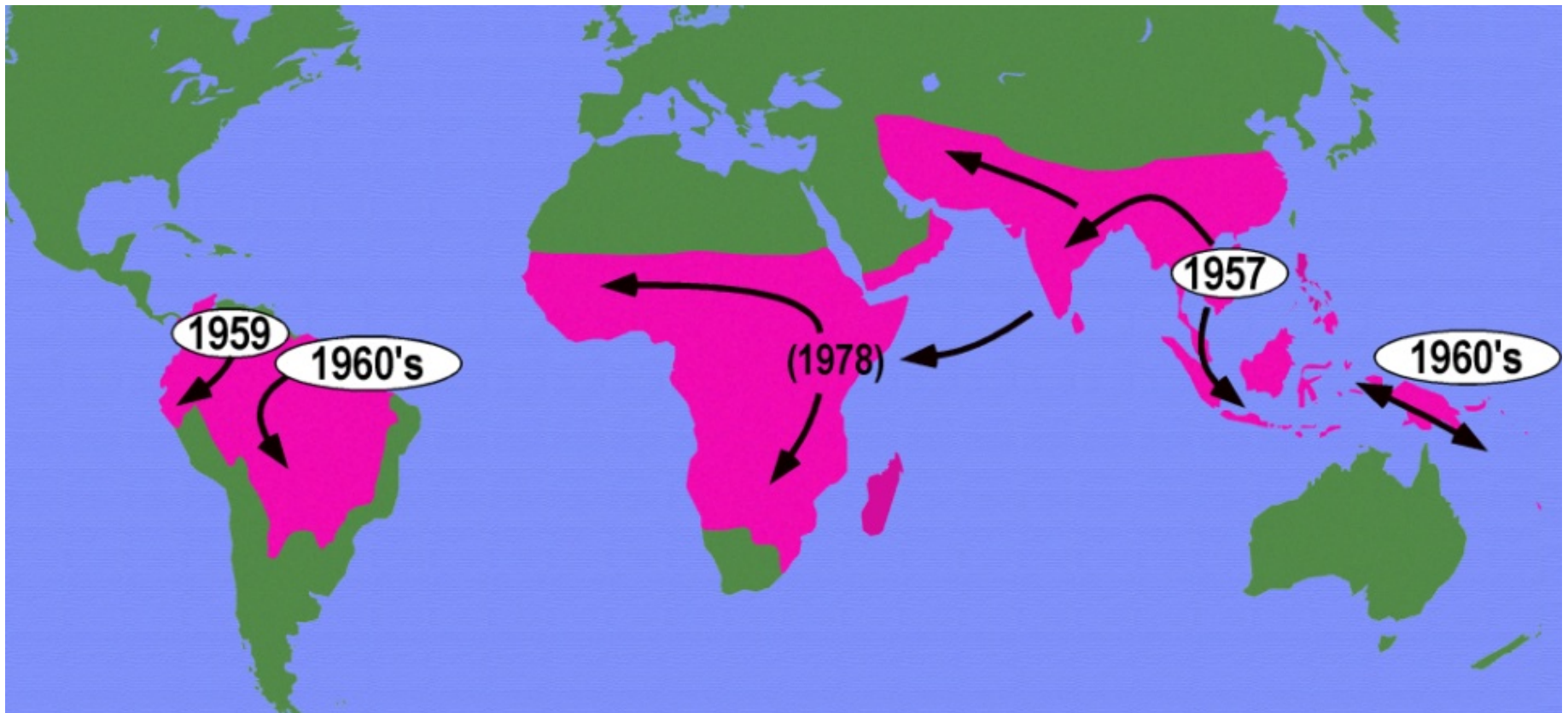
# Parasite side



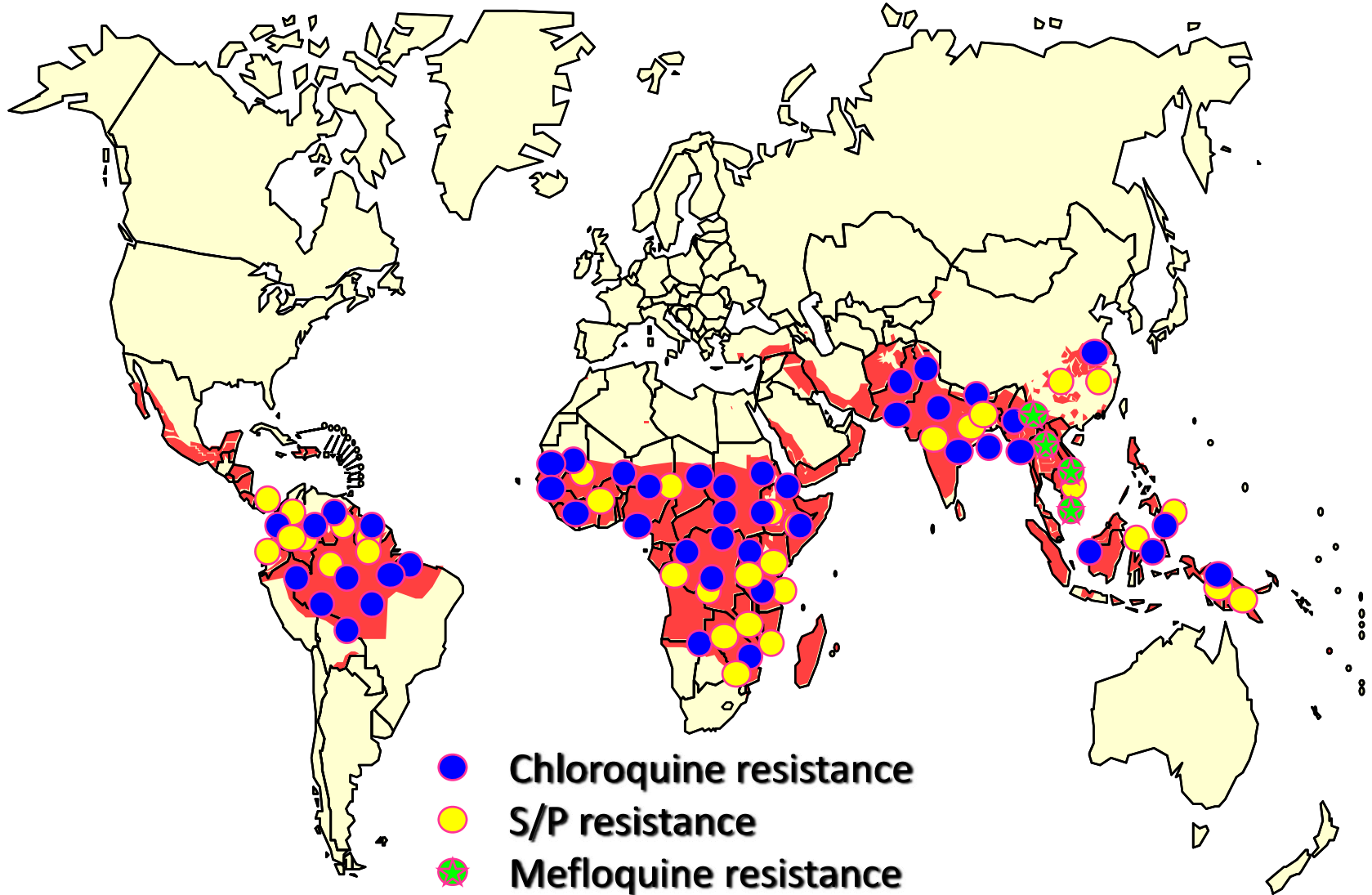
# Antimalarial drugs

- Chloroquine
- Sulfadoxine - Pyrimethamine
- Mefloquine
- Quinine

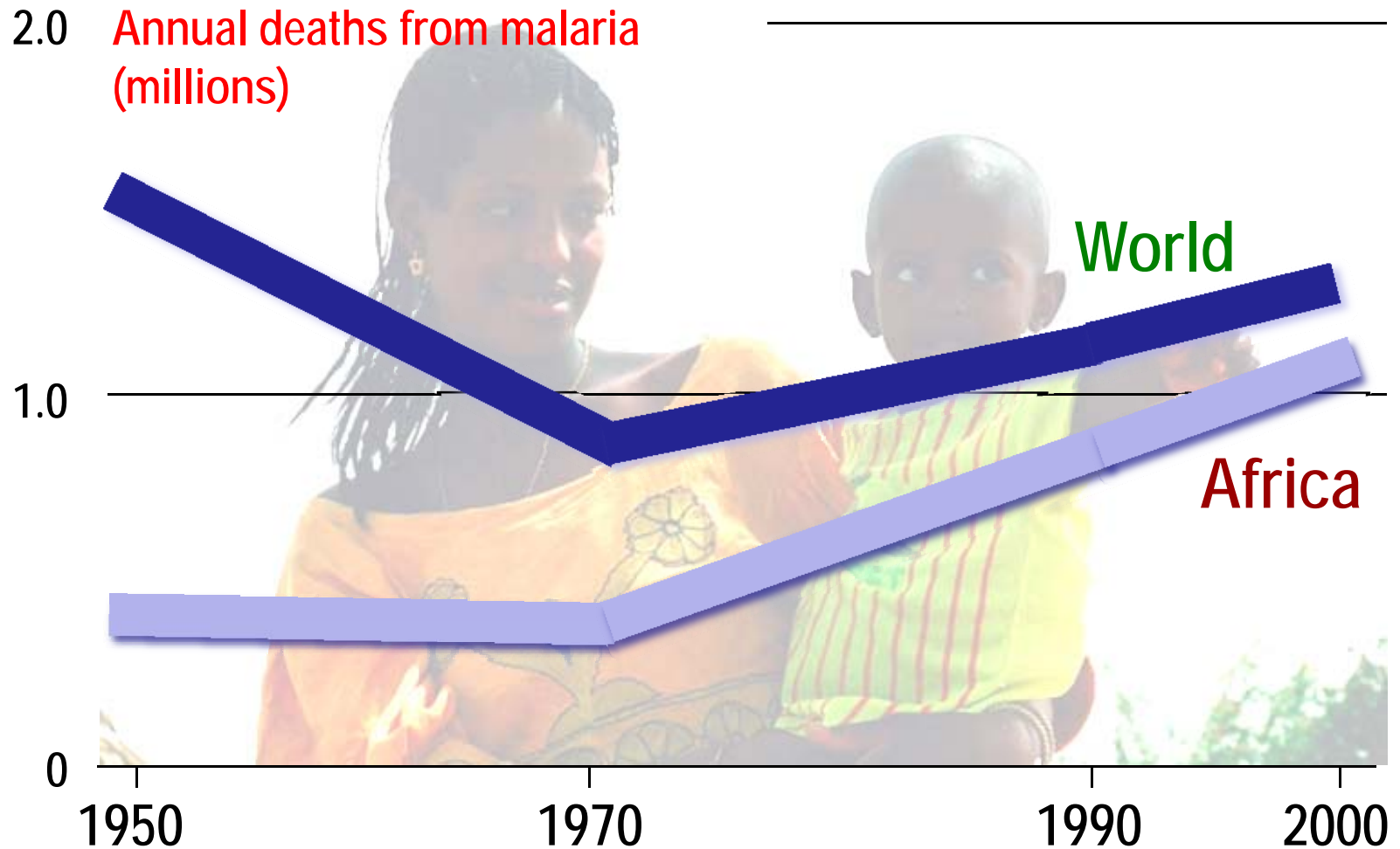
# Chloroquine resistance



# Antimalarial drug resistance worldwide, 2001



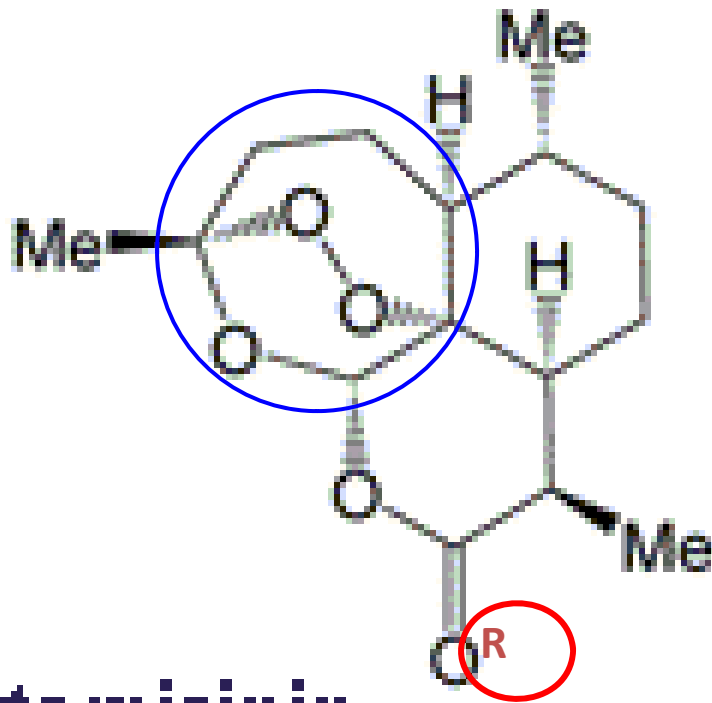
# Malaria winning?



(R. Carter, 1999)

ACT era

# Artemisinin

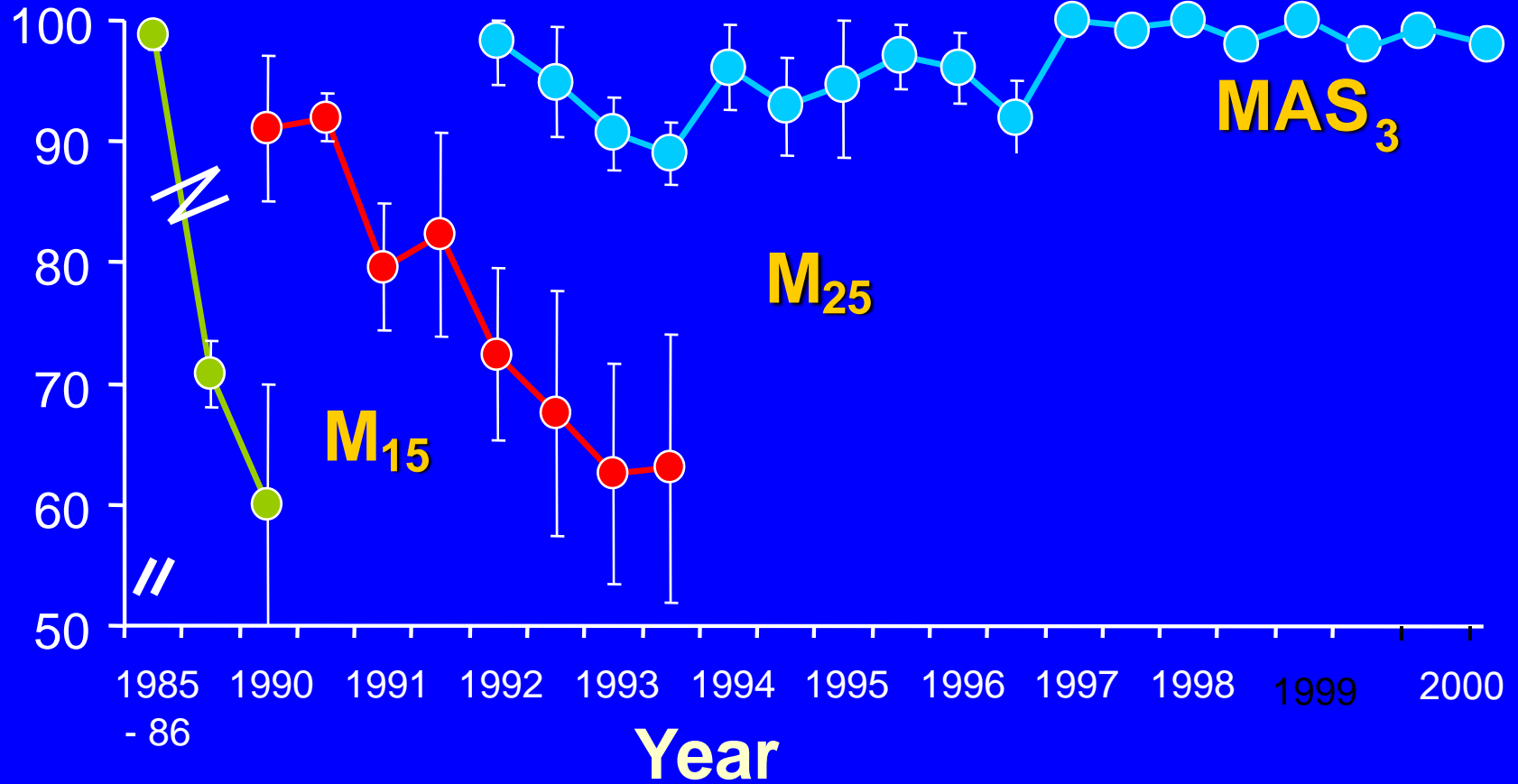


**arte misinin**

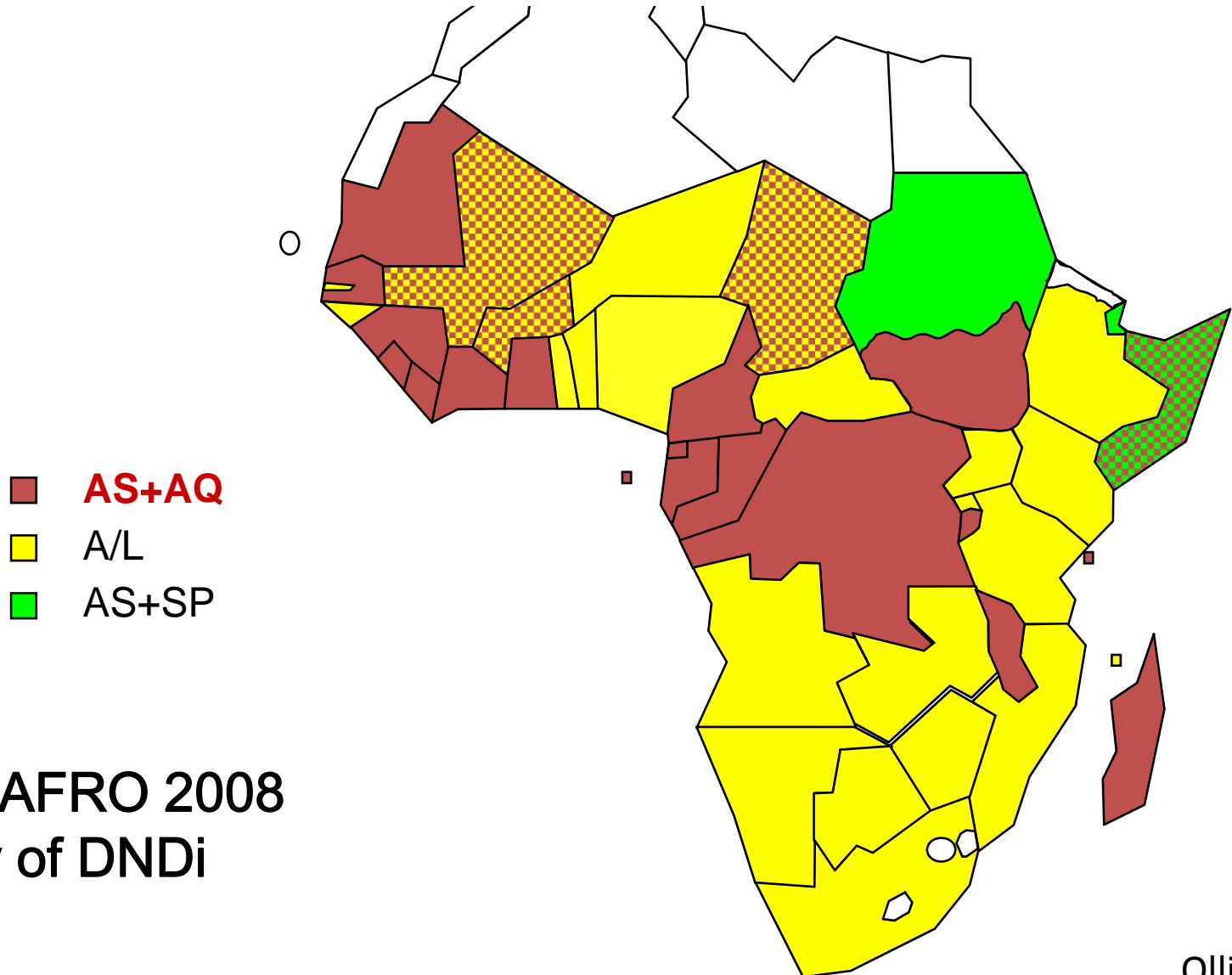
<u>R</u>	<u>Derivé</u>
H-	Dihydroartemisinin
CH3-	Artemether
CH2CH3-	Arteether
NaOOC(CH2)2COO-	Na Artesunate

NW border of Thailand; therapeutic responses to mefloquine

Cured (%)



# Countries where ACTs are 1<sup>st</sup> line for uncomplicated malaria



Source: AFRO 2008  
courtesy of DNDi

# Malaria Vaccines: Stages and Impact

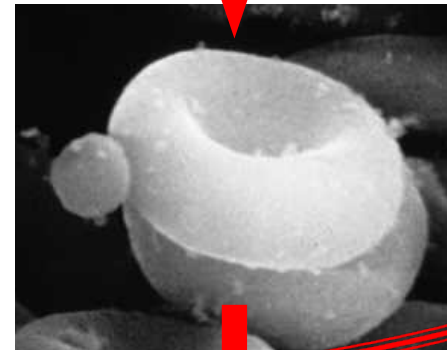
## Pre-erythrocytic

Vaccines to prevent infection and impact disease



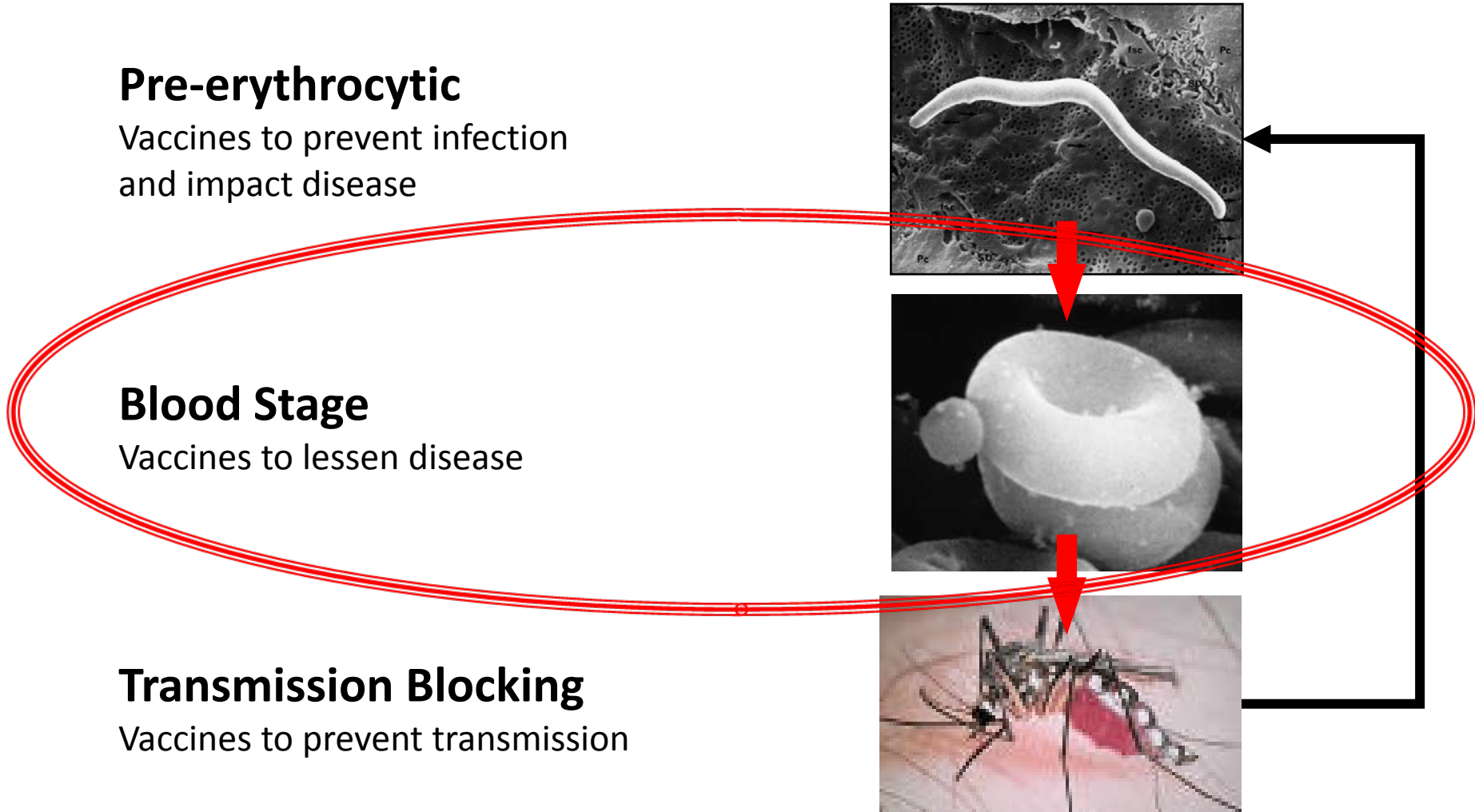
## Blood Stage

Vaccines to lessen disease



## Transmission Blocking

Vaccines to prevent transmission



# Vaccine story (cont.)

- The most advanced and leading candidates have been MSP1, AMA1, MSP3, and CSP based vaccines.
- Notably MSP1 based vaccines have made to Phase II clinical trials but have resulted into good antibody response but no protection in the field.
- Similarly, AMA1 based vaccine candidates have been in clinical trial at Phases I and II
- The most advanced vaccine is the CSP based RTS,S vaccine. This vaccine has showed encouraging protective effect mainly in decreasing the number of severe malaria cases in a number of Phase II trials. Phase III trials have recently been launched in several sites in sub-Saharan Africa.

# RTS,S: *Alonso et al., Lancet, 2004*

**Findings** 115 children in cohort 1 and 50 in cohort 2 did not receive all three doses and were excluded from the per-protocol analysis. Vaccine efficacy for the first clinical episodes was 29.9% (95% CI 11.0–44.8;  $p=0.004$ ). At the end of the 6-month observation period, prevalence of *P falciparum* infection was 37% lower in the RTS,S/AS02A group compared with the control group (11.9% vs 18.9%;  $p=0.0003$ ). Vaccine efficacy for severe malaria was 57.7% (95% CI 16.2–80.6;  $p=0.019$ ). In cohort 2, vaccine efficacy for extending time to first infection was 45.0% (31.4–55.9;  $p<0.0001$ ).

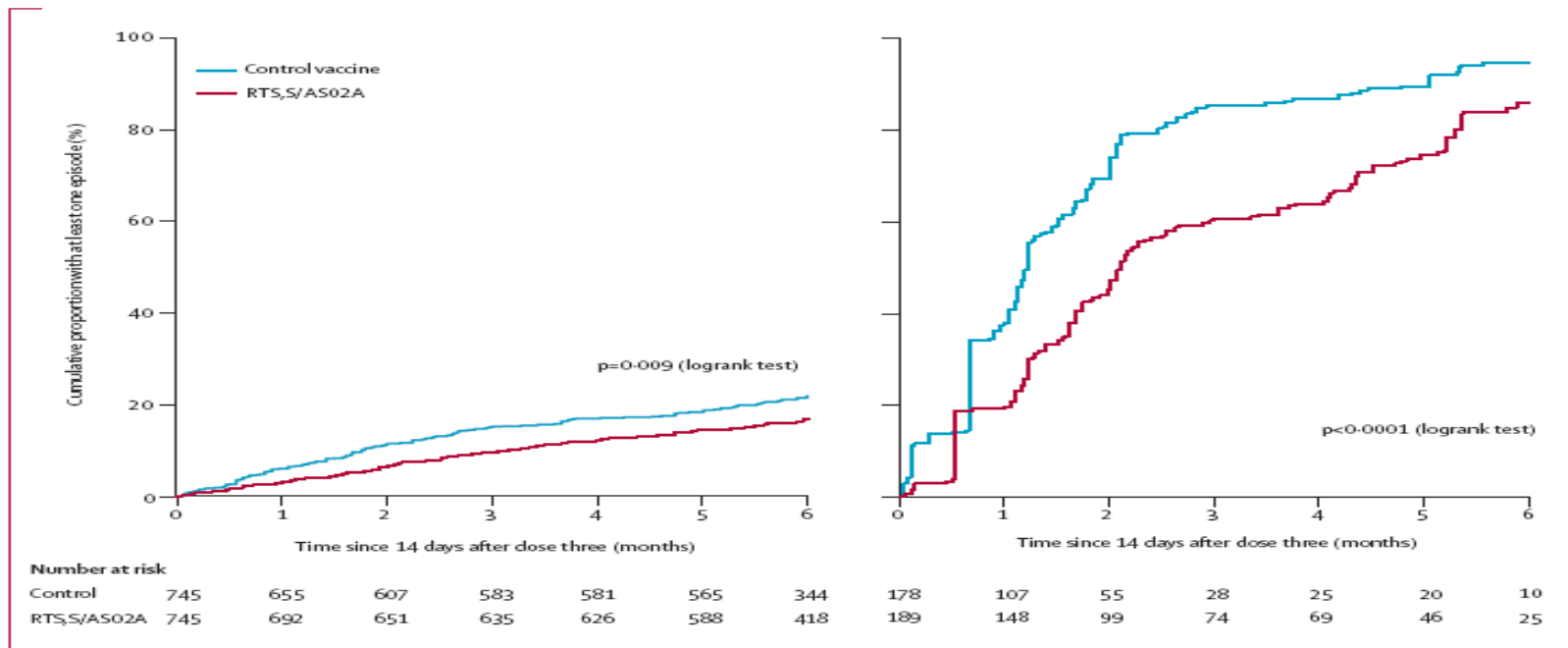
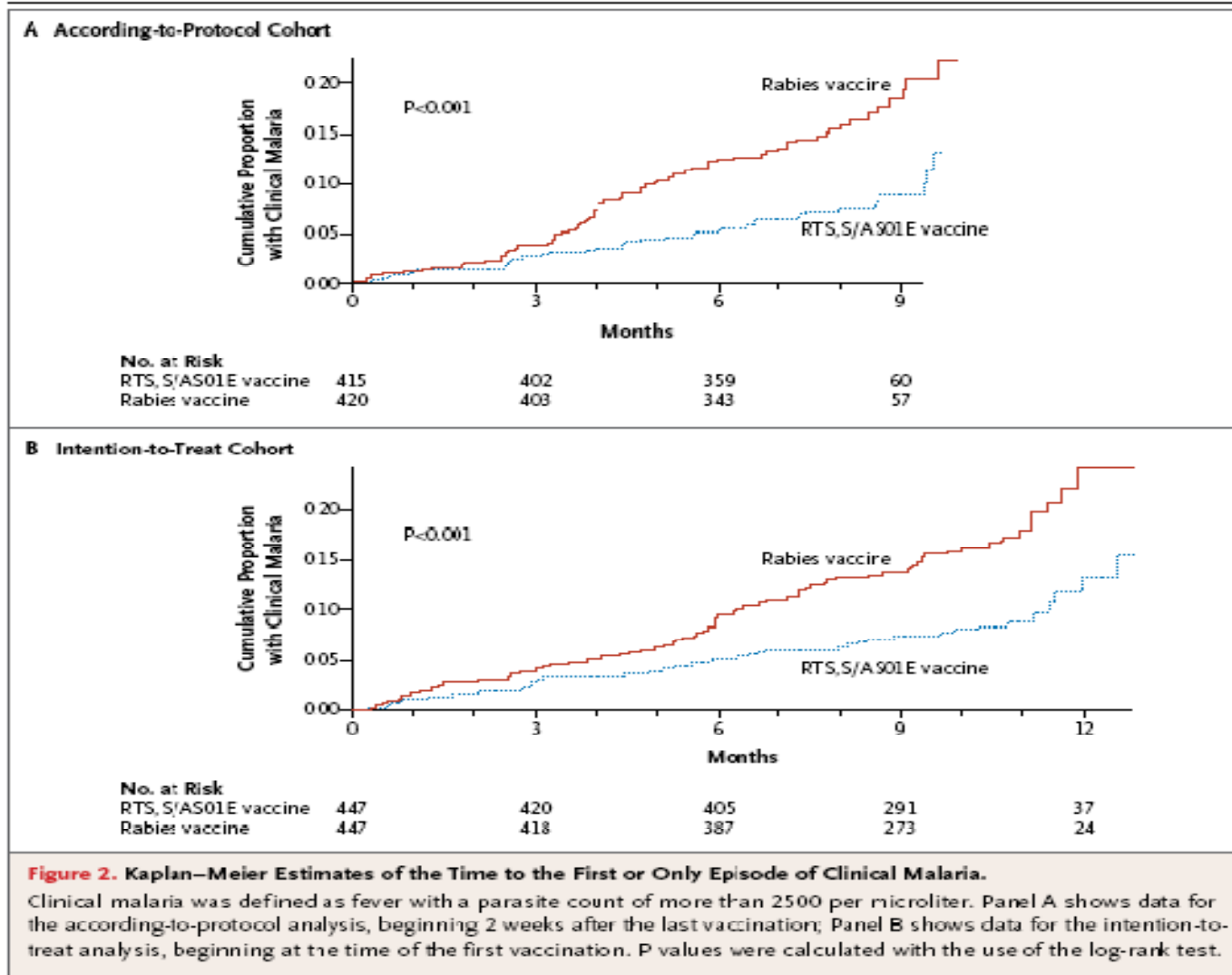


Figure 4: Kaplan-Meier curves for cumulative proportion with at least one episode of clinical malaria (left) or malaria infection (right)

# Bejon et al., NEJM, 2008



# Vaccines of tomorrow

- Historically, sporozoite attenuated by irradiation showed the most protection.
- However, technical difficulties in producing enough sporozoites
- Extraordinary efforts by Steve Hoffman *et al.* is raising hope for this type of vaccine.
- The production, irradiation, conservation and delivery processes appear to have been worked out.
- Phase I trials are underway in the United States.

# Vaccines of tomorrow (2)

- Development of genetically modified live parasites that are capable of invading hepatocytes but stop at various steps in the liver.
- Vaccine against gametocyte specific antigens Pfs48/45, Pfs25 and Pvs25 are under development
- The sequencing and continued annotation of the genome of *Plasmodium falciparum* is yielding new potential candidate antigens on a regular basis.

# Funding increase

- Funding significantly increased from private foundations, governments, non-governmental organizations and public-private partnerships.
- Major institutions that traditionally fund research have also increased their support for malaria research.
- Sharp increase in the overall level of funding for
  - malaria research,
  - large scale deployment of new tools (ITN, IRS, ACT)
  - Financial accessibility through subsidies

# Decline of malaria in selected foci

- A combination of IRS, case management with ACTs and active case detection resulted in the near elimination of malaria from Kwazulu Natal, South Africa.
- Large scale deployment ACT & ITN led to a sharp decrease of malaria in Zanzibar
- Similar decreases of malaria morbidity and mortality have been documented from Eritrea, Ethiopia, some parts of Kenya and The Gambia.

The “e-” word!

# Definitions

- Control of malaria: ***malaria is no longer a public health problem***
- Elimination of malaria: ***all local transmission stopped***
- Eradication of malaria: ***parasites have disappeared from earth, lab stocks still available***
- Extinction of malaria: ***parasite have completed disappeared from the Globe***

# Challenges on the road to elimination/eradication

# Mosquito resistance challenges

- Development of insecticide resistance to pyrethroids
- Prevalence of *kdr* gene mutations
- Changes in the behavior of the vector
- Need for new insecticides/combination of insecticides

# **Drug resistance challenges**

# Global Portefolio of Drug Development

Translational			Development	
Preclinical	Phase I	Phase II	Phase III	Approved <sup>†</sup>
MK 4815	Q2 430 Moraes/UMMC/STI	Artemone/ piperazine Rantony	Eurosim Sigma-Tau/MMV	Coartem-D Novartis/MMV
OSK pyridones 2 compounds	Isaquine GSK/MMV	Artemifone LI-KST/MMV	Pyrimax Shin-Puong/University of Iowa/MMV	Colticum sanofi-aventis/DNDI
(-)- Mefloquine Trosqui	Talaroquine Liverpool University	Fuansibmycin clindamycin Janssen	ASMO Far-Manguinho/ DNDI	
Novartis 2 compounds	4-Pyridone GSK/MMV	Felisoquine/ artesunate sanofi-aventis	Azithromycin/ chloroquine Pfizer	
Troxoquine Palumed/ sanofi-aventis	AQ-13 Innoco/Tulane	SAR 97276 CNRS/sanofi-aventis		
	CDR1 9776 Ipcu Laboratoires & CDR1	Methylene blue/ artemisinin Heidelberg/GDM		
		Tarbutamol WRAIR		

<sup>†</sup>with stringent international regulatory authority or prequalified.

P. Olliaro and T. Wells, 2009

## First reports of artemisinin resistance in S E Asia

# ACT treatment selects molecular markers of resistance to partner drug

## In Vivo Selection of *Plasmodium falciparum* *pfmdr1* 86N Coding Alleles by Artemether-Lumefantrine (Coartem)

Christin Sisowath,<sup>1</sup> Johan Strömberg,<sup>1</sup> Andreas Mårtensson,<sup>1</sup>  
Mwinyi Mselle,<sup>2</sup> Christine Obondo,<sup>3</sup> Anders Björkman,<sup>1</sup>  
and José P. Gil<sup>1</sup>

The Journal of Infectious Diseases 2005;191:1014-7

*Am. J. Trop. Med. Hyg.*, 78(5), 2008, pp. 459-461  
Copyright © 2008 by The American Society of Tropical Medicine and Hygiene

## Efficacy, Safety, and Selection of Molecular Markers of Drug Resistance by Two ACTs in Mali

Abdoulaye A. Djimdé,<sup>\*</sup> Bakary Fofana, Issaka Sagara, Bakary Sidibe, Sekou Toure, Demba Dembele, Souleymane Dama, Dinkorma Ouologuem, Alassane Dicko, and Ogobara K. Doumbo

***It is urgent to develop new antimalarial drugs***

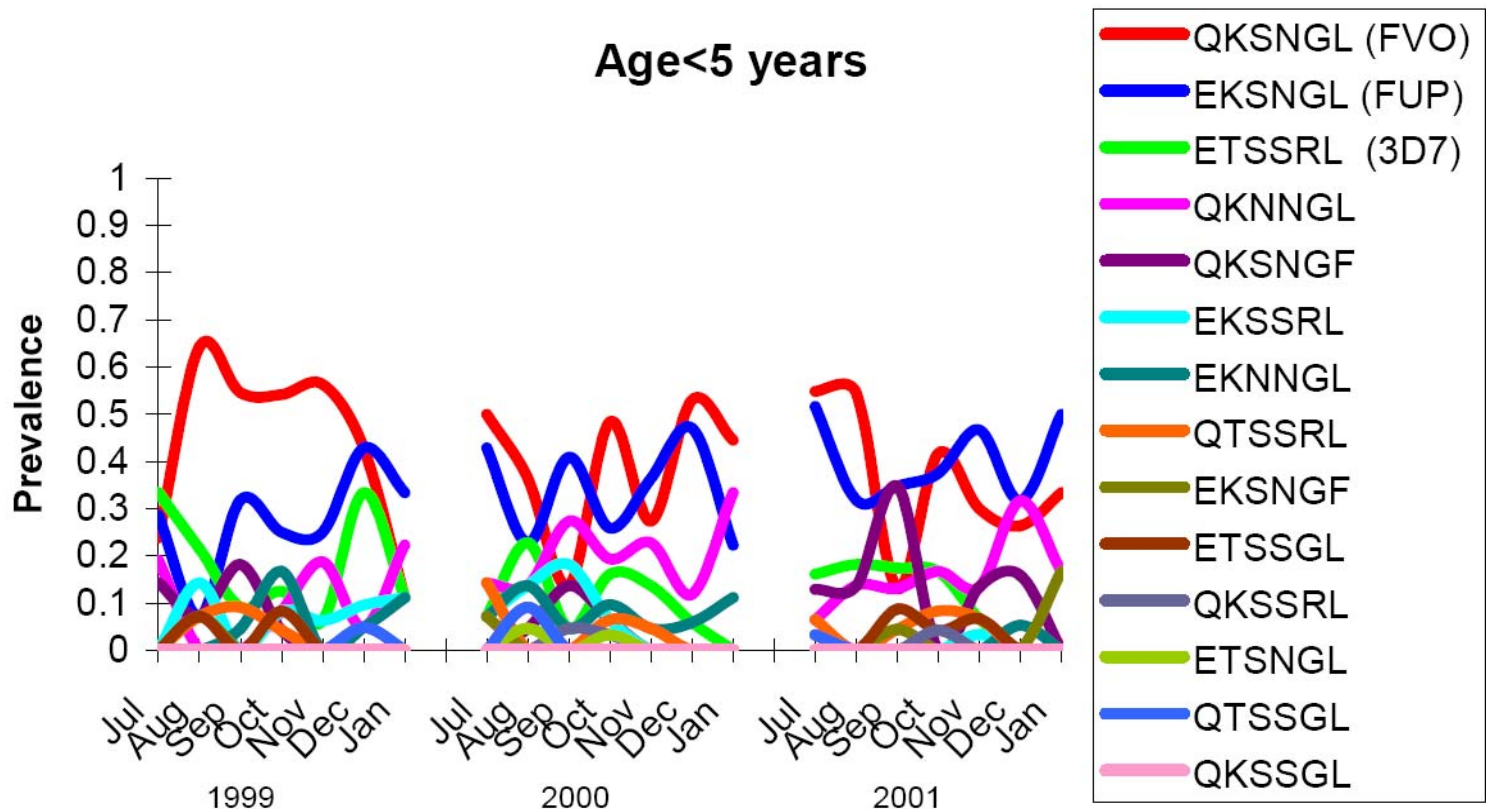
# VACCINE CHALLENGES

# Blood stage vaccines

- MSP1 & AMA1 have so far come short of expectations
  - MSP1
    - No efficacy in Phase 2b in Kenya => Reformulation
  - AMA1-C1/Alhydrogel
    - No efficacy in Phase 2b => Reformulation
- AMA1/AS02A
  - Results for Phase 2b pending
- AMA1-C1/Alhydrogel + CPG
  - Phase 1 in adult in progress
- MSP3
  - Phase 2b in progress

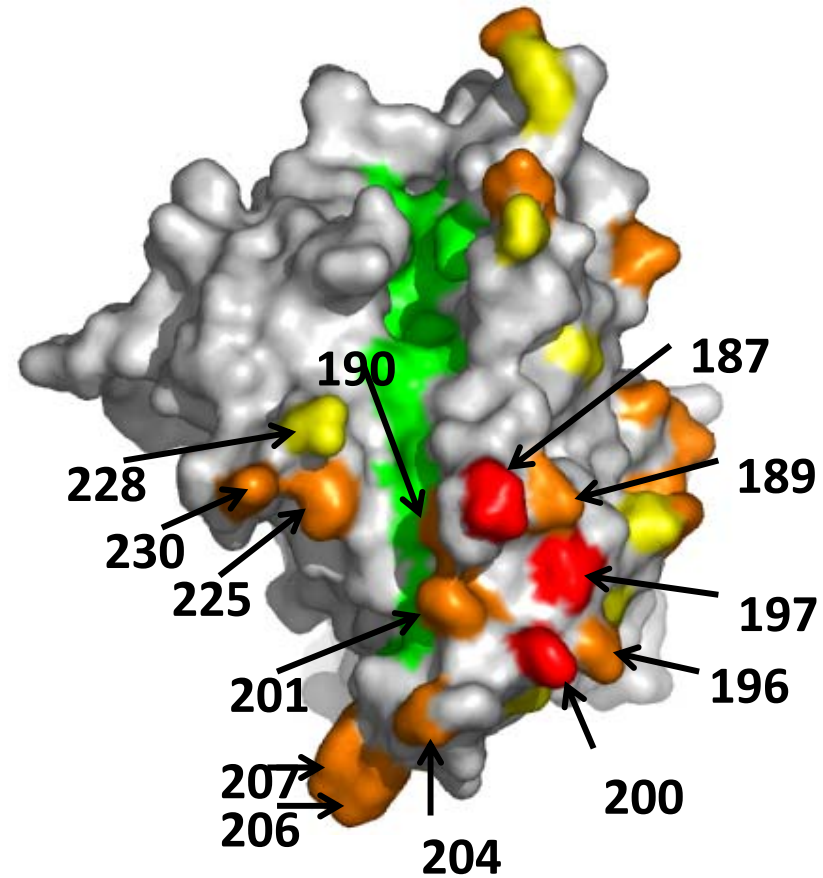
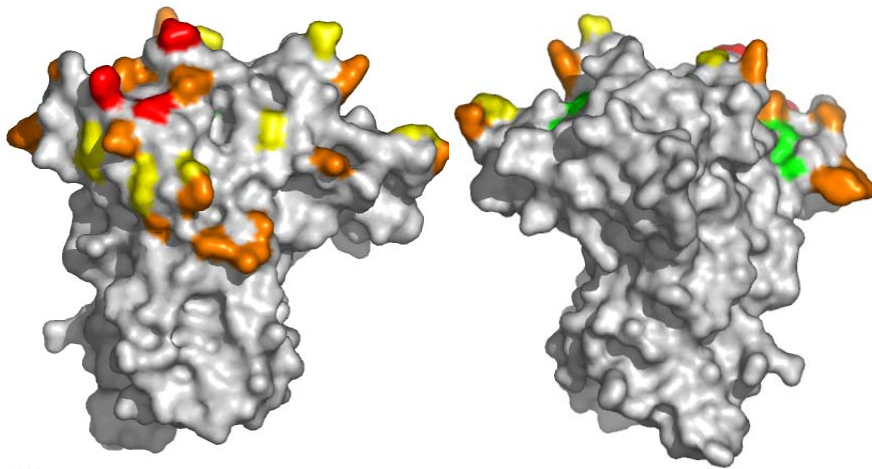
# Polymorphism in $MSP-1_{19}$ at a vaccine trial site

- 6 SNPs, 18 haplotypes among 1,369 infections
- 46% FVO
- 36% FUP
- 16% 3D7 – Vaccine strain



# Polymorphism in AMA-1

- 65 non-synonymous SNPs
- 450 sequences
- 201 unique haplotypes



# RTS,S

- RTS,S is known to provide  $\sim 50\%$  of protection from severe malaria
- How would RTS,S perform on the test of geography and time?

# Irradiated sporozoites

- Vaccine based on irradiated sporozoite is also now feasible and may soon be in trials in the field.
- In its current formulation this vaccine needs to be kept frozen until it is injected. This obviously will create daunting logistical issues in most malaria endemic countries where the maintenance of such an effective cold chain will be very difficult.

# Funding challenges

- Malaria continues to impose an intolerable burden on too many people.
- Despite the increase in funding, the current level of funding is not close to what is required to have a lasting impact on malaria in endemic countries, particularly in sub-Saharan Africa.
- It is estimated that \$9B will be needed per year to eradicate malaria. However, ~ \$4.5B is currently being actually spent on malaria

# Additional challenges

- **Health system challenges/scaling up delivery of ACTs and ITNs.**
  - The optimal delivery of the current tools has proven to be much more difficult than expected.
  - Level of organization and efficiency of the health systems in most sub-Saharan African countries.
  - Level of literacy of the population, level of training of health personnel, socio-cultural and economical considerations all contribute to the observed slow implementation of ACTs and ITNs in most African countries.
- **Capacity development challenges for scientists and institutions in the South.**
  - Low level of most researchers and research institutions in sub-Saharan Africa.
  - Need to improve the level of expertise and train a critical mass of scientists in disease endemic countries,
  - Critical to create, equip and nurture competent research institutions in the very places where malaria hits hardest if we really want to eliminate and eradicate malaria.

What are we doing about some of these challenges?

# Post-genomic era

- The entire genomes of the human host, the mosquito vector and the *P. falciparum* parasite have been sequenced.
- This resulted in a boom of “omics” including genomics, proteomics, metabolomics, transcriptomics etc.
- These new and vibrant fields of research have greatly increased our understanding of numerous processes in the biology of all these three parties of the malaria disease.
- New genes, proteins, RNAs, metabolic pathways, drug targets, vaccine targets, and diagnostic tools are being discovered and/or confirmed
- Sequencing technology experienced an unprecedented development.

# Genome-wide associations studies

- it is now possible to conduct genome-wide association studies that look at association of complex disease phenotypes with genetic variants across the entire genome of either the host, the vector or the parasite.
- Because of the scale of these analyses, they typically require very large samples sizes that can no longer be obtained by a single laboratory or a small number of investigators.
- One such landmark study was the WTCCC work on a number of diseases in the UK population

# Large sample sizes are needed

- *Many different genetic factors* may be involved. Individually they may be of modest magnitude.
- *Gene-gene and gene-environment interactions*
- *False positive associations* arise when hundreds of thousands of SNPs are tested. Large sample sizes needed to differentiate these from true positives.

# Malaria Genomic Epidemiology Network

## MalariaGEN

45 investigators in

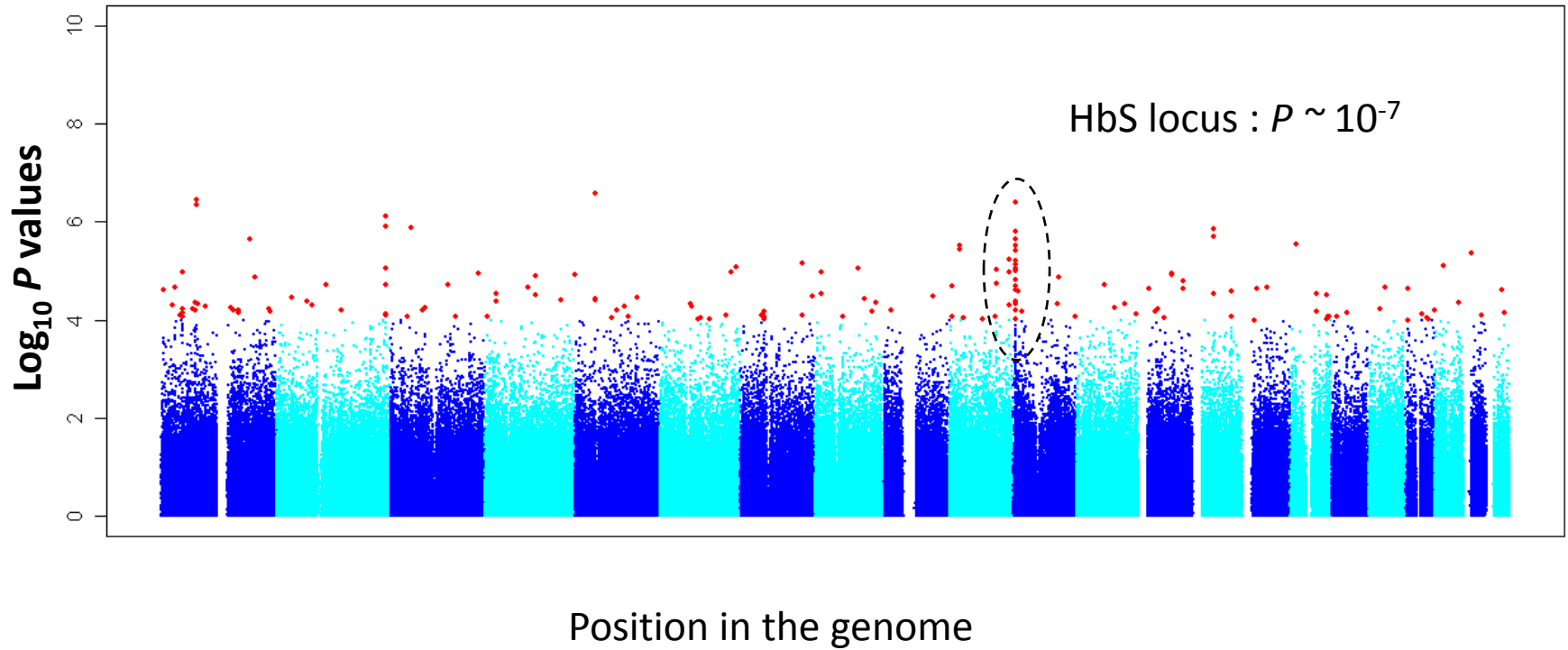


- **15 malaria endemic countries:** Burkina Faso, Cameroon, Gambia, Ghana, Ghana, Kenya, Malawi, Mali, Nigeria, Papua New Guinea, Senegal, Sudan, Tanzania, Thailand, Vietnam
- **6 non-endemic countries:** France, Germany, Italy, Sweden, UK, USA

We have developed a resource of DNA and clinical data from >50,000 subjects

# Proof-of-principle for GWA analysis in severe malaria

Pilot study of 500,000 SNPs typed in 1000 Gambian children with severe malaria and 1500 population controls



# Microarray platform at MRTC, Bamako



# Training workshop on chip hybridization



# Summary

- The technology is getting in place to interrogate malaria right from the field
- The challenges ahead can be summarized in two questions:
  - how can we effectively deliver the existing tools and
  - how can we better exploit the post-genomics era to invent and develop the new tools that are required for the eradication of malaria?

# Conclusion

The road to malaria eradication is still a very bumpy one. To get there we need to heavily invest in basic research to come up with new tools efficacious everywhere, stably efficacious and practical to deliver in the conditions of malaria endemic countries

# Support

- EDCTP
- HHMI
- NIAID/NIH
- MIM/TDR
- IAEA
- MalariaGEN Community