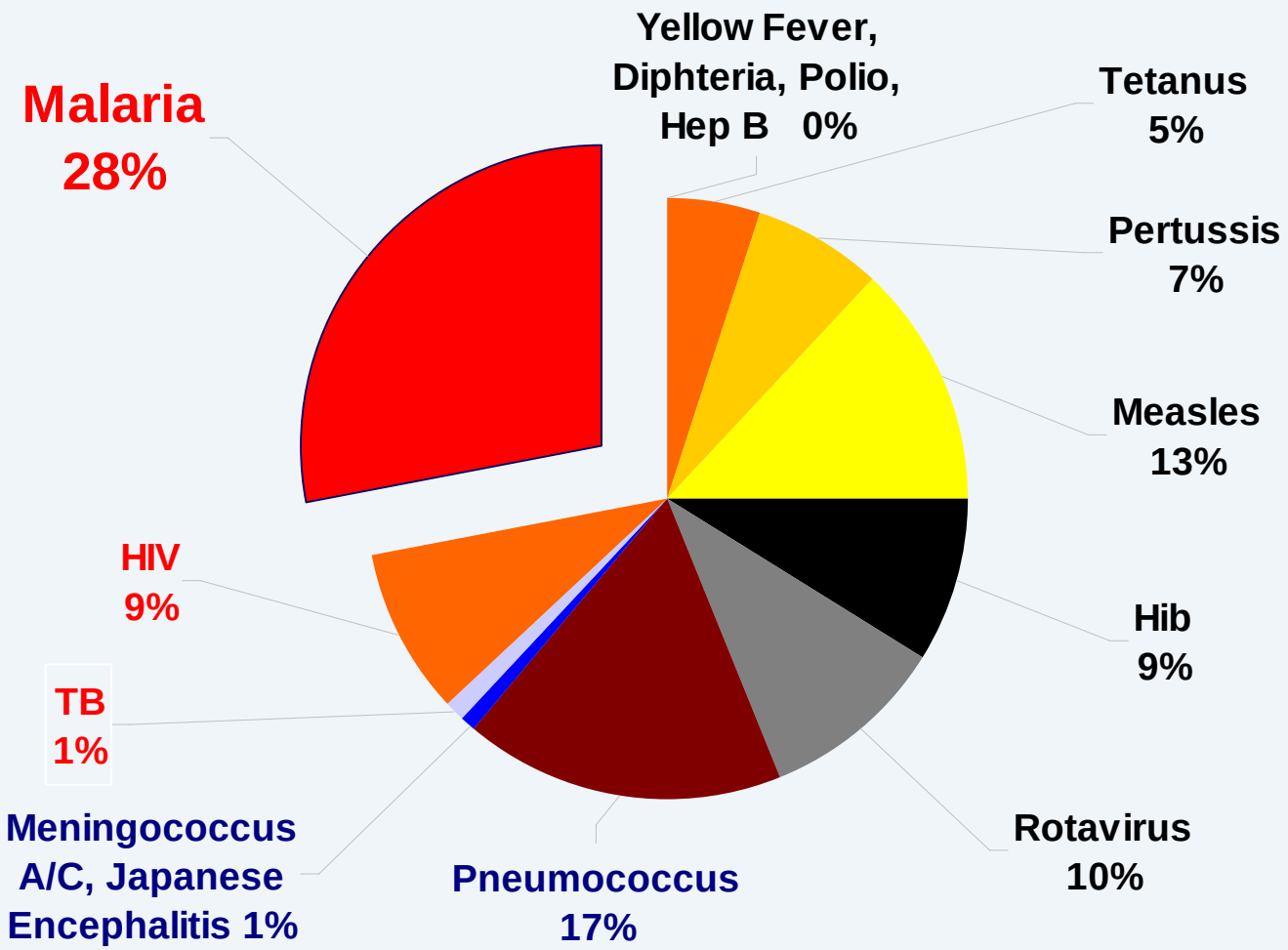
Development of a Malaria Vaccine for Sub-Saharan African Children

December 3, 2009
Lode Schuerman

Agenda

- Malaria
  - Disease burden
  - Prevention and vaccine development
- RTS,S vaccine
  - Vaccine design
  - Phase I early development
  - Phase II: overview of results
  - Phase III study design

Millions of children still die from preventable infectious diseases



WHO World Health Report 2004

The intolerable burden of malaria

3.3 billion people at risk, 50% of the world's population

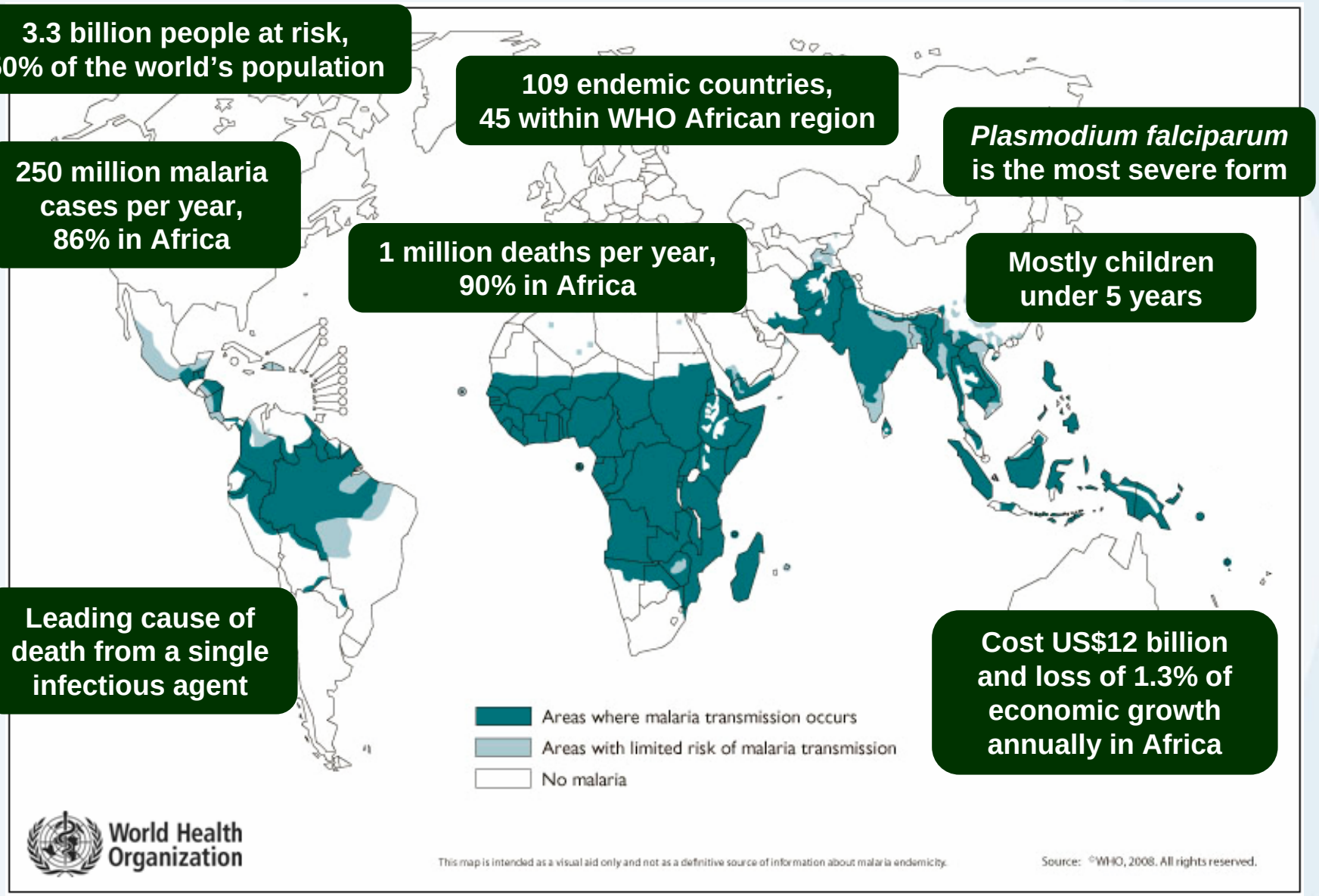
109 endemic countries, 45 within WHO African region

***Plasmodium falciparum* is the most severe form**

250 million malaria cases per year, 86% in Africa

1 million deaths per year, 90% in Africa

Mostly children under 5 years



Leading cause of death from a single infectious agent

Cost US$12 billion and loss of 1.3% of economic growth annually in Africa

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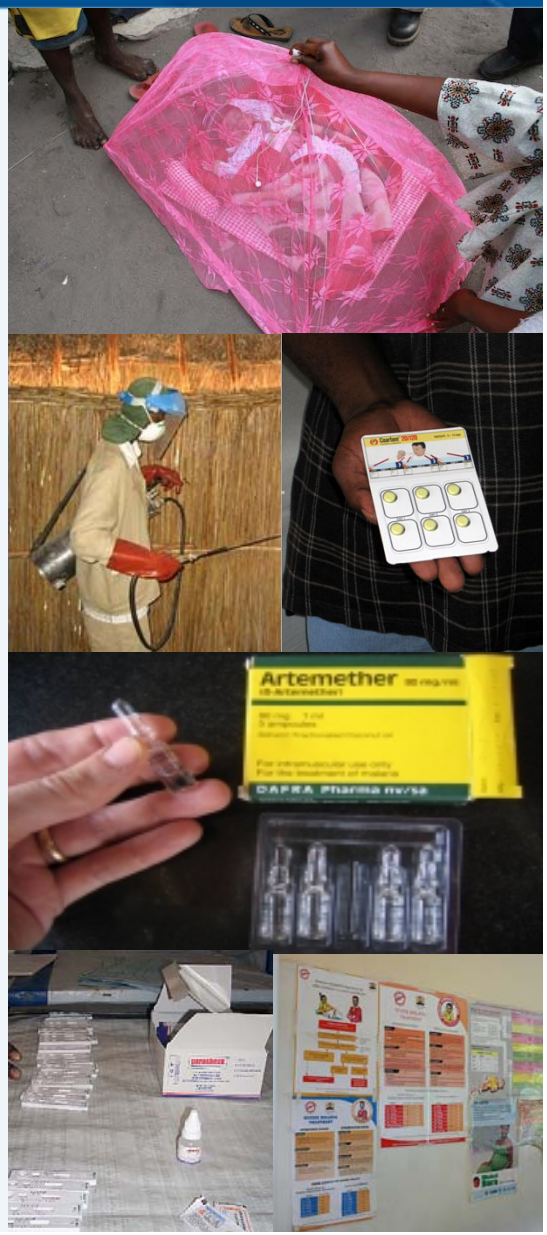
Fighting against malaria: tools available today

Preventive

- Insecticide Treated bedNets (ITNs) and Long-Lasting Insecticidal Nets (LLINs)
- Indoor Residual Spraying (IRS) and other Vector Controls
- Intermittent Preventive Treatment (IPT)
  - in pregnancy (IPTp)
  - in infancy (IPTi) or children (IPTc)

Curative

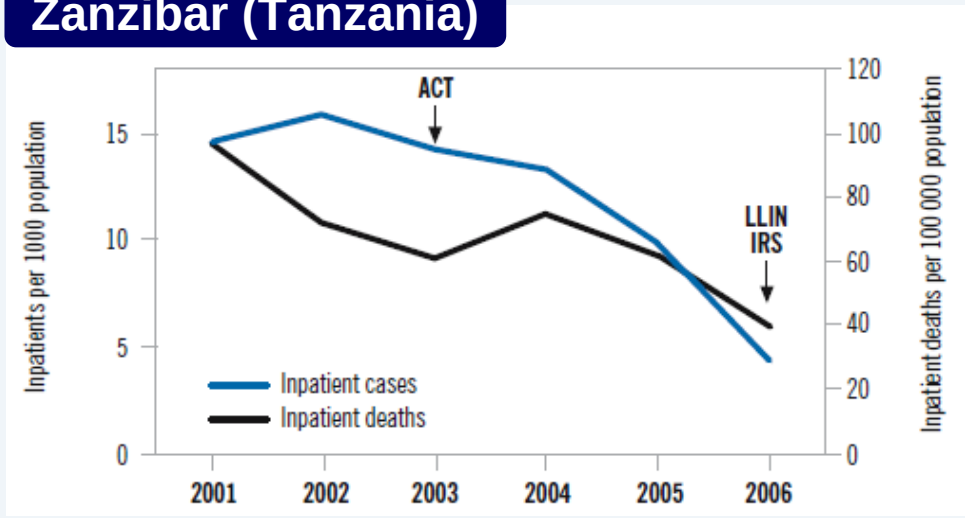
- Anti-malarial Drug Treatment (ACT, Artemisinin Combinations Therapy)
- Improved Malaria Case Management (RDTs, Rapid Diagnostic Tests)



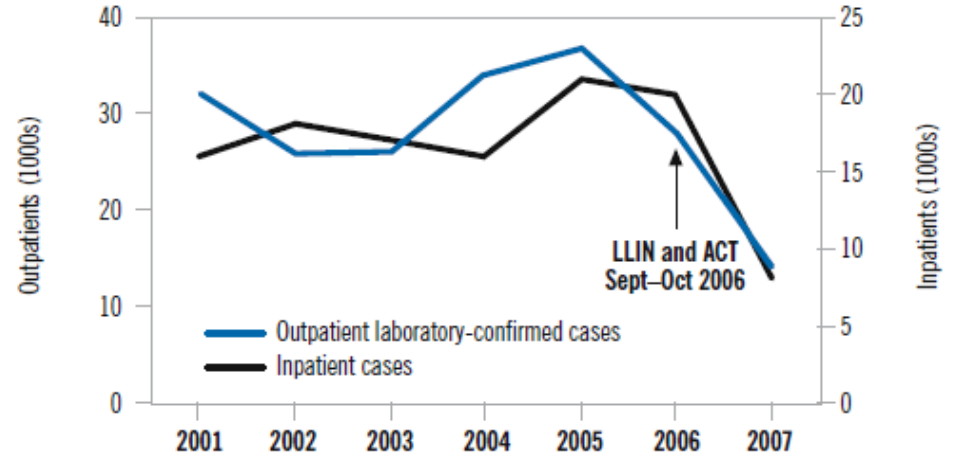
RBM Partnership web site. Global Malaria Action Plan, GMAP. Available from: <http://www.rbm.who.int/gmap/index.html> [Accessed: 15 June 2009]

Recent trends in malaria incidence

Zanzibar (Tanzania)



Rwanda



- **What caused these trends ?**
  - Usage of RDT ?
  - Implementation of LLIN ?
  - Treatment by ACT ?
  - Improved health care (training) ?
  - Changes in rainfall pattern and climate (droughts) ?
  - Changes in health information systems (in Zanzibar for example all other causes of hospitalization also decreased) ?

- **In Rwanda, malaria incidences increased again in 2008-09…**

The need for a malaria vaccine

- Important malaria disease burden, but those with the greatest need can least afford current prevention and control measures
- Challenges to Malaria Control in the SSA setting:
  - Parasite resistance to drugs
  - Mosquito resistance to insecticides
  - HIV co-infection
  - Climate change increasing suitable mosquito habitats
  - Inadequate infrastructure for delivery of control measures
  - Low compliance to protective measures
- Additional tools (such as a malaria vaccine channeled through EPI) would help to meet public health policy goals and targets

WHO IVR 2005, WHO 2008 malaria report, RBM GMAP 2008

A malaria vaccine will be an essential component of future malaria prevention and control measures

The development of a malaria vaccine

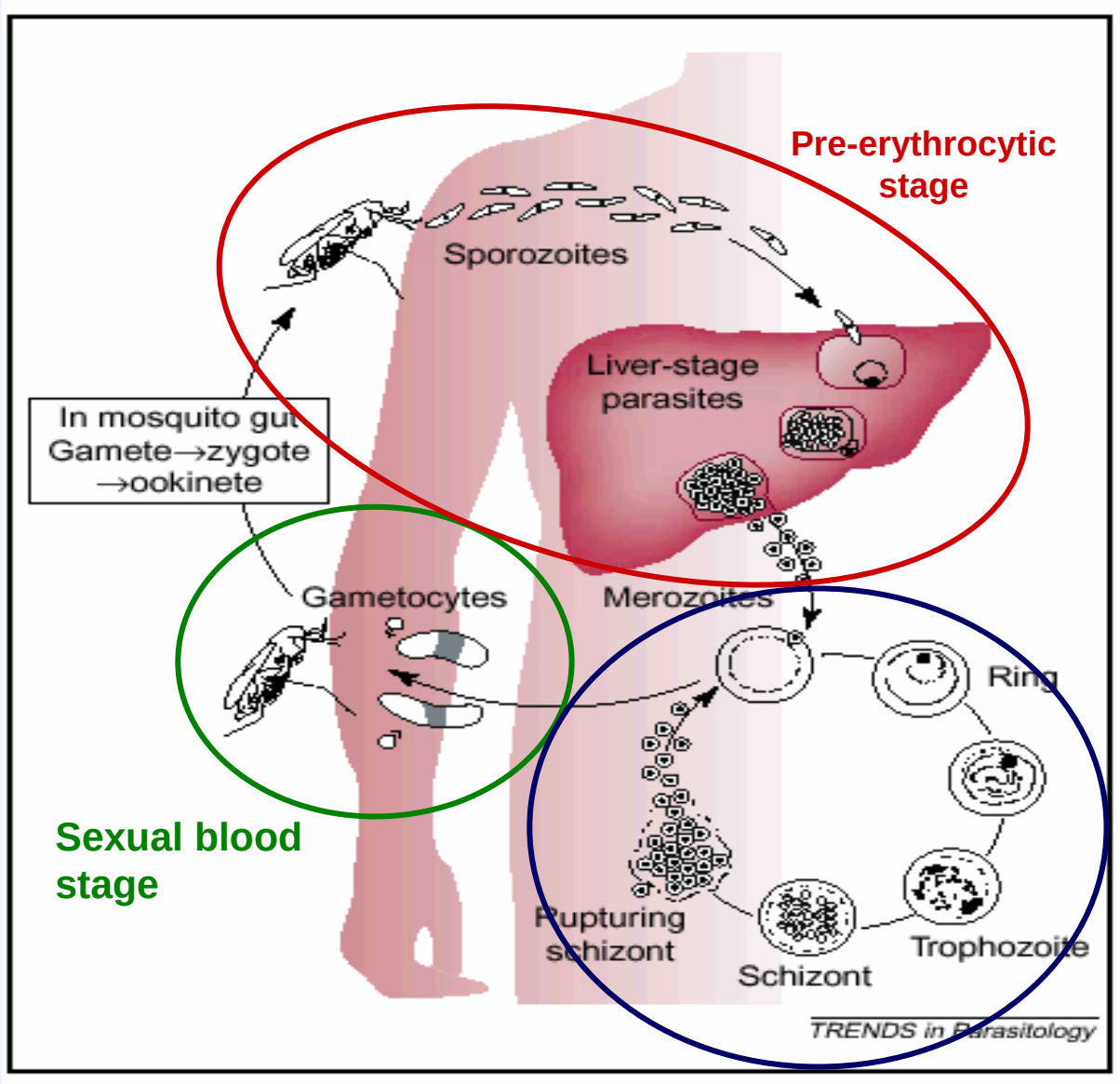
Challenging …

- Protozoan with a large genome: 14 chromosomes, 5-6000 genes
- Multistage life cycle with stage specific expression of proteins
- Allelic and antigenic variation
- Human immune response is complex and genetically variable

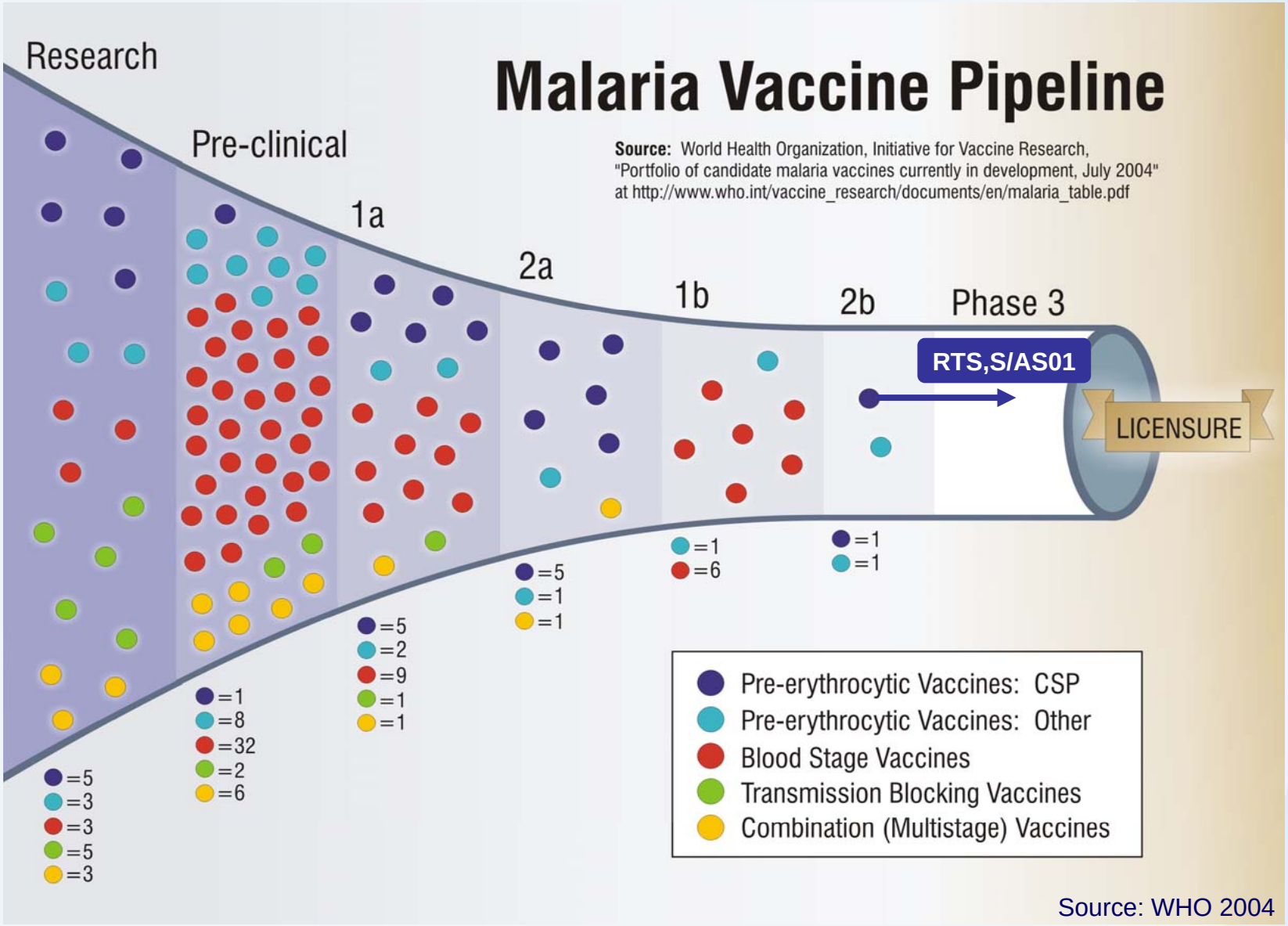
… but feasible

- Acquisition of natural immunity against disease in individuals living in endemic regions
- Protective immunity has been achieved in several malaria animal models (by active immunization as well as passive transfer of monoclonal antibodies and T cells)
- Passive transfer of protection by purified immunoglobulins obtained from immune adults
- Active immunization of mice and humans with radiation-treated sporozoites confers sterile immunity

Plasmodium falciparum life cycle



Malaria Vaccine Pipeline



Source: WHO 2004

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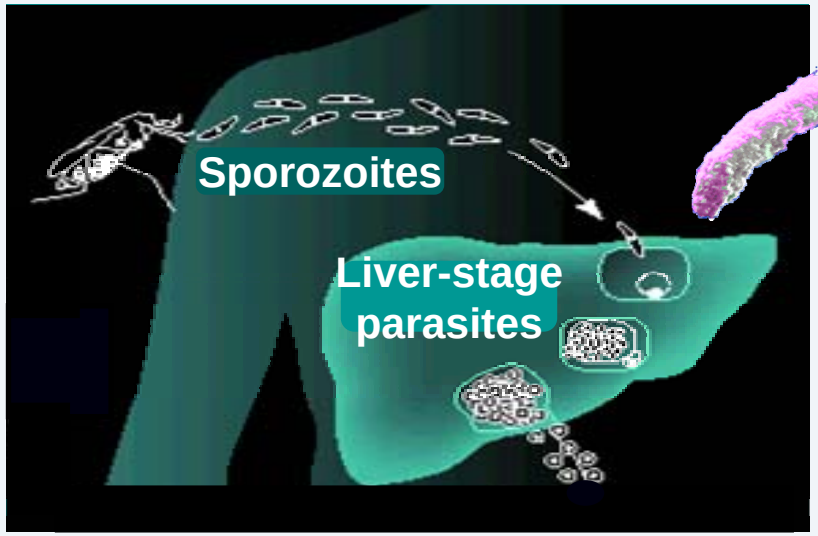
Objectives of the RTS,S Malaria Vaccine Candidate Development Program

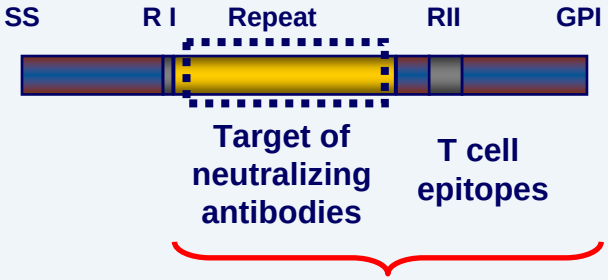
- ✓ **Develop a vaccine that will protect infants and children residing in malaria endemic regions from clinical disease and severe malaria resulting from *Plasmodium falciparum* infection**
- ✓ **Safe and well tolerated**
- ✓ **Compatible with standard EPI vaccines (DTPw , HBV, Hib, OPV…)**
- ✓ **Implementable through existing delivery programs such as the EPI**
- ✓ **Complements existing malaria control measures**

The RTS,S pre-erythrocytic antigen



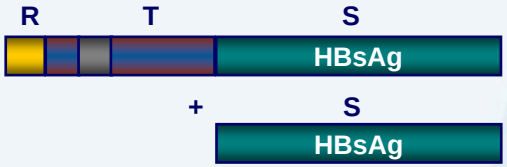
Circumsporozoite Protein:

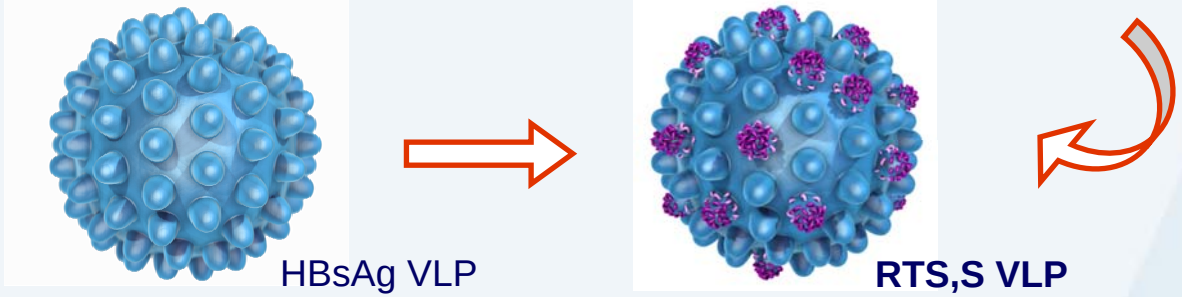
- ✓ Major surface protein of the sporozoite
- ✓ Involved in binding of sporozoite to liver cells



Generation of RTS,S virus-like particles

Co-expression of RTS (fusion protein) and HBS protein in *Saccharomyces cerevisiae*. Spontaneously assemble into mixed virus-like particles (VLP)





Gordon et al. J Infect Dis 1995

The Adjuvant System

- Designed to induce strong antibody and Th-1 cell mediated immune responses
- Immunostimulants:
  - QS21: Saponin extract of *Quillaja saponaria*
  - MPL: Monophosphoryl Lipid A

with:

- Oil-in-water emulsion (= AS02)
  or
- Liposome suspension (= AS01)

} Clinical development with both adjuvant systems in parallel

⇨ select the best one for phase III

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First Proof of Concept (PoC) for efficacy of the RTS,S vaccine against *P. falciparum* infection

Human challenge model at the Walter Read Army Institute of Research

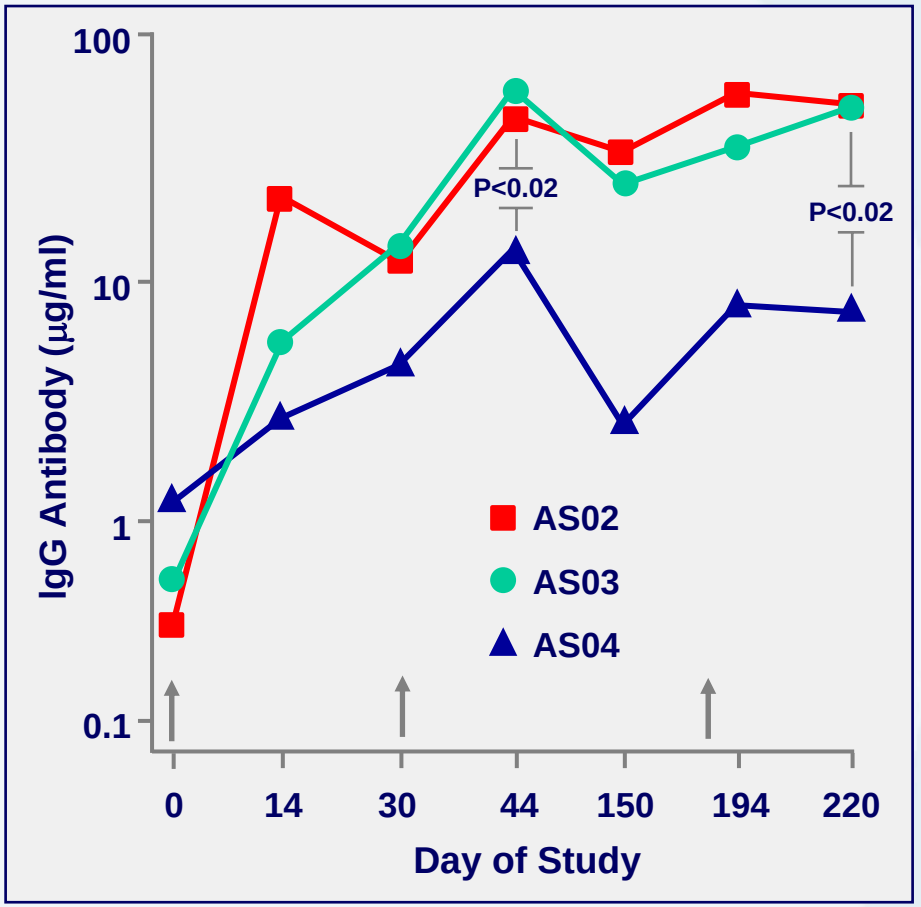
Vaccine	# Challenged	# Infected
None	6	6
RTS,S/AS04	8	7
RTS,S/AS03	7	5
RTS,S/AS02	7	1

The most efficacious formulation is the one that consistently induced the best humoral and CMI responses in preclinical testing

Stoute JA et al. N. Engl. J. Med. 336(2), 86–91 (1997)

Antibodies against the CS protein of *Plasmodium falciparum* in vaccinated volunteers

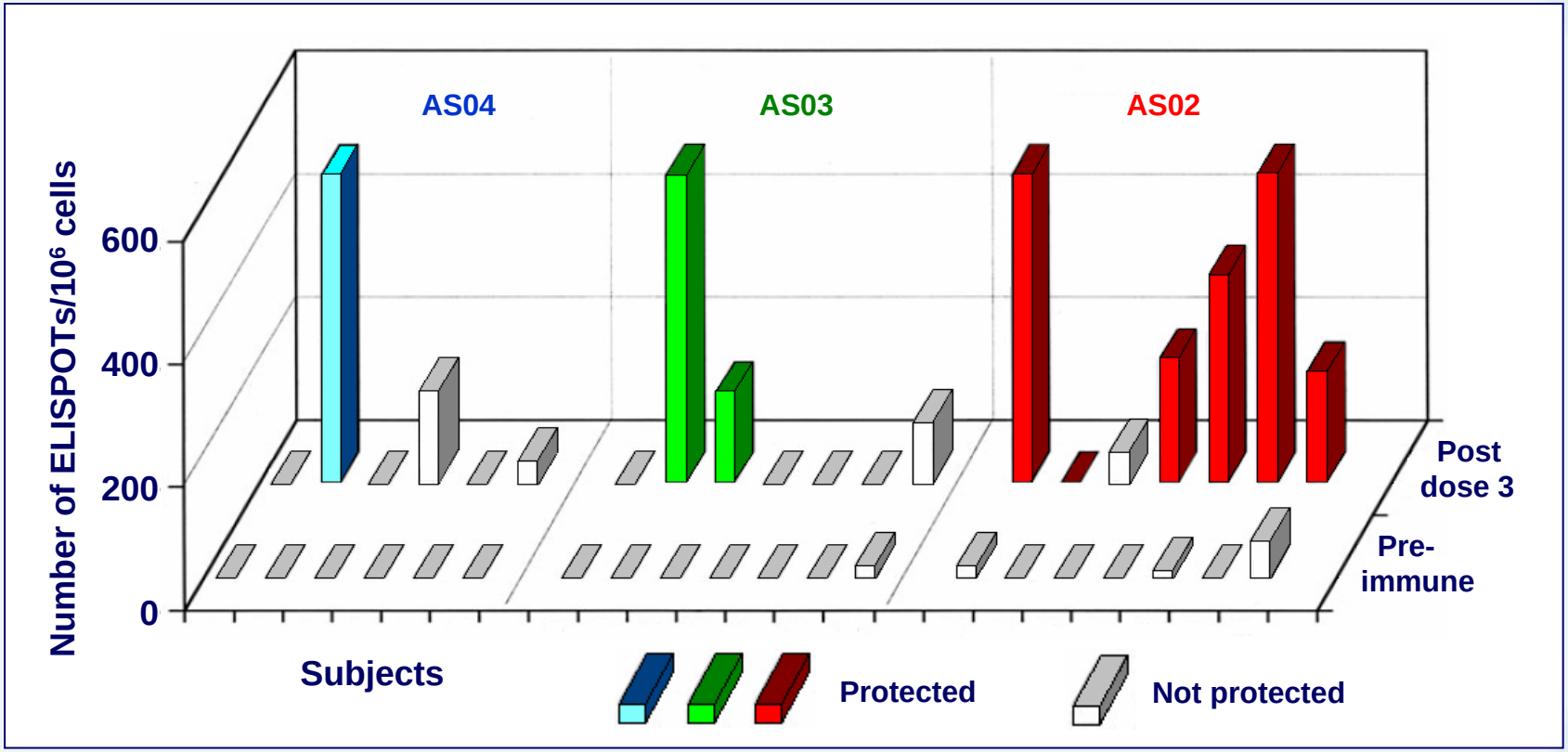
- Different RTS,S vaccine formulations with different Adjuvant Systems
- Antibody responses against tandem-repeat epitopes (ELISA with recombinant R32LR)



Stoute JA et al. N. Engl. J. Med. 336 (2), 86–91 (1997)

Cell mediated immune responses in vaccinated volunteers

IFN γ responses in volunteers immunized with different formulations of RTS,S and association with protective efficacy



Sun et al J of Immunol: 171 (2), 6961-7 (2003)

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Efficacy of RTS,S/AS against malaria in African children (supported by PATH-MVI)

Population (age)	Vaccine Efficacy	Efficacy	Significance (p-value)	Duration of follow-up
1-4 years[1,2,3]	Clinical malaria	**35%**	<0.001	18 months
	Severe malaria	**49%**	0.02	18 months
	Hospitalized malaria	**31%**	0.032	18 months
	All clinical episodes	**26%**	<0.001	42 months
	Severe malaria	**38%**	0.045	42 months
5-17 months[4]	Clinical malaria	**53%**	<0.001	8 months
	All clinical episodes	**56%**	<0.001	8 months
10 weeks[5]	Clinical malaria	**66%**	0.007	3 months
8 weeks[6] (+EPI)	Clinical malaria	**43%**	0.24	6 months

- **Unprecedented and significant reduction of clinical & severe malaria episodes, across different malaria transmission settings**
- **Clinical benefit extending over 42 months following vaccination**
- **Could have a major impact on burden of malaria**

1. Alonso et al, Lancet 2004; 364: 1411-20 – 2. Alonso et al, Lancet 2005, 366: 2012-18 – 3. Sacarlal et al JID 2009, 200: 329-36 – 4. Bejon et al 2008 NEJM 359; 24: 2521-32 – 5. Aponte et al. Lancet 2007; 370: 1543-51 – 6. Abdulla et al. NEJM 2008; 359: 2533-44

RTS,S safety and tolerability profile

- Over 8,000 doses of RTS,S/AS02 or AS01 administered to more than 3,000 children/infants (6 wks to 6 yrs of age)
- Reactogenicity pattern comparable to control vaccines including routine EPI vaccines
- Laboratory safety monitoring: no apparent safety signal
- Favourable assessment of differences in frequency of SAEs (RTS,S vs control)

1. Alonso et al. Lancet 2004; 364: 1411-20 – 2. Alonso et al. Lancet 2005, 366: 2012-18 – 3. Sacarlal et al. JID 2009, 200: 329-36 – 4. Bejon et al 2008 NEJM 359; 24: 2521-32 – 5. Aponte et al. Lancet 2007; 370: 1543-51 – 6. Abdulla et al. NEJM 2008; 359: 2533-44 – 7. Agnandji et al MIM 2009

SAEs following RTS,S/AS01 in infants (N=341, Tanzania, Ghana & Gabon)

	RTS,S/AS01(012) + DTPw-HepB/Hib (N = 170)		DTPw-HepB/Hib (N = 171)	
	%	(95% CI)	**%**	(95% CI)
Any SAE	**22.9**	(17 – 30)	**21.1**	(15 – 28)
Gastroenteritis	**11.2**	(7 – 17)	**8.2**	(5 – 13)
Pneumonia	**6.5**	(3 – 11)	**5.8**	(3 – 11)
Anaemia	**3.5**	(1 – 8)	**8.2**	(5 – 13)
***P. falciparum* infection**	**2.9**	(1 – 7)	**9.4**	(5 – 15)
URTI	**2.4**	(1 – 6)	**3.5**	(1 – 8)
Impetigo	**1.8**	(0 – 5)	**2.3**	(1 – 6)

SAEs occurring within 8 months of follow-up, in at least 2% of subjects in any of the vaccine groups

Agnandji et al MIM 2009

Anti-CS immune responses

- Strong antibody response to the *P. falciparum* circumsporozoite (CS) repeat domain (anti-CS) in all age groups
- Anti-CS antibodies consistently associated with protection against infection in the adult challenge model and in field trials with children and infants, but no correlate of protection could be defined.
- Anti-CS antibody levels wane over time, but remain significantly higher compared to control groups up to 42 months after the last vaccine dose
- Robust CS-specific CD4 T-cell responses induced in malaria naïve adult volunteers and associated with protection against infection in challenge model (Kester et al. JID 2009)

Summary of Phase 2 findings

- Unprecedented and consistent efficacy demonstrated in different transmission settings in Kenya, Mozambique and Tanzania
  - Beneficial effect on clinical and severe disease up to 42 months after the last vaccine dose
  - Trend toward higher efficacy against severe forms of disease
  - Trend toward higher efficacy with the AS01 Adjuvant System (Kester et al. JID 2009; Bejon et al NEJM 2008)
- Favorable safety & reactogenicity profile
  - Trend towards clinical benefit on all cause morbidity and mortality
- Can be co-administered within routine infant EPI immunizations (compatible in terms of safety, efficacy & immune responses)
- Induction of CS-specific humoral and cell mediated Immune responses shown to be associated with protection against infection

« GO » FOR PHASE 3!

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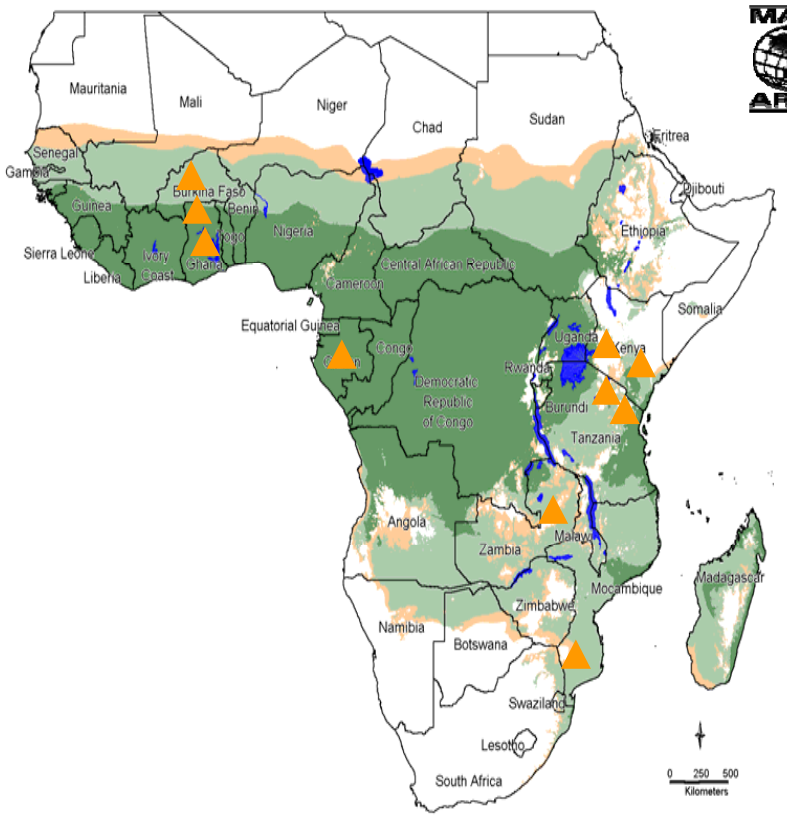
Phase 3 multi-center efficacy trial

- 11 centers in 7 African countries
- Sites represent different malaria transmission settings
- Up to 16,000 children in 2 age categories:
  - 6 weeks to 12 weeks in EPI co-ad
  - 5 to 17 months
- Designed in collaboration with scientific community, with feedback of MALVAC*, WHO, FDA, EMEA and African National Regulatory Agencies



Number of months of suitable climate

	No transmission in average year
1-3 months	Epidemic or strongly seasonal
4-6 months	Endemic and seasonal
7-12 months	Endemic and perennial

**Moorthy V. et al. Vaccine 2008*
http://www.clinicaltrials.gov/ct2/show/NCT00866619?term=malaria+efficacy&rank=2

Efficacy Objectives

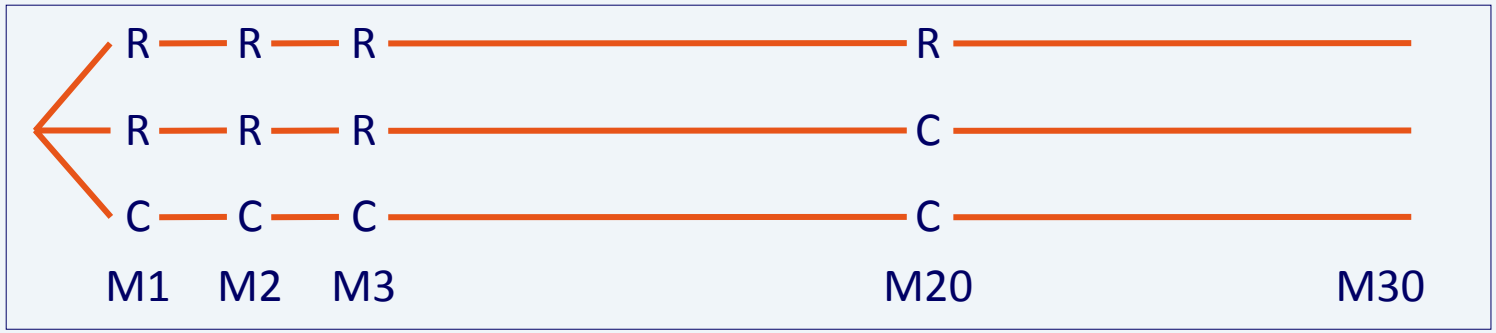
- **Co-primary objectives:**
  - Efficacy against clinical malaria disease over 1 year post dose 3 in:
    - Children aged 5 to 17 months
    - Infants aged 6 weeks at first dose (EPI co-administration)
- **Secondary objectives:**
  - Efficacy against severe malaria disease
  - Prevention of malaria hospitalization
  - Prevention of anemia
  - Efficacy against clinical malaria in different transmission settings
  - Duration of efficacy to 2.5 years post dose 3
  - Requirement for a booster dose
  - Efficacy against fatal malaria and all-cause mortality*
  - Efficacy against other serious illness*
  - All-cause hospitalization, sepsis and pneumonia

*uncertain power

http://www.clinicaltrials.gov/ct2/show/NCT00866619?term=malaria+efficacy&rank=2

Duration of efficacy

- Duration of efficacy up to 30 months post primary series
  - Time periods: overall, pre and post booster
  - Assessed as efficacy against first episodes and all episodes
- Evaluation of requirement for a booster at 18 months post primary
  - Evaluated as efficacy post booster



R = RTS,S/AS01 **C = Control vaccine**

http://www.clinicaltrials.gov/ct2/show/NCT00866619?term=malaria+efficacy&rank=2

Conclusion from clinical studies to date

- The RTS,S vaccine is the first malaria vaccine candidate to demonstrate that young children and infants exposed to intense *Plasmodium falciparum* transmission can be protected from infection and malaria disease.
- If this vaccine is licensed (after the level of efficacy across various transmission settings has been clarified in the ongoing phase 3 study), it could have a major societal, economic and public health impact in malaria-endemic regions in Sub-Saharan Africa.

Abdulla et al. NEJM 2008;359:2533-44 – Ally Olotu et al. MIM 2009 – Alonso et al. Lancet 2004;364:1411-20 – Alonso et al. Lancet 2005;366: 2012-8 – Aponte et al. Lancet 2007;370:1543-51 – Bejon et al 2008 NEJM 359; 24: 2521-32 – Sacarlal et al. JID 2009;200:329-36

Clinical development conducted in partnership with PATH-Malaria Vaccine Initiative, GSK and:

Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso

Kumasi Centre for Collaborative Research & School of Medical Sciences Kumasi, Ghana

Kintampo Health Research Centre, Ghana

Albert Schweitzer Hospita

KEMRI-Walter Reed Projec

KEMRI-Wellcome Trust Re

KEMRI/CDC Research and

University of North Caroli

Centro de Investigação en

Ifakara Health Research D

National Institute of Medic

Prince Leopold Institute of Tropical Medicine, Belgium

University of Copenhagen, Denmark

University of Tuebingen, Germany

Bernhard Nocht Institute, Germany

University of Barcelona, Spain

Swiss Tropical Institute, Switzerland

London School of Hygiene & Tropical Medicine, UK

Center for Disease Control and Prevention, USA

University of North Carolina at Chapel Hill, USA

Walter Reed Army Institute of Research, USA

In collaboration with the Malaria Clinical Trials Alliance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