Malaria Vaccine:
Will it be available soon?

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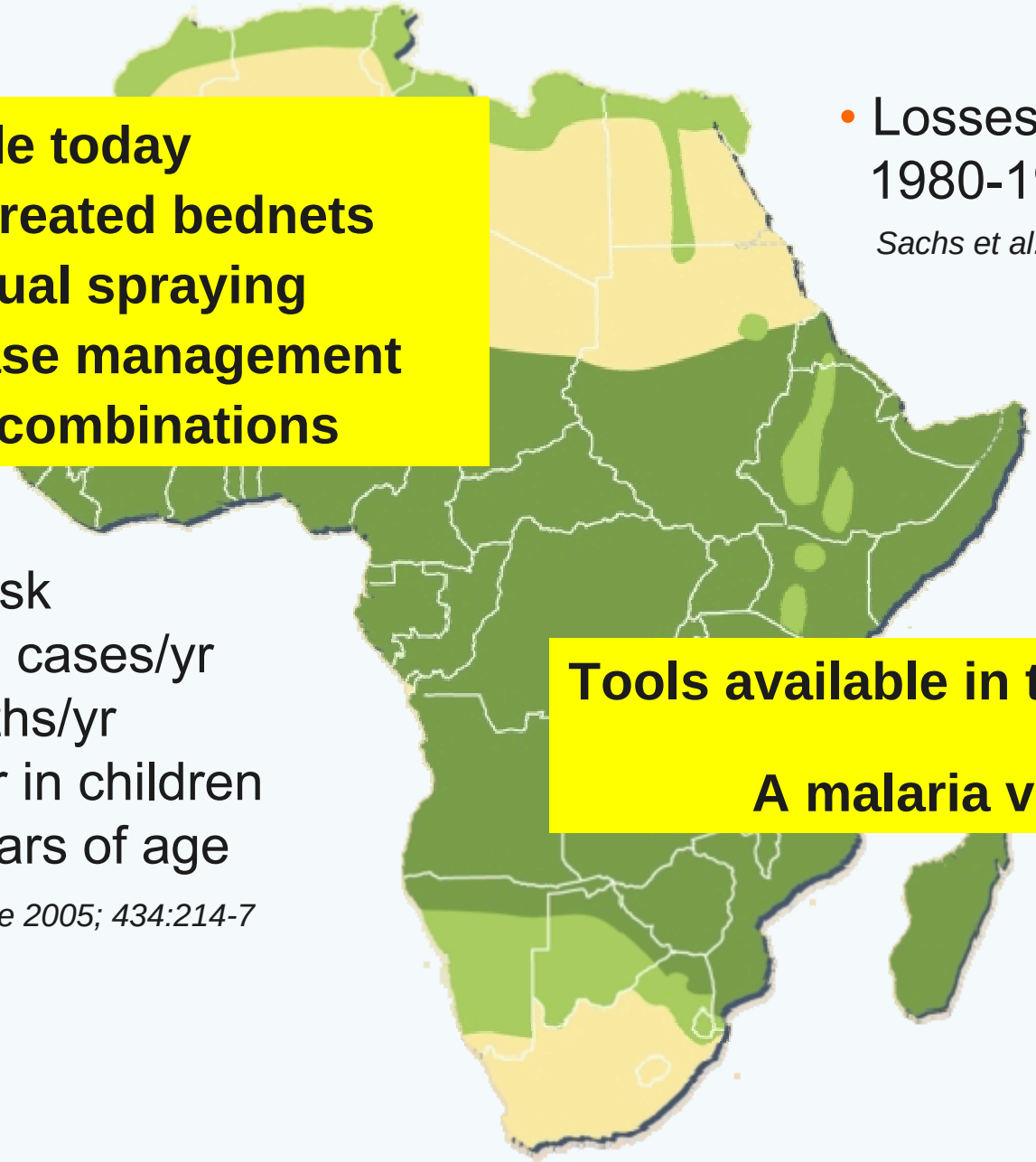
The Intolerable Burden of Malaria

Tools available today

- **Insecticide-treated bednets**
- **Indoor residual spraying**
- **Improved case management**
- **Artemisinin combinations**

- Losses to economies 1980-1995: $74 billion

Sachs et al., Nature 2002; 415:680-5



- 600 M at risk
- 300-500 M cases/yr
- 1-3 M deaths/yr
- Most occur in children under 5 years of age

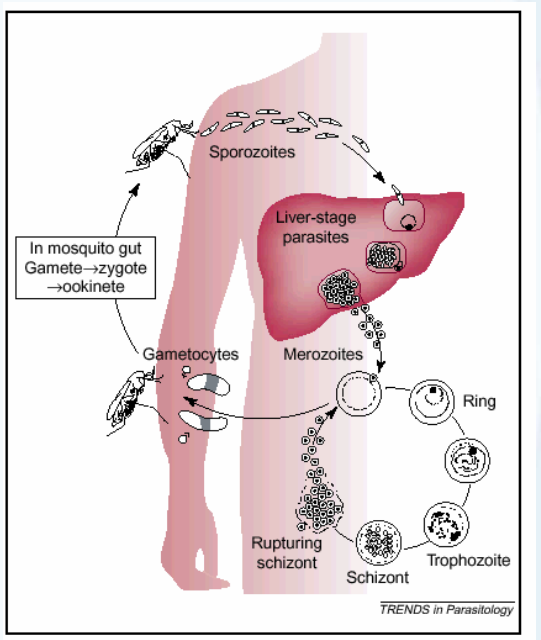
Snow et al., Nature 2005; 434:214-7

Tools available in the future?

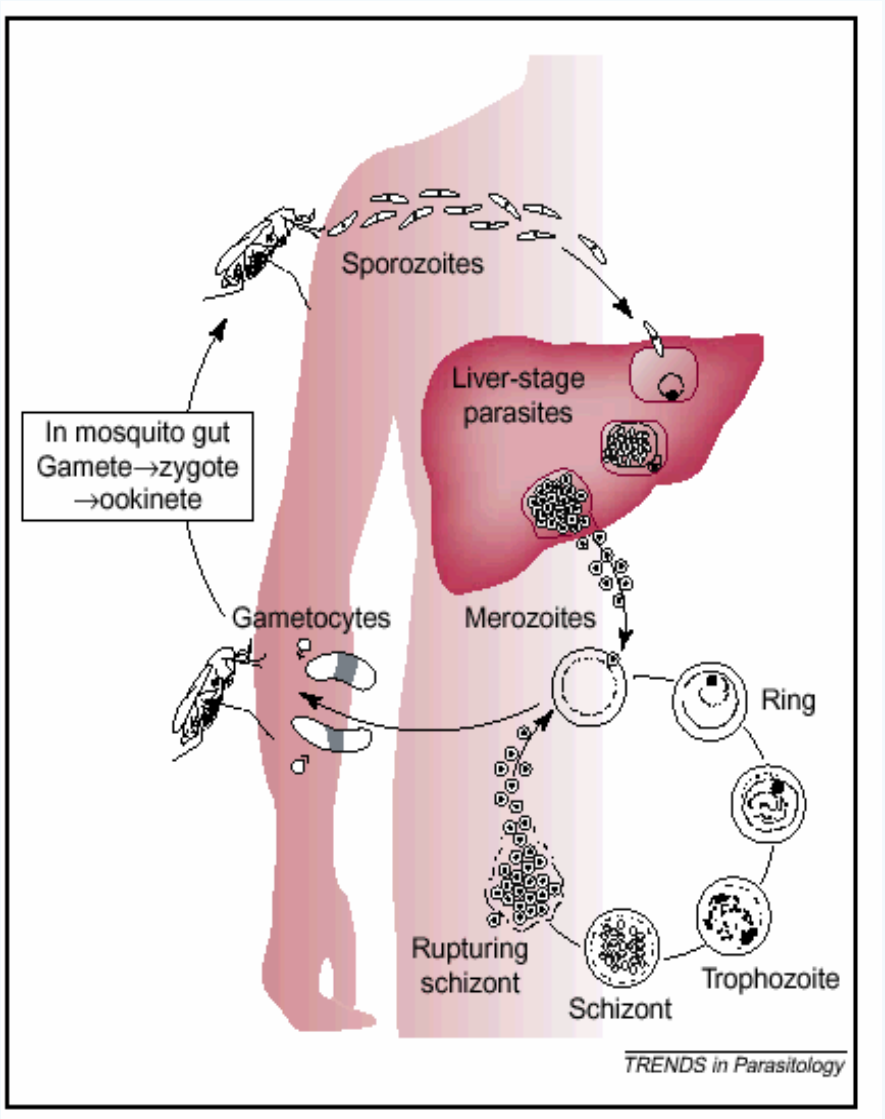
A malaria vaccine

The challenges: Plasmodium, the etiologic agent of Malaria

- Protozoan with a large genome : 26-30 megabases; 5-6000 genes; 14 chromosomes
- Allelic and antigenic variation
- Complex, genetically variable, human immune response
- Multistage life cycle with stage specific expression of proteins



The challenges: Parasite life cycle, disease and vaccine

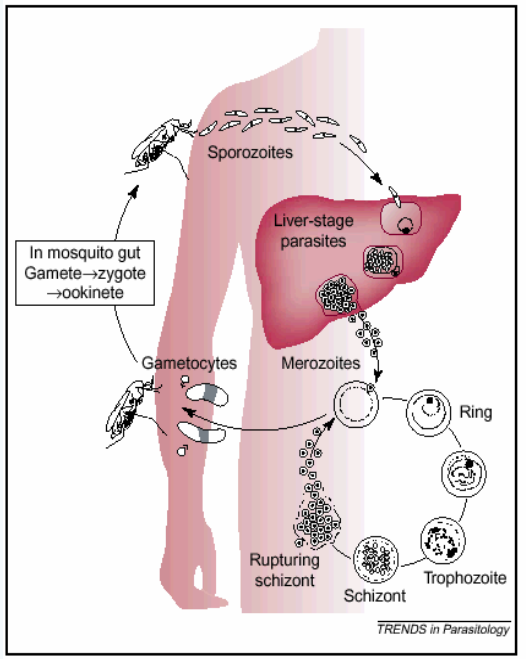


Pre-Erythrocytic Asexual Erythrocytic

Transmission Blocking

Malaria Vaccine Development strategies are stage specific

- Pre or exo-erythrocytic stage vaccine (sporozoites and intra-hepatic parasites): **prevents infection and/or reduces incidence and severity of disease**
- Asexual blood stage vaccine (free merozoites and parasitized RBCs): **reduces disease incidence and severity**
- Sexual blood stage / transmission blocking (altruistic) vaccine (gametocytes, gametes and/or zygotes): **prevents man to mosquito transmission**



Objectives of the GSK Malaria vaccine program

- **Primary objective**:
  - Develop a malaria vaccine that will protect infants/ children, residing in malaria endemic regions, from clinical disease and severe malaria resulting from infection by *Plasmodium falciparum*
  - Integrated into:
    - EPI distribution system
    - Malaria Control programs
- **Longer term objectives:**
  - Adults in endemic regions
  - Travelers (leisure, business, military)
  - *P. vivax*

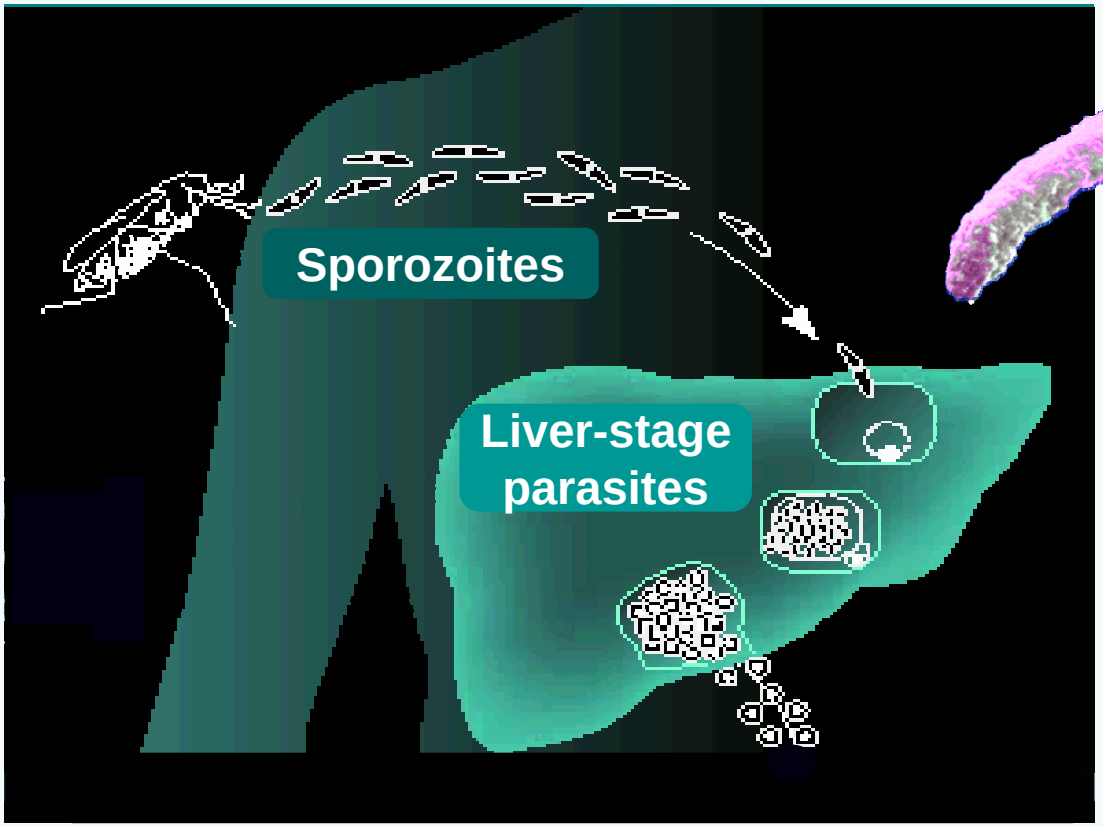
GSK lead candidate: the RTS,S/AS02A vaccine

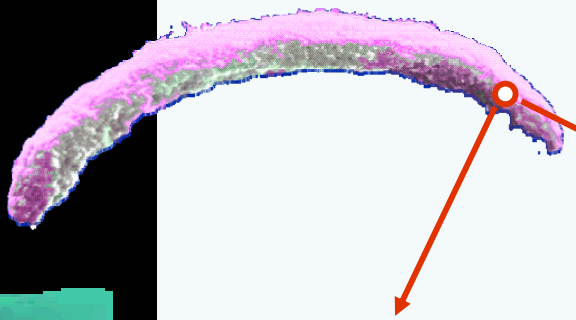
- R&D work on this vaccine initiated at GSK Bio in **1987**
- Multiple collaborations (WRAIR, etc.)
- GSK/MVI at PATH partnership for pediatric development (since Jan. 2001)
- **Phase 2b PoC for efficacy in children achieved in 2004/2005**
- **Phase 2b PoC for efficacy in EPI-aged infants achieved in 2007**

Hypothesis underlying the GSK malaria vaccine development program

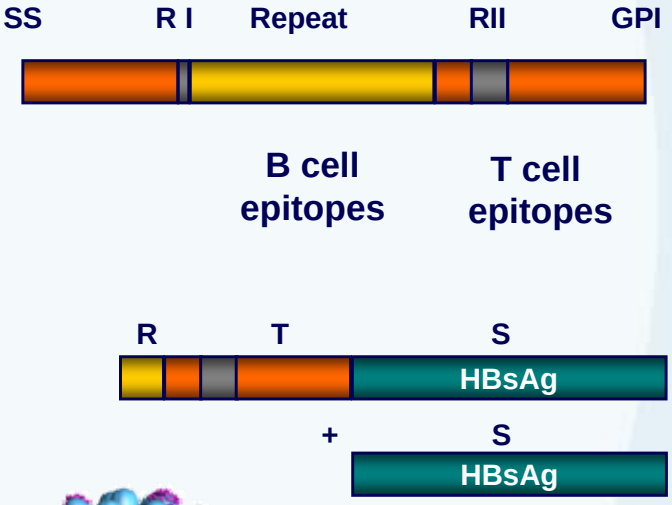
- The Circumsporozoite Protein (CSP) is target of protective immune responses
- Both Ag-specific humoral and CMI responses play a role in protection
- Adequate presentation and formulation required for optimal immune responses/efficacy
- Lab challenge predictive of field efficacy
- Beyond “sterile” efficacy, partial protection vs preE stage will impact on blood stage ⇨ protection vs disease

The RTS,S/AS Pre-erythrocytic Stage Vaccine: The antigen

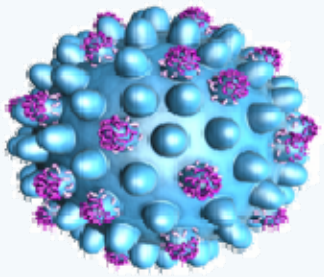




Circumsporozoite protein



Good Manufacturing Practices:
Fermentation,
Extraction,
Purification,
Formulation,
Lyophilisation
Quality Control

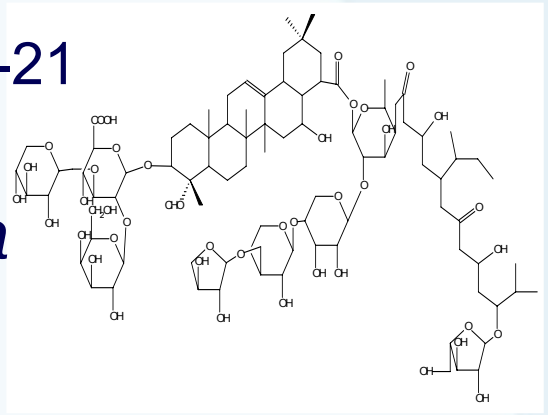


RTS,S Particle

The RTS,S/AS Pre-erythrocytic Stage Vaccine: The Adjuvant System

- Designed to induce strong antibody and Th-1 cell mediated immune responses

QS-21

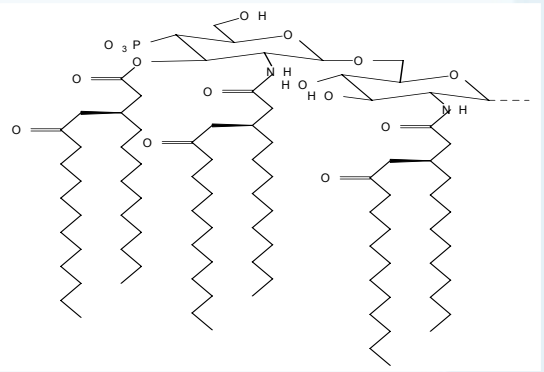


- QS21: Saponin extract of *Quillaja saponaria*

+

- MPL: Monophosphoryl Lipid A

MPL



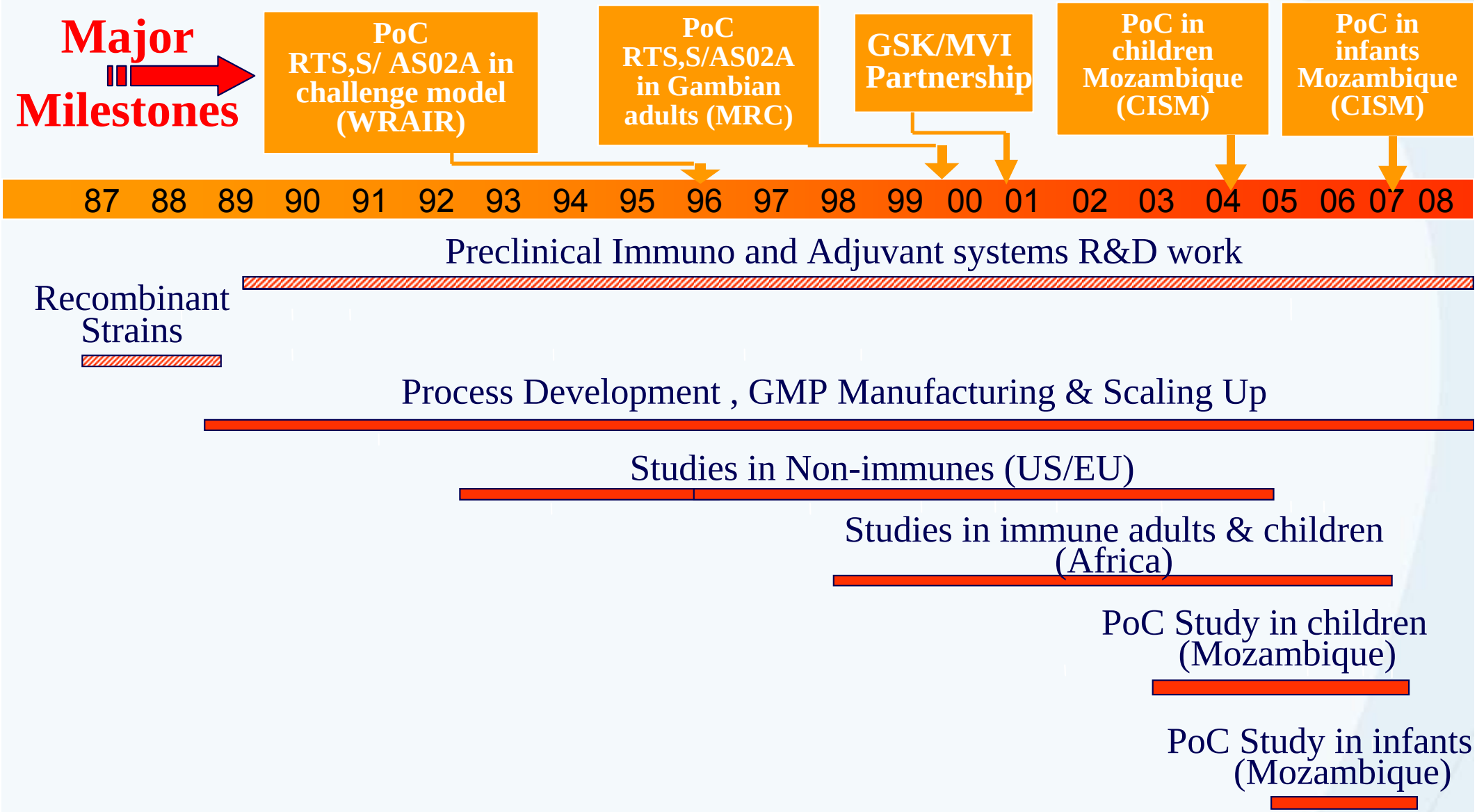
with

- Oil-in-water emulsion (= AS02)

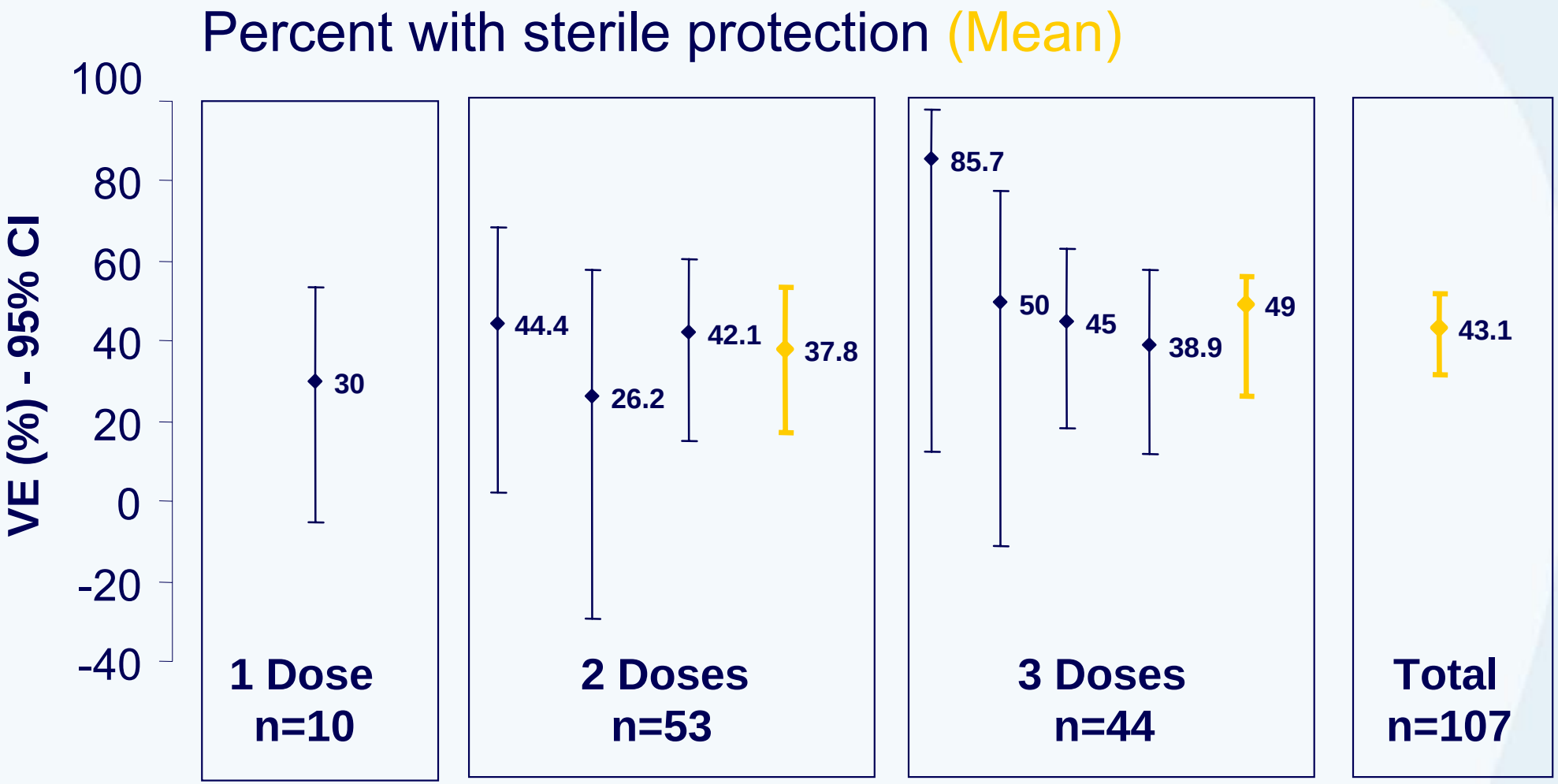
or

- Liposome suspension (= AS01)

HISTORY and MAJOR MILESTONES of the RTS,S/AS program

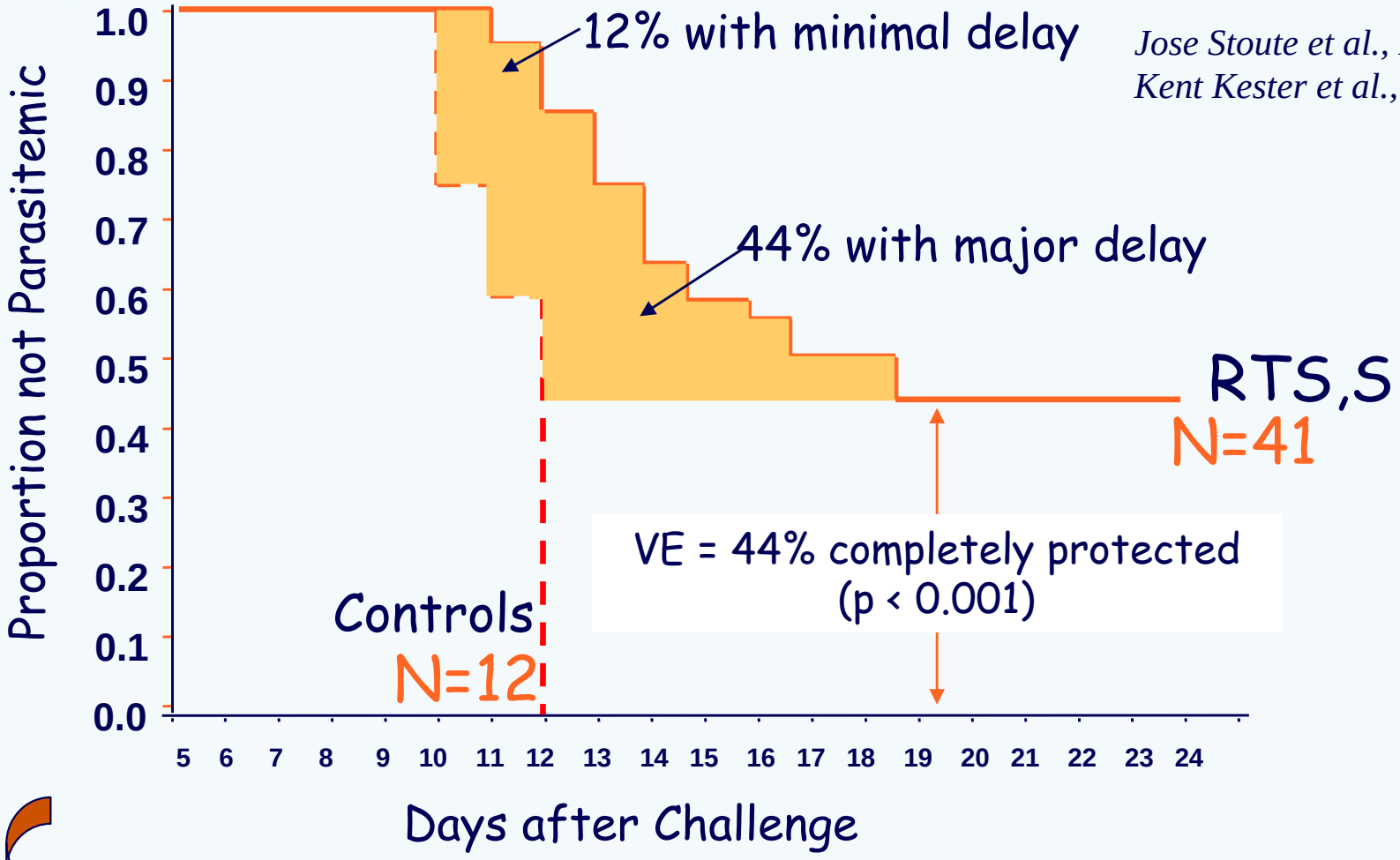


PoC in challenge model (several studies): Consistent efficacy against infection



Jose Stoute et al., NEJM 1997; 336: 86-91
Kent Kester et al., JID 2001; 183: 640-7

PoC in challenge model: Efficacy against infection & delay in pre-patent period



Jose Stoute et al., NEJM 1997; 336: 86-91
Kent Kester et al., JID 2001; 183: 640-7

Delay in pre patent period reflects a significant decrease in the load of Merozoïtes emerging from the liver to initiate the blood stage infection

Impact on course of blood stage infection and clinical disease?

PoC in Gambian adults: Phase IIb field efficacy trial - Results

Efficacy (over 1 transmission season):

Time to infection:

34% (8 - 53%, p = 0.014)

Clinical disease (over 1 transmission season):

31% (-7 to 56%, p = 0.096)

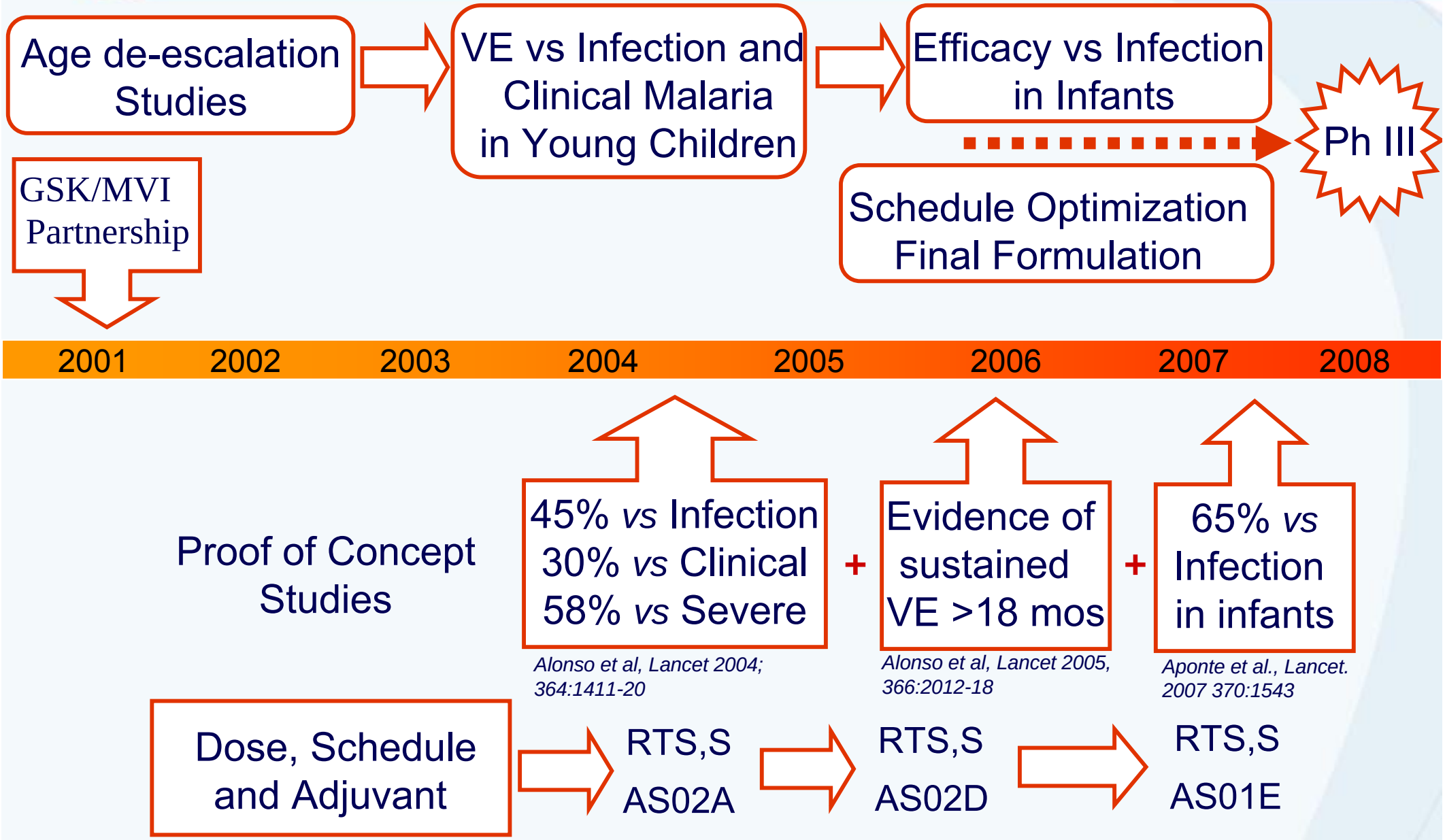
Efficacy following boost in 2nd year (over 1 transmission season):

47% (4 – 71%, p = 0.037)

⇒ **Challenge model results validated in the field**

Bojang et al., Lancet 2001; 358:1927-34

The Pediatric Clinical Development Pathway



Phase IIb PoC of Efficacy in Children (Malaria 026)

- CISM (Manhiça, Mozambique)
- N ~2000, 1-4 years old
- Safe and well tolerated
- Highly immunogenic to CSP and HBSAg

C1	➢ **VE clinical malaria:**	**35.3% (95% CI 22-47; p < 0.0001)**	**18 m FU**
	➢ **VE severe malaria:**	**48.6% (95% CI 12-71; p = 0.02)**	**18 m FU**
	➢ **VE hospitalized malaria:**	**30.5% (95% CI 4-50; p = 0.032)**	**18 m FU**
C2	➢ VE infection:	44.9% (95% CI 31-56; p < 0.001)	6 m FU

Alonso et al, Lancet 2004; 364:1411-20

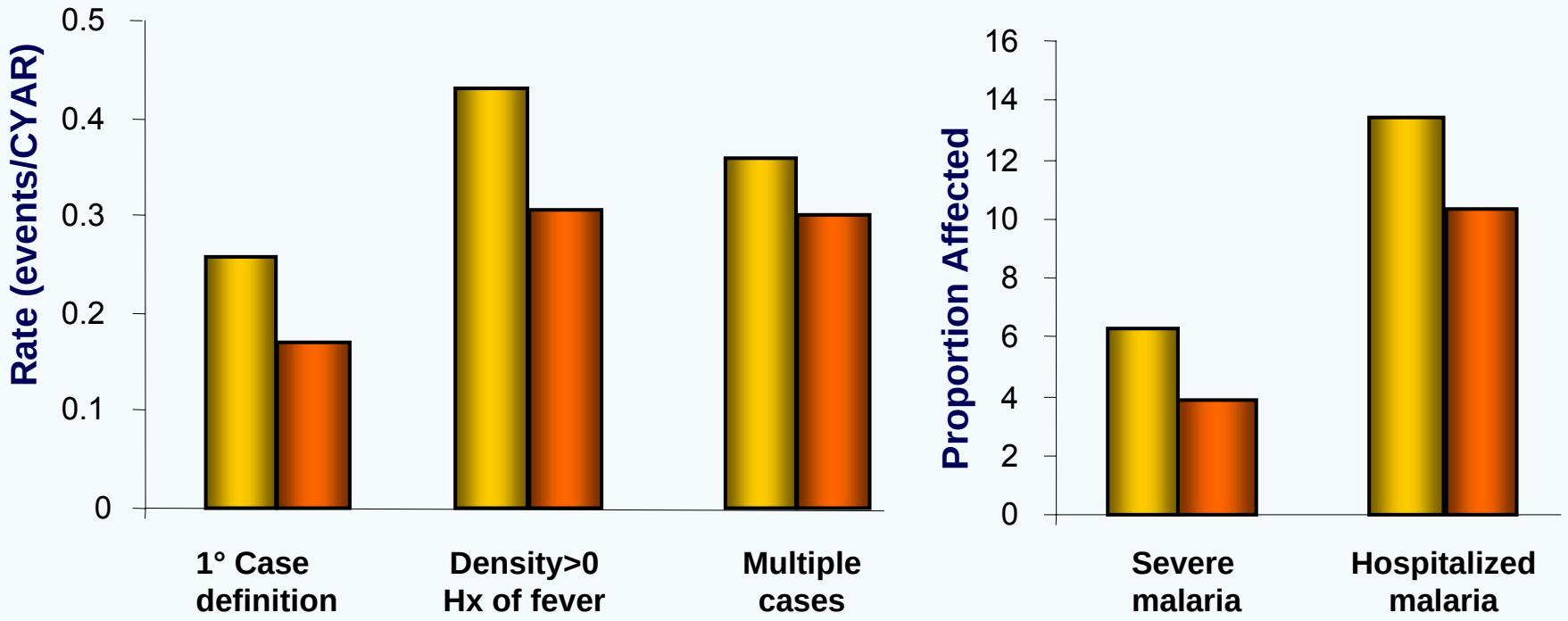
Alonso et al, Lancet 2005, 366:2012-18

Evidence of sustained efficacy:
Efficacy data over 45 mos (Mal 026/039)

Control
RTS,S/AS02

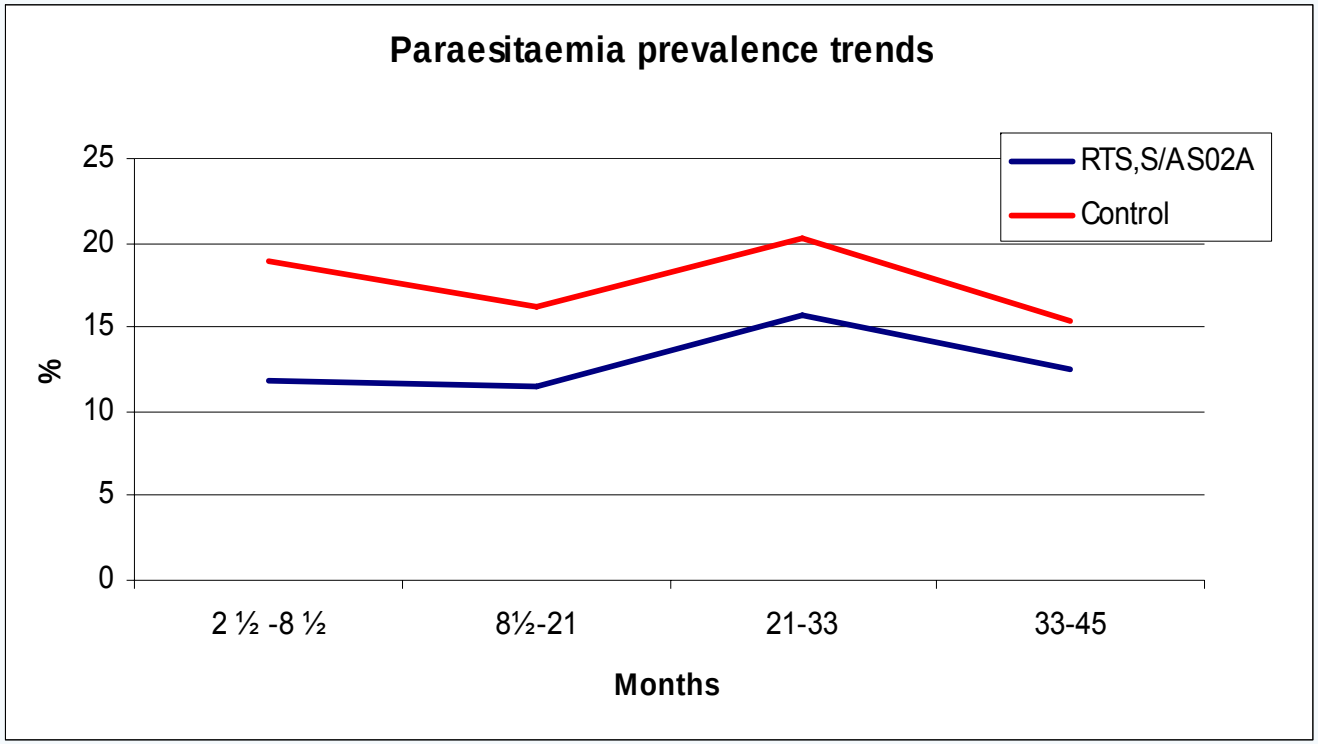
Clinical episodes

1° Case definition	Density>0 Hx of fever	Multiple cases	Severe malaria	Hospitalized malaria
30.5%	31.9%	25.6%	38.3%	23.0%
95% CI 19-40	95% CI 22-40	95% CI 12-37	95% CI 3-61	95% CI -2 - 42
p < 0.001	p < 0.001	p = 0.0006	p = 0.045	p = 0.078



Sacarlal et al presented at ASTMH 2007

Evidence of sustained efficacy: *Parasite prevalence at cross-sectional surveys over 45 mos (Mal 026/039)*



%: Proportion with asexual parasitaemia

P=0,0069 – ongoing protection

Time (month)	RTS,S		CONTROL		
	+/total	%	+/total	%	p
8½	82/688	11,9	131/692	18,9	0,0003
21	77/666	11,5	106/653	16,2	0,017
33	93/590	15,7	121/596	20,3	0,049
45	71/568	10,2	105/574	15,4	0,0069

Sacarlal et al presented at ASTMH 2007

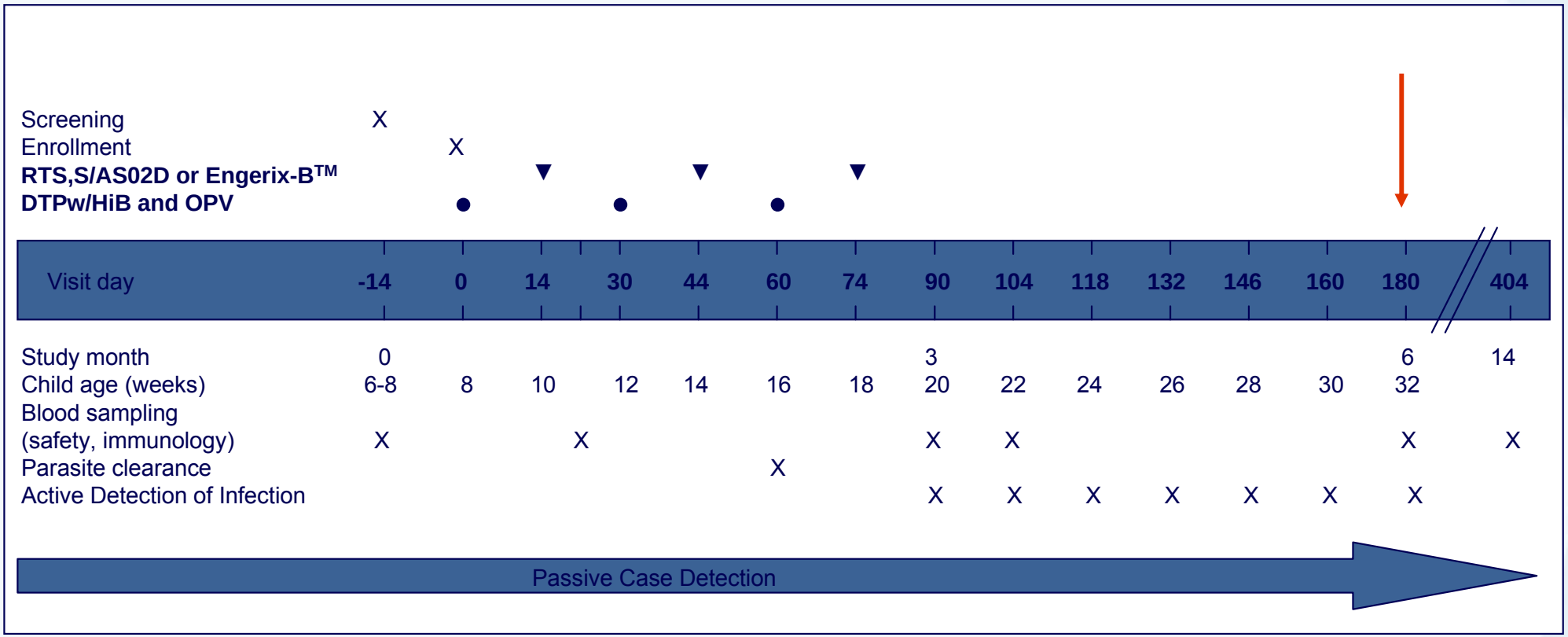
Serious Adverse Events [0 -45m] (Mal 026/039)

	RTS,S/AS02A (n=1012)			Control vaccines (n=1010)			
	n	%	(95% CI)	n	%	(95% CI)	
Serious Adverse events	**235**	23	(21-26)	**326**	32	(29-35)	
Cerebral malaria	2	0.2	(0.0-0.7)	4	0.4	(0.1-1.0)	
Severe malaria anemia	12	1.2	(0.6-2.1)	15	1.5	(0.8-2.4)	
Severe malaria (others)	37	3.7	(2.6-5.0)	58	5.7	(4.4-7.4)	
							p- values
All deaths	12	1.2	(0.6-2.1)	22	2.2	(1.4-3.3)	**0.0866**
Excluded Trauma	11	1.1	(0.5-1.9)	18	1.8	(1.3-2.8)	0.1969
Malaria deaths	1	0.1	(0.0-0.5)	5	0.5	(0.1-1.1)	0.1242

No “rebound” effect
Further indications of potential public health benefits

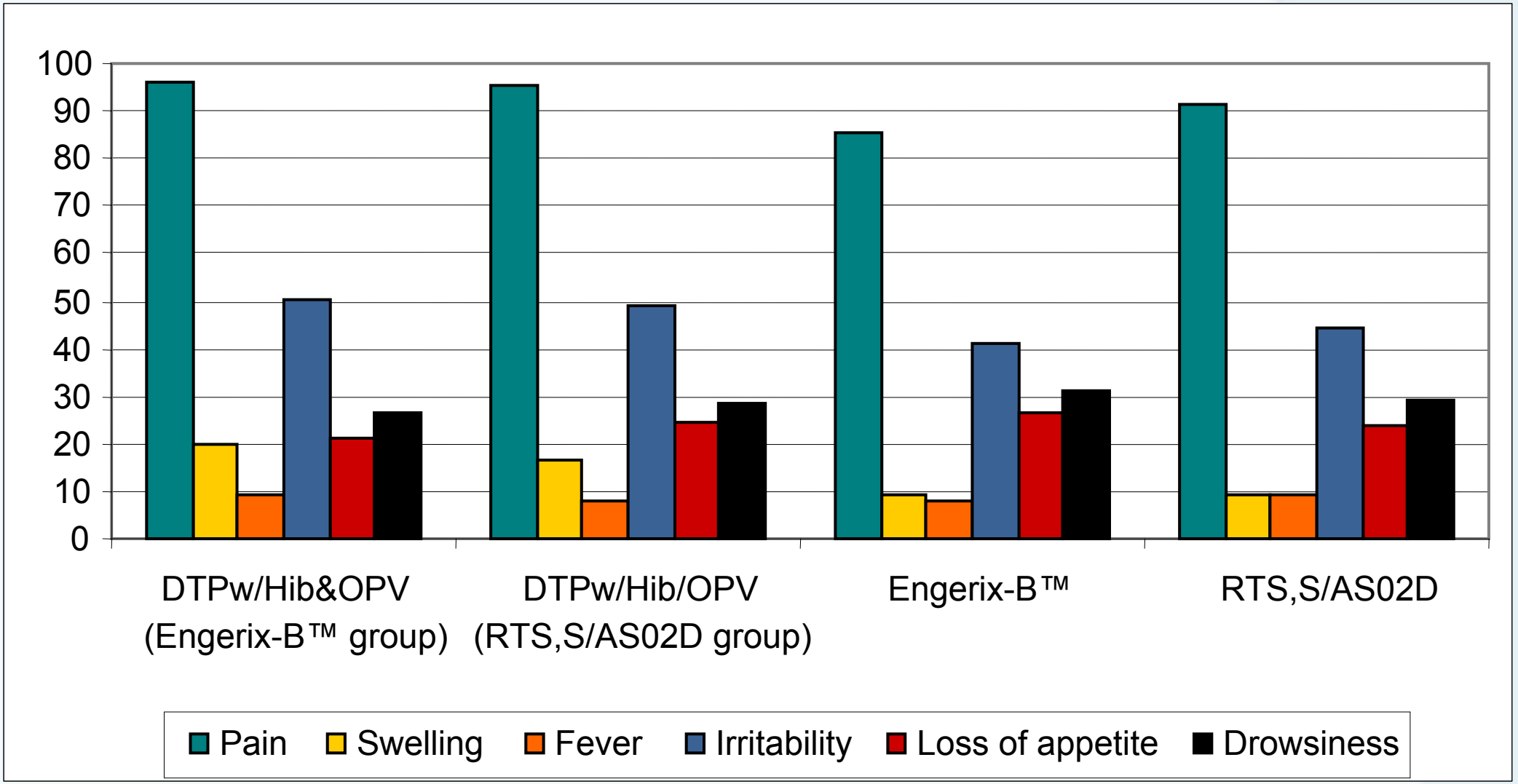
Sacarlal et al presented at ASTMH 2007

Proof of Concept in Infants



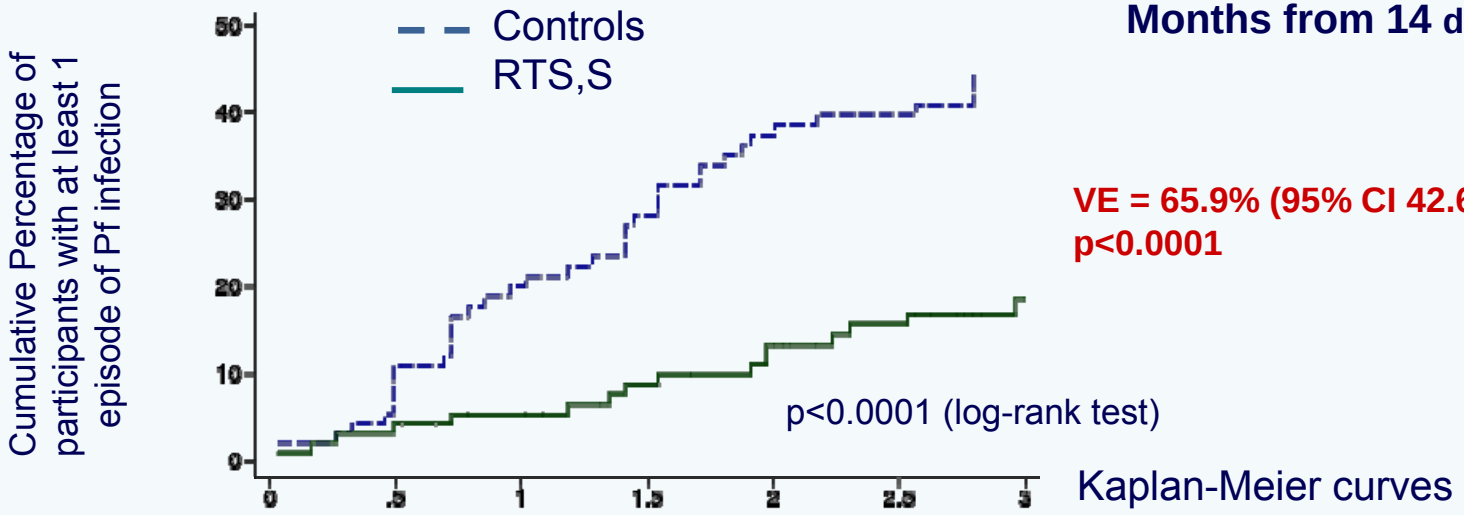
Aponte et al., Lancet. 2007 370:1543

Reactogenicity Similar to EPI Vaccines



Aponte et al., Lancet. 2007 370:1543

RTS,S/AS02 efficacy in infants EPI age
(stagered administration of EPI & RTS,S/AS02) (Mal 038)

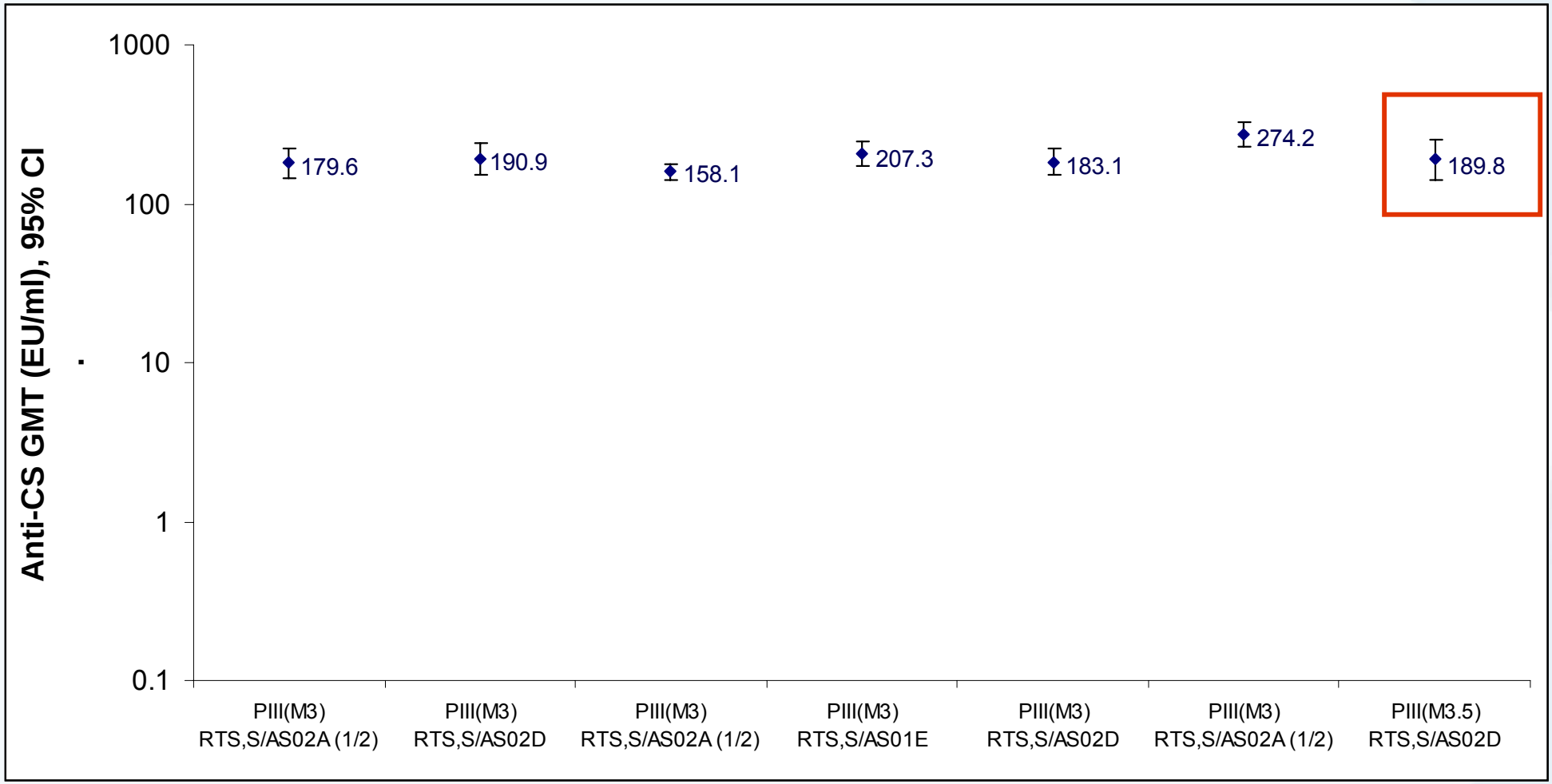


	Engerix-B			RTS,S/AS02D			Adjusted vaccine efficacy	
	Events	PYAR	Rate	Events	PYAR	Rate	Efficacy (95%CI)	P
Malaria infection								
First or only episode of parasitaemia>0	46	17.2	2.7	22	21.8	1.0	**65.9%** (42.6 - 79.8)	<0.0001
Clinical malaria								
1st or only episode of fever & parasitaemia > 500 per µL	22	19.6	1.1	9	22.6	0.4	**65.8%** (25.3 - 84.4)	0.007
1st or only episode of fever or history of fever & parasitaemia >0	35	18.2	1.9	17	22.4	0.8	**63.1%** (33.6 - 79.6)	0.0009

PYAR-Person-years at risk. Rate-event/PYAR. Vaccine efficacy estimates adjusted by distance from health facility and community

Aponte et al., Lancet. 2007 370:1543

Consistent RTS,S induced anti-CS AB titers across the age groups



Potential improvement of adjuvant for phase III

- **Alternative Adjuvant System**
  - Encouraging results with alternative Adjuvant System AS01
  - Confirm and bridge in phase II
  - Switch from AS02 to AS01 in phase III

MAL027 Efficacy First Challenge

		Pro	Inf	VE
Cohort 1	**AS01**	**10**	**7**	59%
	AS02	**9**	**15**	38%
Cohort 2	**AS01**	**8**	**11**	42%
	AS02	**5**	**15**	25%

Pooled AS01 VE: 50% (95%CI: 35;66)

Pooled AS02 VE: 32% (95%CI: 20;47)

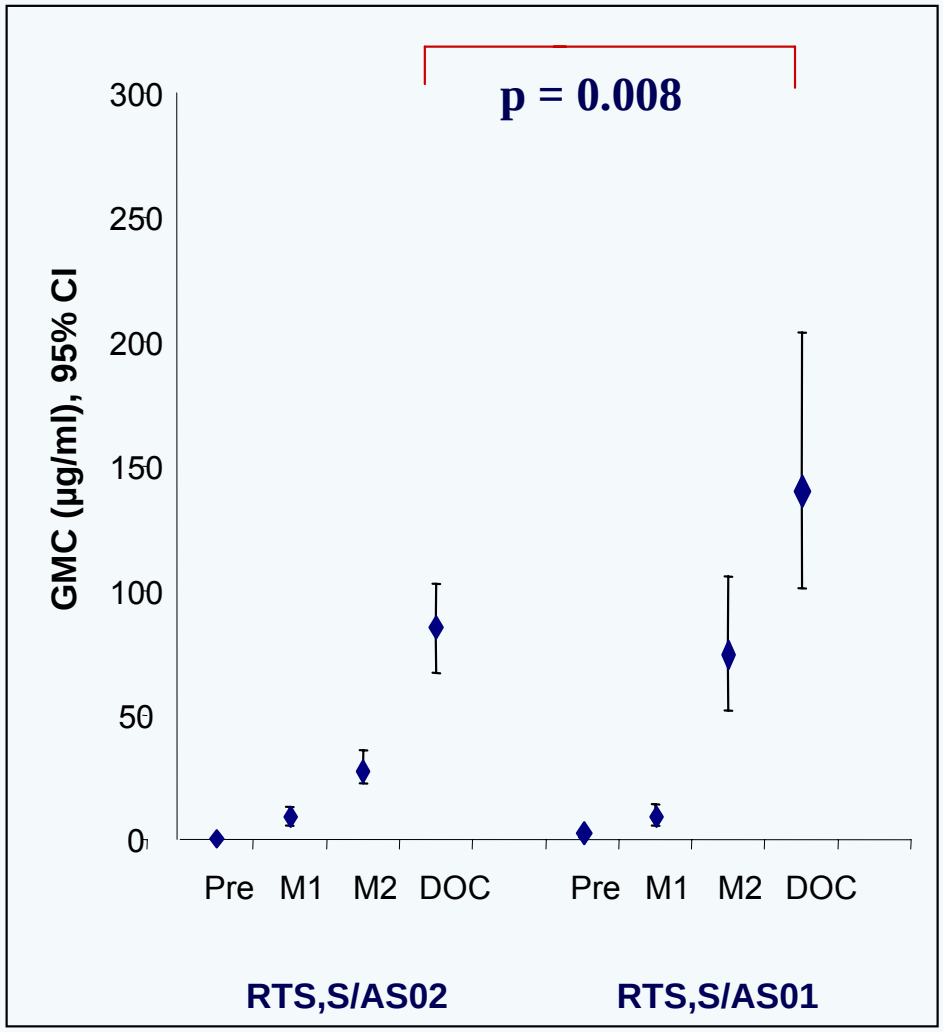
p = 0.11

Trend toward better efficacy with AS01 vs AS02

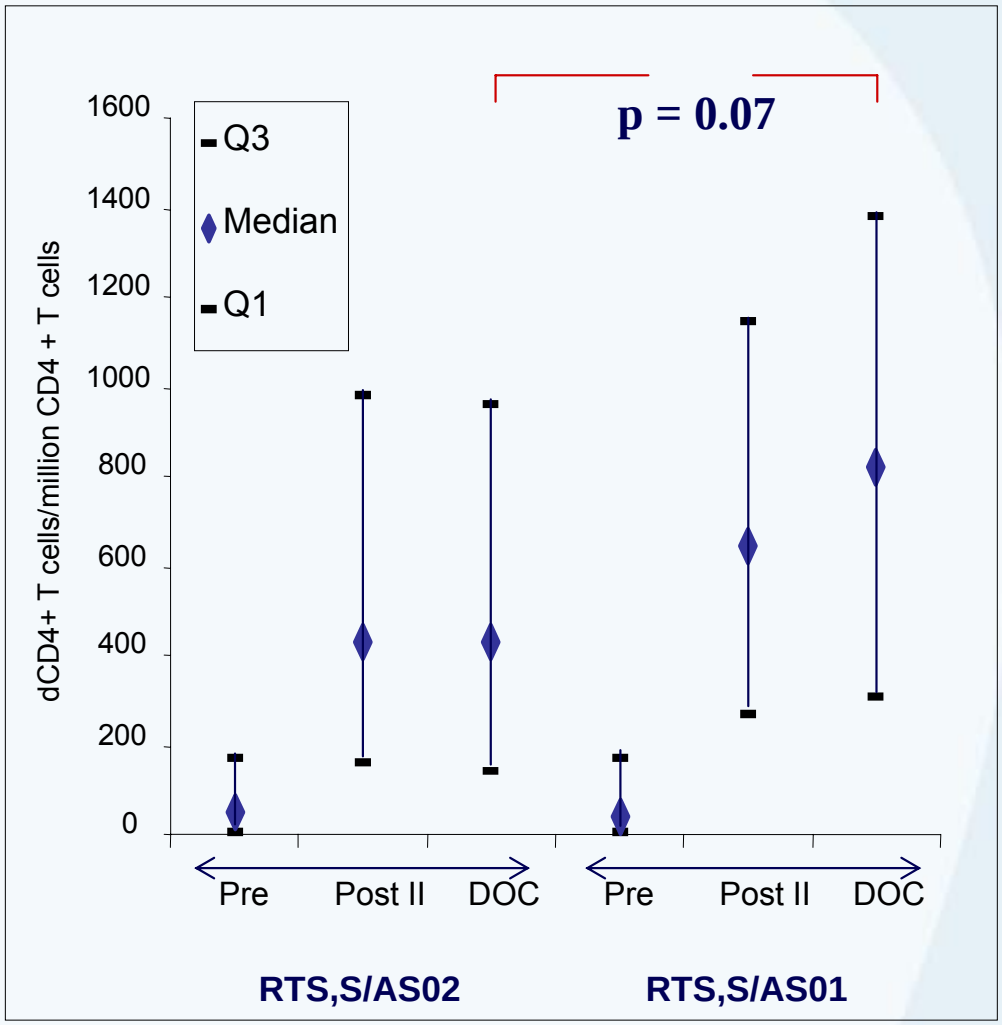
Kester et al. Presented at ASTMH 2006

Increased Immunogenicity with RTS,S/AS01

IgG CS Repeats



Double + CD4 for CD40L, IL2, TNFα, or γIFN



Kester et al. Presented at ASTMH 2006

Conclusions from existing Phase 2 data

- RTS,S/AS has a promising safety and reactogenicity profile in all age groups tested
- Robust anti-CS humoral response with trend towards infants/children > adults
- Efficacy against clinical disease demonstrated in children and infants and against severe malaria in children
- Indication of sustained efficacy in children over 45 months of follow up
- Suggestion that the Adjuvant System AS01 is superior to AS02 (immunogenicity and efficacy in challenge model)

Expected from still ongoing Phase 2 studies

- Confirmation of Adjuvant System selection
- Compatibility in co-administration with EPI vaccines
- Final schedule selection (0, 1, 2 vs 0, 1,7)

→ **All needed data for Phase III GO available by 3Q 08**

Current RTS,S Phase II/III Study Sites

Clinical Trial Partnership Committee
A collaboration of Northern and Southern academic groups

Southern

Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso
Kumasi Centre for Collaborative Research, Ghana
School of Medical Sciences Kumasi, Ghana
Kintampo Health Research Centre, Ghana
Albert Schweitzer Hospital, Gabon
Kenya Medical Research Institute, Kilifi, Kenya
Wellcome Collaborative Research Programme, Kilifi, Kenya
Kenya Medical Research Institute, Kisumu, Kenya
University of North Carolina Project, Lilongwe, Malawi
Centro de Investigação em Saude de Manhiça, Mozambique
Ifakara Health Research Development, Tanzania
National Institute of Medical Research, Tanzania

Northern

Prince Leopold Institute of Tropical Medicine, Belgium
University of Copenhagen, Denmark
University of Tuebingen, Germany
Bernhard Nocht Institute, Germany
University of Barcleona, Spain
Swiss Tropical Institute, Switzerland
London School of Hygiene & Tropical Medicine, UK
University of North Carolina at Chapel Hill, USA
Walter Reed Army Institute of Research, USA
Center for Disease Control and Prevention, USA

Phase III Efficacy Trial (Malaria-055)

- At least 10 sites representing different transmission settings
- Up to 16 000 children in 2 age categories:
  - 6 weeks to 12 weeks (6 000 minimum)
  - 5 to 17 months (6 000 minimum)
- Designed to provide
  - Key safety and efficacy data to support file
  - Full evaluation of relevant disease and public health endpoints to inform implementation planning

Malaria-055: Efficacy Objectives

Co-primary:

- Effic… dose 3:
- I… de… EPI co-administration)

Secondary

- Efficacy against severe malaria disease
- Prevention of malaria hospitalization
- Prevention of anemia
- Efficacy against clinical malaria in different tra…
- Efficacy of a booster dose
- Efficacy against parasitemia
- Efficacy against all-cause hospitalization, sepsis and pneumonia
- Efficacy against malaria-specific and all cause mortality

Critical for Licensure

Critical for Implementation

Conclusions

- GSK is committed to its malaria vaccine program:
  an uninterrupted 23 years R&D effort
- PoC for efficacy in children and infants living in endemic regions has been reached: **a significant breakthrough**
- If efficacy is confirmed in Phase 3, the RTS,S vaccine could have **a major public health impact in endemic regions**
- GSK is working in partnership with leading African scientists, MVI, international donors and global health authorities to ensure:
  - ✓ Rapid development and registration
  - ✓ Large scale manufacturing is ready
  - ✓ Financing mechanisms are in place
  - ✓ Wide-spread implementation and access to those who need it most
- Second generation vaccine that will address:
  - ✓ Improvements of RTS,S
  - ✓ P. Vivax
  - ✓ Travelers vaccine

Acknowledgements

➢ Collaborating Institutions

Southern

Institut de Recherche en Science de la Santé, Nanoro, Burkina
Kumasi Centre for Collaborative Research, Ghana
School of Medical Sciences Kumasi, Ghana
Kintampo Health Research Centre, Ghana
Albert Schweitzer Hospital, Gabon
Kenya Medical Research Institute, Kilifi, Kenya
Wellcome Collaborative Research Programme, Kilifi, Kenya
Kenya Medical Research Institute, Kisumu, Kenya
University of North Carolina Project, Lilongwe, Malawi
Centro de Investigação em Saude de Manhiça, Mozambique
Ifakara Health Research Development, Tanzania
National Institute of Medical Research, Tanzania

Northern

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London School of Hygiene & Tropical Medicine, UK
University of North Carolina at Chapel Hill, USA
Walter Reed Army Institute of Research, USA
Center for Disease Control and Prevention, USA

Acknowledgements

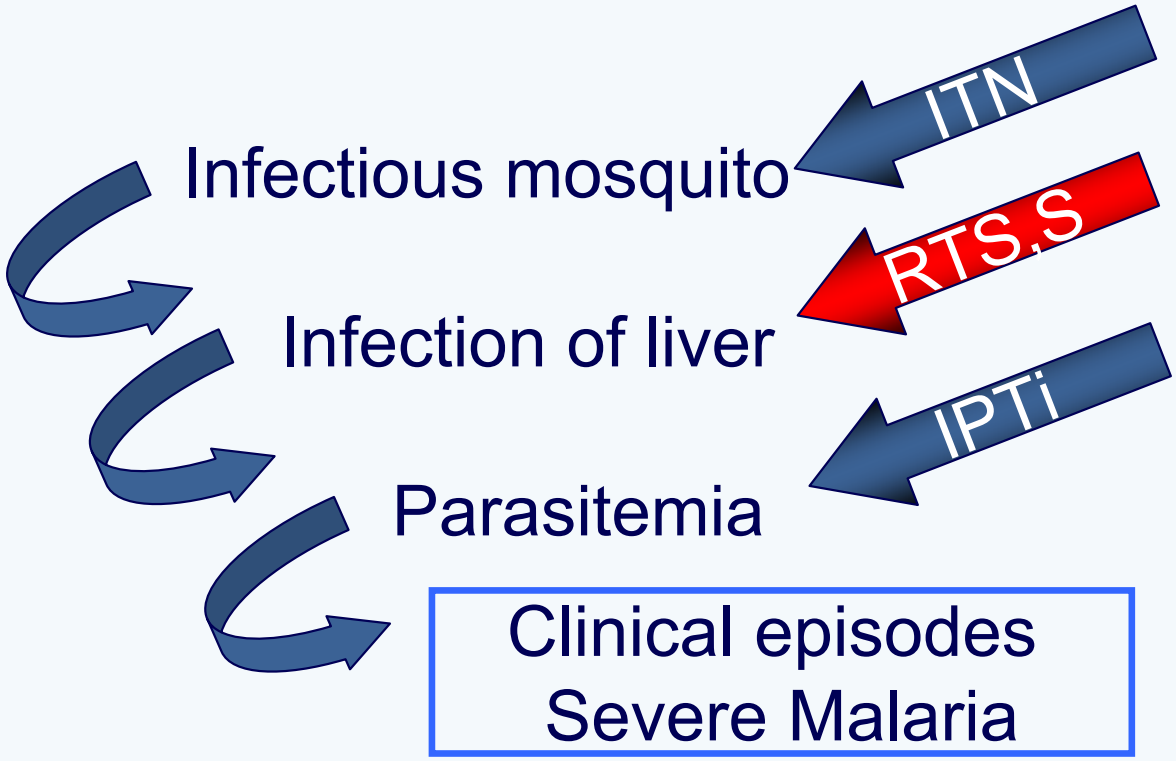
- The Malaria Vaccine Team at GSK
- The Malaria Vaccine Initiative at PATH: our partner in this endeavour
- The Malaria Clinical Trial Alliance: for support to several trial sites

and

- The volunteers, their families and their communities: for their participation in the trials

BACK UP SLIDES

Synergy with Other Interventions?



Efficacy against Severe Malaria

45% (95% CI 20 to 63)
Lengeler C, Cochrane Database Syst Rev 2004

49% (95% CI 12 to 71)
Alonso P et al., Lancet 2005; 366:2012

50% (95% CI 8 to 73)
Schellenberg D et al., Lancet 2001; 357:1471

Number of doses administered to children in Phase II program for all RTS,S-based candidate malaria vaccines

	RTS,S/AS02		RTS,S/AS01	
Children 5 months – 6 years	**Doses**	**Subjects**	**Doses**	**Subjects**
Malaria-020*	89	30	-	-
Malaria-025	86	30	-	-
Malaria-026	2926	1012	-	-
Malaria-034	581	200	-	-
Malaria-046	262	90	261	90
Malaria-047	580	225	533	270
Malaria-049**	-	-	1335	445
SUB-TOTAL	**4524**	**1587**	**2129**	**805**
Infants from 10 weeks of age no EPI c-administration				
Malaria-038	301	107	-	-
SUB-TOTAL	**301**	**107**	**-**	**-**
Infants from 6 weeks of age in EPI co-administration				
Malaria-040	490	170	-	-
Malaria-050**	-	-	1020	340
SUB-TOTAL	**490**	**170**	**1020**	**340**
TOTAL	***5315***	***1864***	***3149***	***1145***

RTS,S/AS02 = RTS,S/AS02A and RTS,S/AS02D
Table includes 3-dose schedules only
*Subject and dosing numbers for 0.25 mL RTS,S/AS0A dose only
** Estimated values for ongoing studies

MPL and QS21: modes of action

MPL:

- Binds TLR4
- Induces APC maturation (e.g. costimulatory molecules)
- Induces pro-inflammatory cytokines and chemokines

QS21:

- Induces a set of proinflammatory cytokines and chemokines *in vivo* and *in vitro*
- does not induce detectable CD80/CD86/CD40 expression by DCs *in vivo*
- But QS21 induces expression of IFN-γ by DCs *in vivo*
- MPL and QS21 synergize both at the level of innate and adaptive immunities