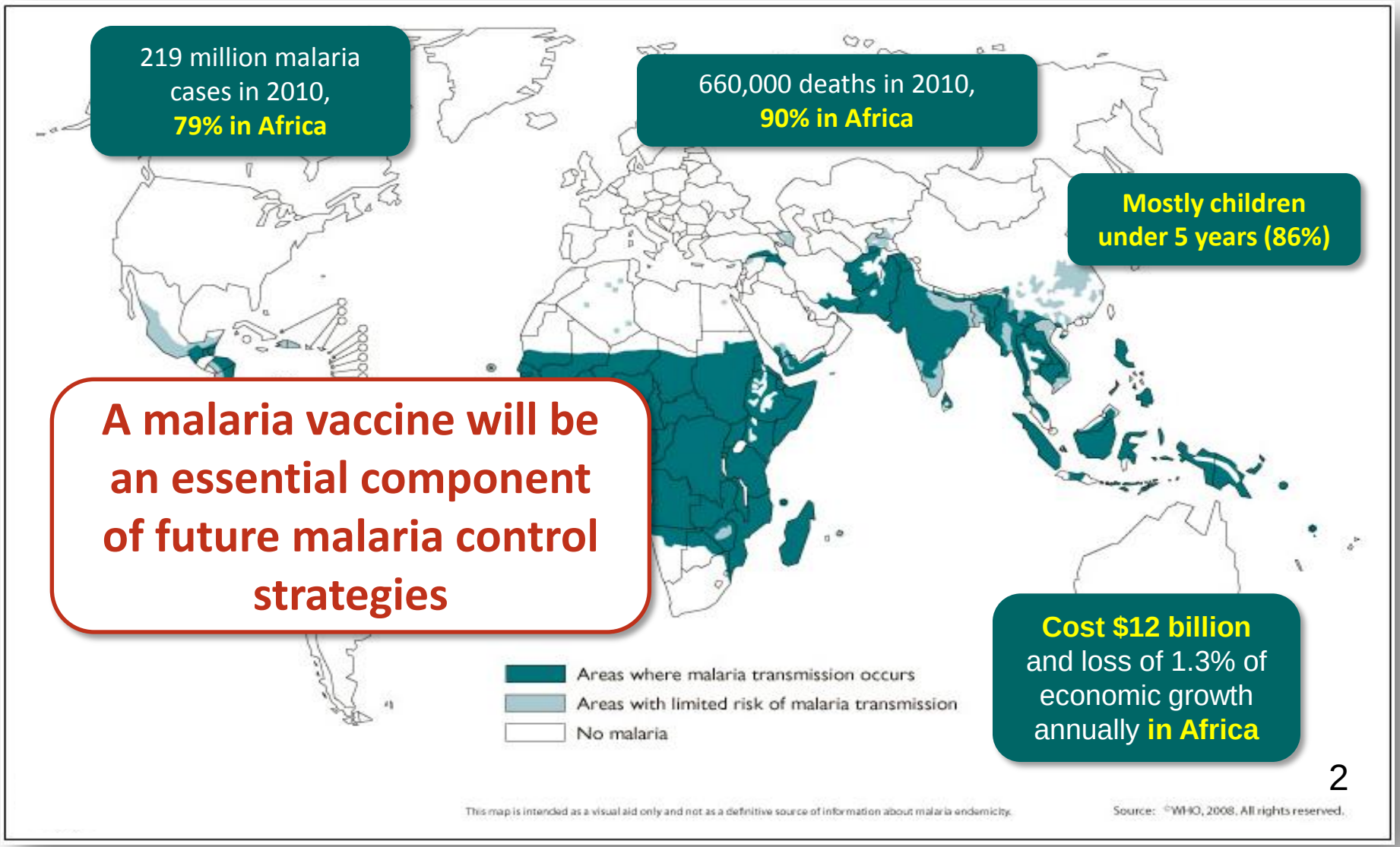
Status of RTS,S/AS01 malaria vaccine candidate

SAGE

Geneva, April 11, 2013

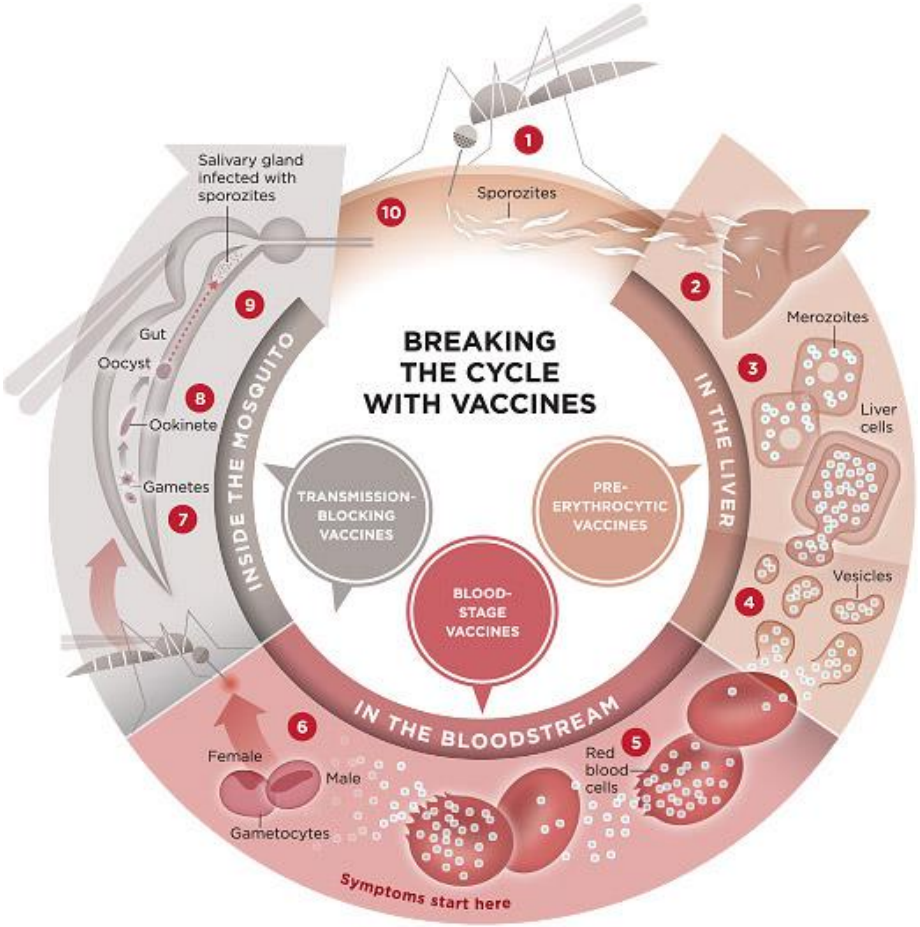
The burden of malaria caused by *Plasmodium falciparum* (the most prevalent malaria pathogen in Africa)



WHO World Malaria Report 2012

Parasite life cycle and vaccine opportunities

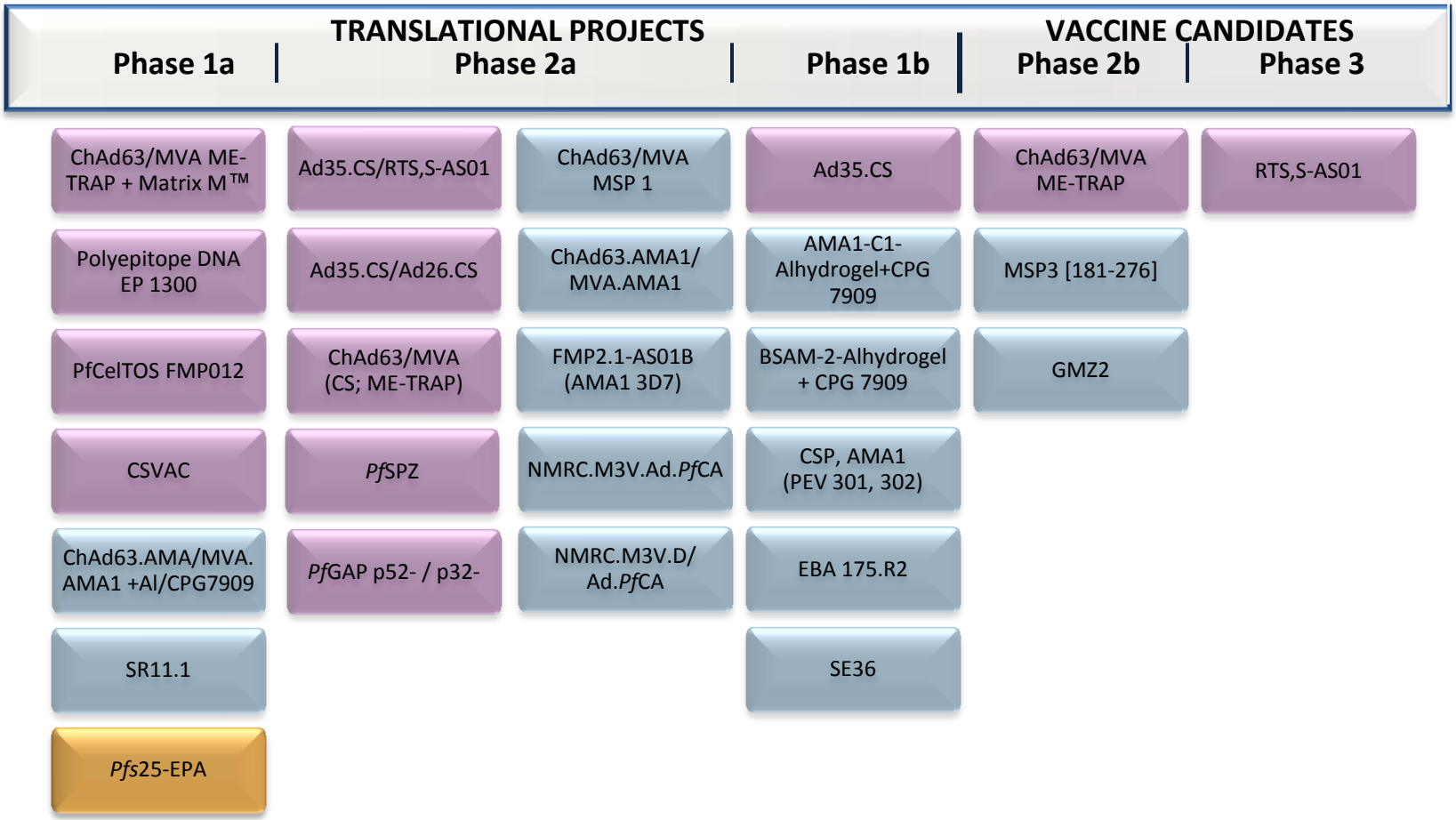
Sexual/ Sporogonic/ Mosquito



Pre-erythrocytic

Asexual Blood

Global malaria vaccine pipeline

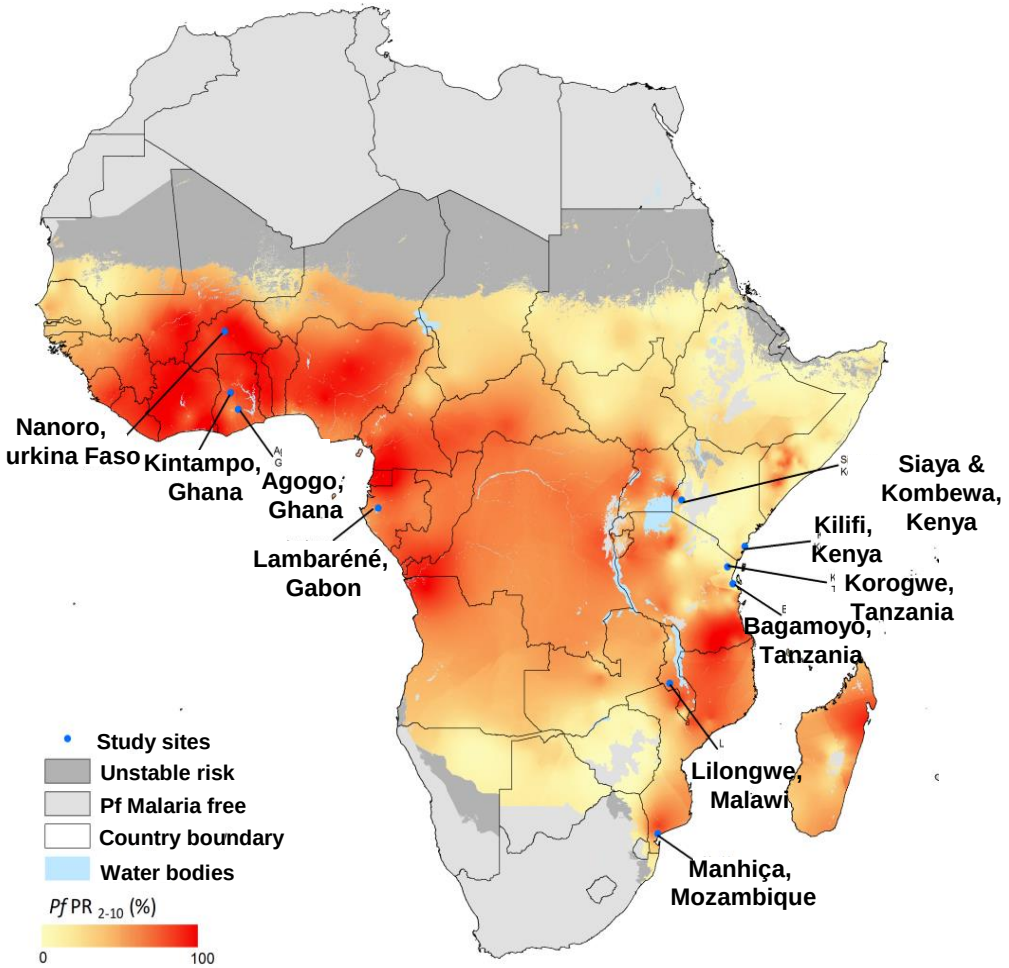


***P. falciparum* vaccines:** Pre-erythrocytic Blood-stage Transmission-blocking
***P. vivax* vaccines:** Pre-erythrocytic Blood-stage Transmission-blocking

Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

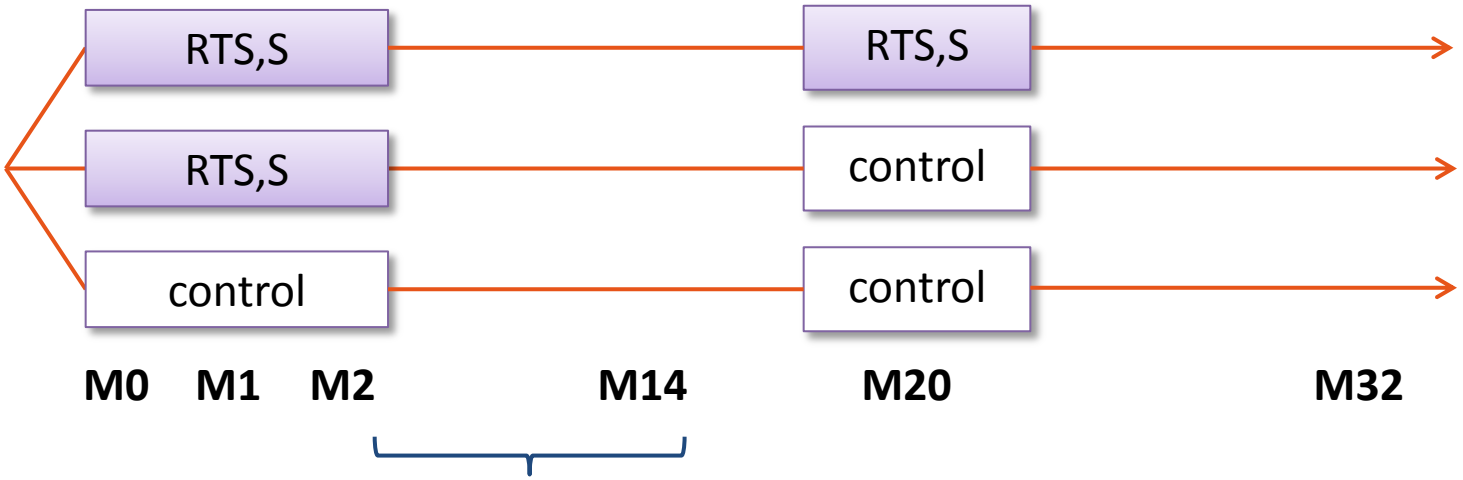
Multi-center RTS,S malaria vaccine efficacy trial

- Phase 3, randomized, controlled, double-blind trial conducted in 11 centers in 7 African countries
- 15,460 children enrolled in two age categories:
  - Children aged 5–17 months
  - Infants aged 6–12 weeks
- Co-primary endpoint:
  Vaccine efficacy against clinical malaria during 12 months of follow-up in each age category.
- Wide range of malaria transmission intensities (0.01 to 2.0 clinical episodes per child per year)
- Efficacy measured in presence of other malaria control interventions:
  86% ITN coverage in 6-12 weeks and 75% in 5-17 months



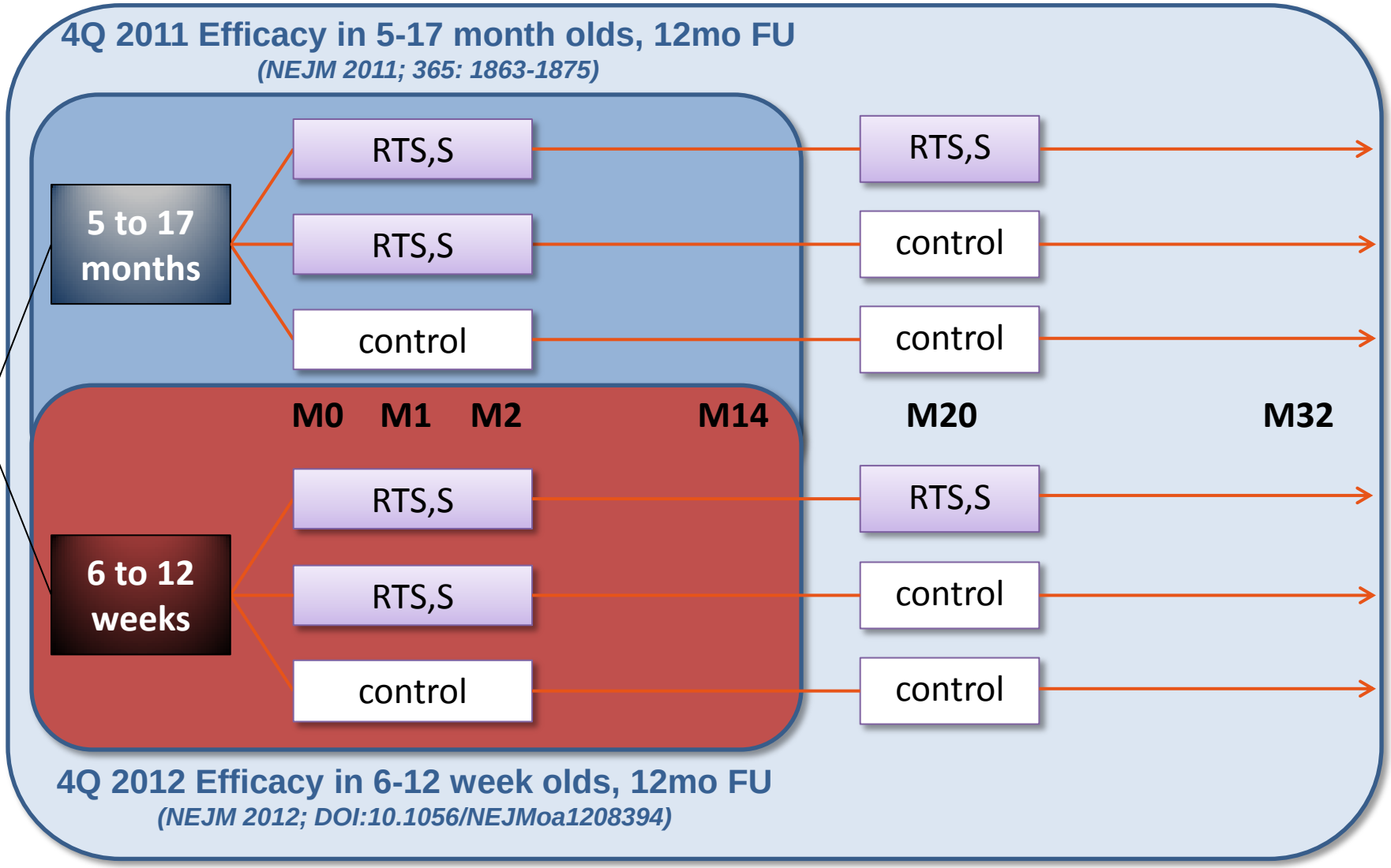
Vekemans J. et al. Malaria Journal 2011;10:221 - Lievens M. et al. Malaria Journal 2011;10:222 – Swysen C. et al. Malaria Journal 2011;10:223 - Leach A. et al. Malaria Journal 2011;10:224

Study design pivotal RTS,S efficacy trial



- Primary endpoints: Efficacy against malaria over first 12 months of follow-up post dose 3 (comparing pooled RTS,S groups to control group)
- Two age groups: Infants 6-12 weeks of age at the time of first vaccination
  Children 5-17 months of age at the time of first vaccination
  5-17 month olds enrolled first ⇨ first results in this age group
- Control vaccines: Rabies vaccine in 5-17 month old children
  MenC-conjugate vaccine in 6-12 week old infants

Study design pivotal RTS,S efficacy trial



Key Phase 3 efficacy and immunogenicity results: 5-17 months and 6-12 weeks age categories

Endpoint	%VE (with 95%CI)	
	5-17 mo	6-12 wk
First episode clinical malaria (ATP, adjusted, co-primary endpoint) (ITT, unadjusted)	**55.8%** (97.5%CI: 50.6; 60.4) **50.4%** (45.8; 54.6)	**31.3%** (97.5%CI: 23.6; 38.3) **30.1%** (23.6; 36.1)
All clinical malaria episodes (ATP, adjusted) (ITT, unadjusted)	**55.1%** (50.5; 59.2) **53.9%** (49.6; 57.8)	**33.0%** (26.4; 38.9) **32.9%** (26.7; 38.5)
Severe malaria (ATP) (ITT)	**47.3%** (22.4; 64.2) **45.1%** (23.8; 60.5)	**36.6%** (4.6; 57.7) **26.0%** (-7.4; 48.6)
Anti-CS antibodies GMTs (EU/mL)	**621.2** (591.7-652.1)	**209.2** (196.8-222.4)
	NEJM 2011; 365: 1863-75	*NEJM 2012; 367: 2284-95*

ATP: According to protocol
ITT: Intent to treat
CS: Circumsporozoite (malaria antigen)
GMT: Geometric Mean Titers

RTS,S/AS01 Phase 3 evaluation 6-12 weeks and 5-17 months age categories: Key differences

		5-17 mo	6-12 wk
Age at first dose (mean)		**11** months	**7** weeks
Prior HBV vaccination: (in RTS,S group)	3 doses	**85%**	0%
	2 doses	4%	0%
	1 dose	2%	1% (birth dose)
	none	9%	**99%**
DTPw-HepB/Hib **co-administration**		0%	100%
Anti-CS antibody responses	GMT (95%CI)	**621.2** (591.7; 652.1)	**209.2** (196.8; 222.4)
		NEJM 2011; 365: 1863-1875	*NEJM 2012; 367: 2284-95*

CS: Circumsporozoite (malaria antigen)
GMT: Geometric Mean Titers

Comparison of incidence and RTS,S/AS01 efficacy between Phase 2 and Phase 3 studies in 6–12 weeks age category

	Phase 2*	Phase 3**
Study center	Kintampo, Bagamoyo, Lambarene	11 study centres
Incidence in control group	**0.62**	**1.25**
DTPwHepB/Hib co-admin	Yes	Yes
HepB vaccine priming	No	No
Anti-CS GMT (95% CI)	**190.3** (154.3-234.7)	**209.2** (196.8-222.4)
% VE (95% CI) (follow up time)	**62** (36-77) (12m)	**32** (25-38) (12m)

Anti-CS = anti-circumsporozoite
GMT = geometric mean antibody titer calculated on all infants
95%CI = 95% confidence interval
VE = vaccine efficacy

Asante et al. Lancet Infect Dis, 2011
**The RTS,S Clinical Trials Partnership, NEJM 2012; 367: 2284-95*

Safety profile of the RTS,S malaria vaccine candidate

- **Serious Adverse Events (SAEs):**
  - Overall reporting comparable between RTS,S and control vaccine groups
  - Fatal SAEs balanced between groups; none considered causally related to study vaccines
- **Reactogenicity:**
  - Injection site reactions and fever reported more frequently in RTS,S than control vaccine groups, but only few reactions were of severe intensity
  - Less local reactogenicity reported at RTS,S than DTwP-HepB/Hib site of injection
- **Generalized convulsive seizures within 7 days after vaccination:**
  - 5-17 month age category: more frequently reported in RTS,S (1/1000 doses) compared to control (0.6/1000 doses) vaccine group
  - 6-12 week age category: reported in RTS,S (0.2/1000 doses) compared to control (0.5/1000 doses) vaccine group
- **Meningitis:**
  - Reported more frequently in the malaria vaccine group, but was considered unlikely to be vaccine-related.

These events will continue to be monitored and full safety review will be conducted by GACVS before the SAGE/MPAC decision session.

Estimated Public Health Impact of RTS,S in Phase III

The absolute number of malaria cases averted depend on **baseline malaria incidence**:

- Given the wide range of transmission intensities across the clinical trial sites involved the Phase III efficacy trial, the number of malaria cases averted will likely vary largely.
- Overall, across all trial sites in the Phase III efficacy trial:

	Number of malaria cases averted (per 1,000 person years at risk)		
	Severe malaria**	Clinical* >5,000 parasites	Clinical **[3] >0 parasites
6-12 weeks[1]	9	269	414
5-17 months[2]	23	733	1088

*primary case definition

**secondary case definition

Calculated from : 1. NEJM 2011;365:1863-75 – 2. NEJM 2012;367:2284-95 and 3. GSK data on file

Impact of RTS,S and that of other vaccines

- **RTS,S**: **Number of malaria cases averted** (per 1,000 person years at risk)

	Severe malaria	Clinical >0 parasites
6-12 weeks[1]	9	414
5-17 months[2]	23	1088

- **PCV**: **Pneumonia cases averted** (per 1,000 PYAR)

	Severe	Clinical
in the Gambia[3]	2	17
in South Africa[4] (HIV-)	1.6	2.7
(HIV+)	20.5	23.0

- **HRV**[5]: **Rotavirus gastroenteritis cases averted** (per 1,000 PYAR)

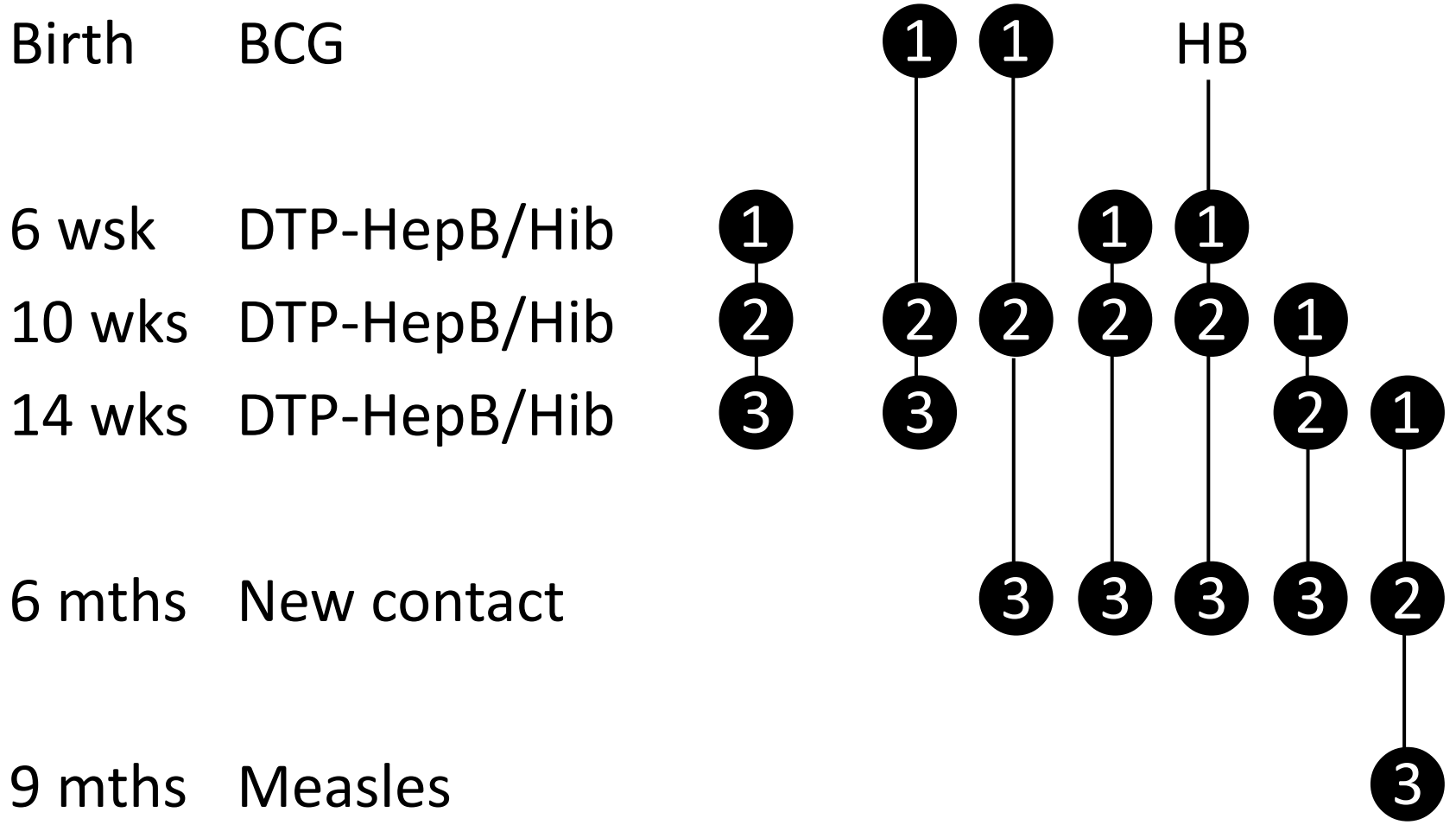
Severe	Clinical
50	117

Calculated from : 1. NEJM 2011;365:1863-75 – 2. NEJM 2012;367:2284-95 and GSK data on file
3. Lancet 2005;365:1139-46 – 4. CID 2005;40:1511-8 – 5. NEJM 2010;362:289-98

Update on other clinical activities

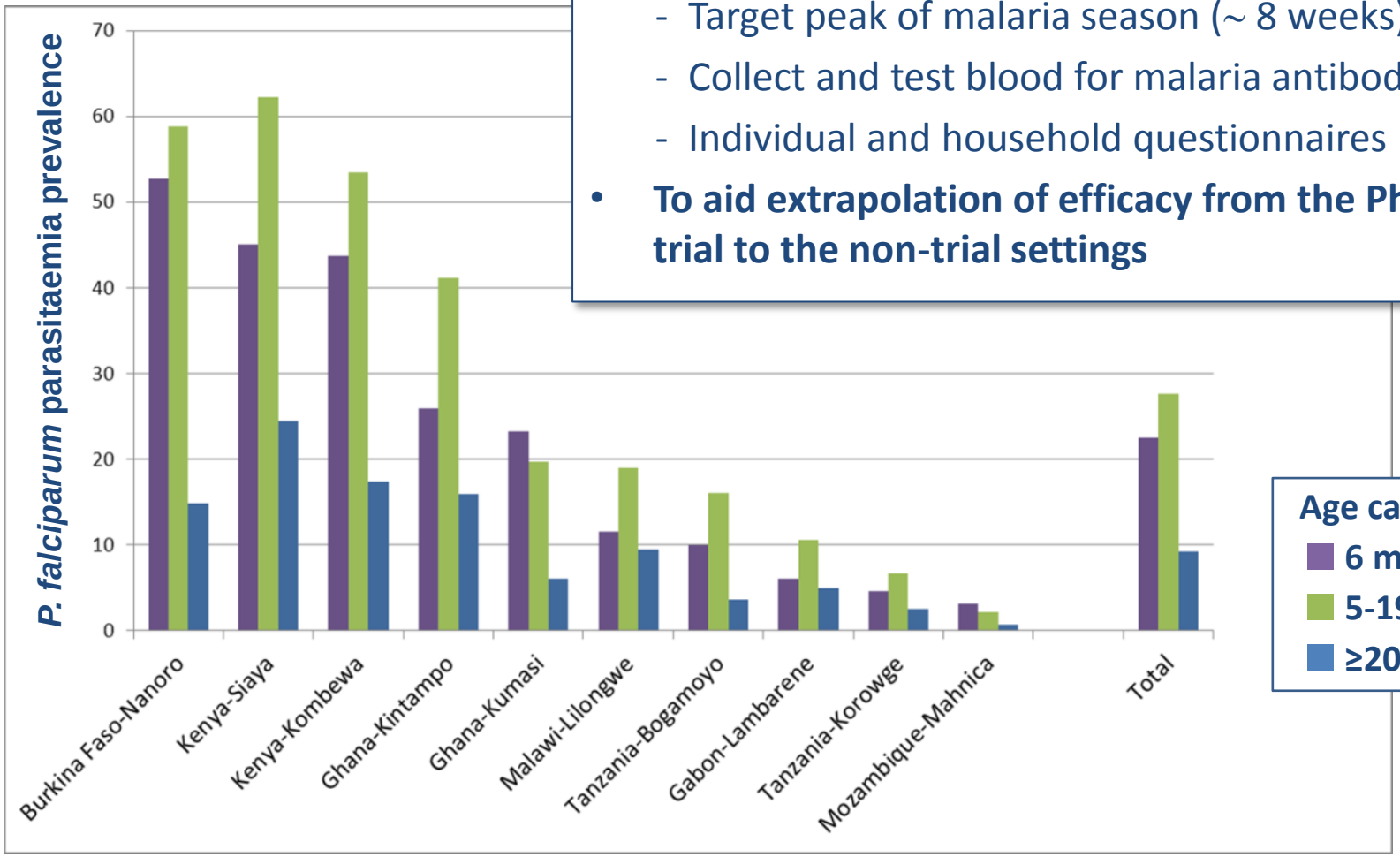
- **Lot-to-lot consistency study (Nigeria)**
  - Healthy 5-17 month olds (80/group)
  - **Results:**
    - Demonstrated equivalence of three consecutive commercial scale lots
    - Demonstrated non-inferiority of commercial to pilot scale lots
    - No safety signal observed - all vaccines were well tolerated
- **Co-administration with Rotavirus and Pneumo-conjugate vaccines**
- **Safety/ Immuno study in HIV+ children**
- **Genotyping (co-sponsored by Harvard School of Public Health)**
  - Selective pressure on the parasite: Specific parasite variants? Change of the number of parasite types?
- **Explore immune correlates of RTS,S-induced protective immunity**
- **Explore new schedules**

Phase 2 (Malawi): Exploring new schedules



Malaria Transmission Intensity: 6405 subjects (ATP)

- **To provide data on malaria transmission intensity in the communities where the trial is being conducted**
  - Primary endpoint: *P. falciparum* parasitaemia
  - Target peak of malaria season (~ 8 weeks)
  - Collect and test blood for malaria antibodies
  - Individual and household questionnaires
- **To aid extrapolation of efficacy from the Phase 3 trial to the non-trial settings**



EMA Timelines

- Target filing in 2014 – contingent on agreement with EMA and in accordance with the following key assumptions:
  - Remaining clinical data available on time and supportive of indication in:
    - 6 weeks to 17 months of age
    - All settings
  - No major technological issues arise prior submission

Acknowledgments

Participants and families

Study staff

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