Development of a Malaria Vaccine for Sub-Saharan African Children

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Disclosure of interests

- Karin Hardt is an employee of GSK Vaccines in Belgium, in charge of Vaccine Medical education and training

Agenda

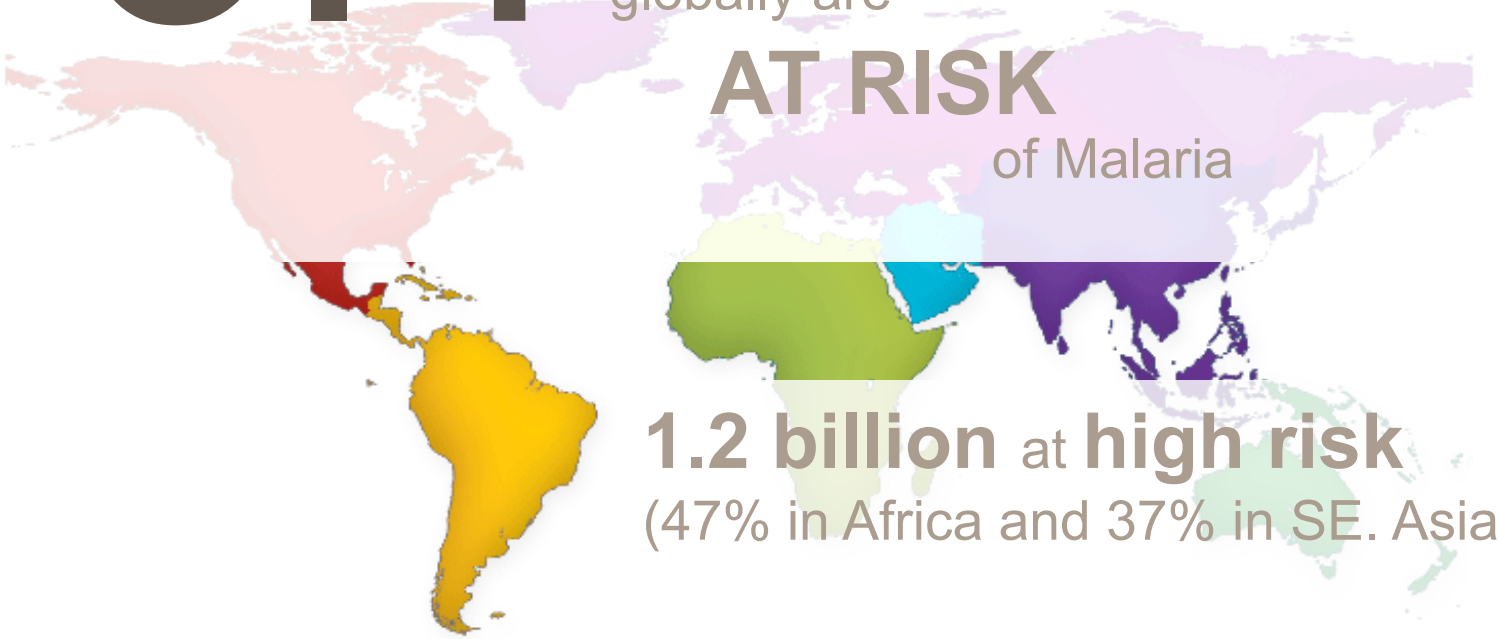
- Malaria
  - Epidemiology, clinical manifestations and prevention
  - Principles of malaria vaccine development
- RTS,S vaccine candidate
  - RTS,S vaccine design
  - Summary of early development
  - Status of ongoing Phase III
  - Next steps

3.4 billion people

globally are

AT RISK

of Malaria



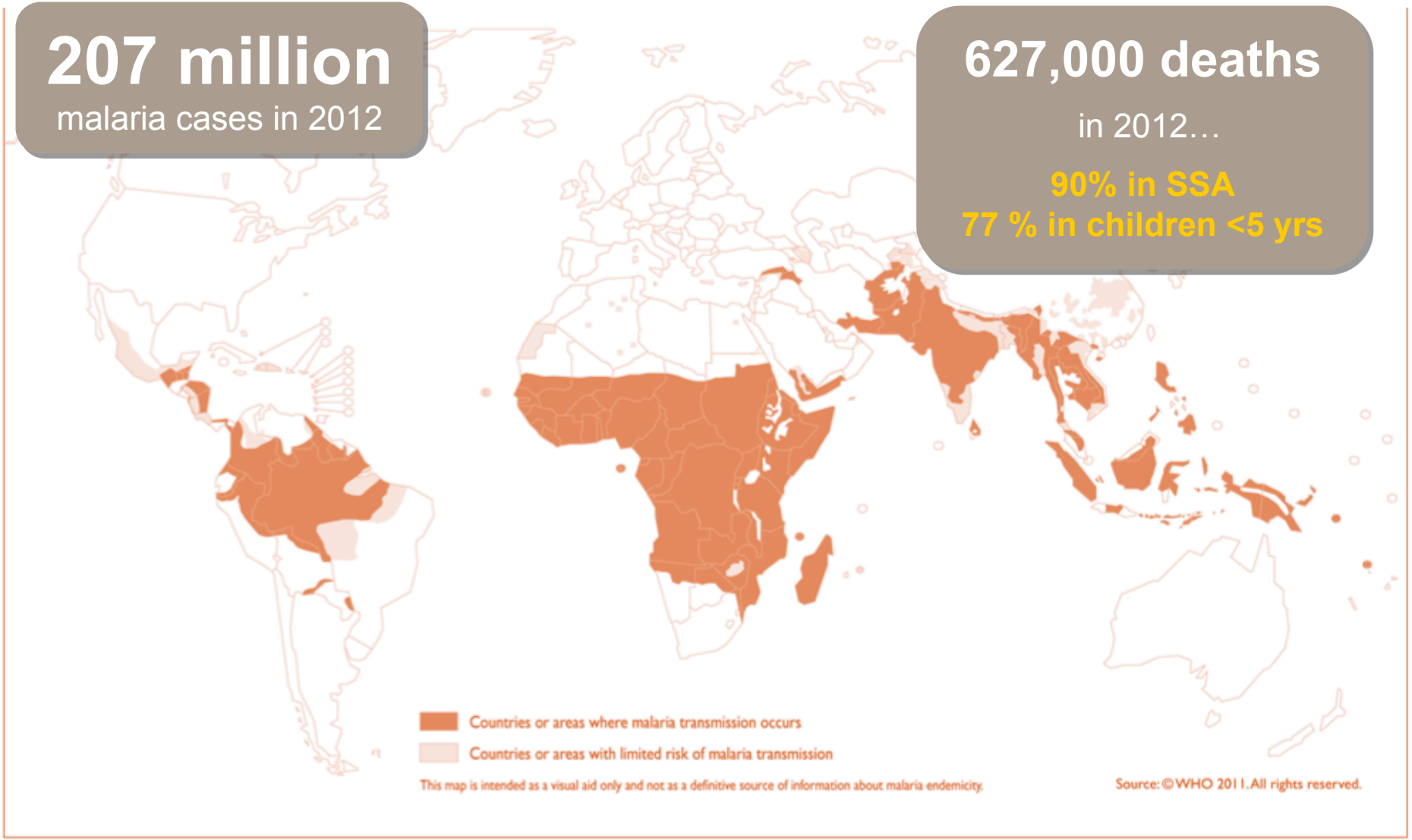
1.2 billion at **high risk**

(47% in Africa and 37% in SE. Asia)

WHO World Malaria Report 2013

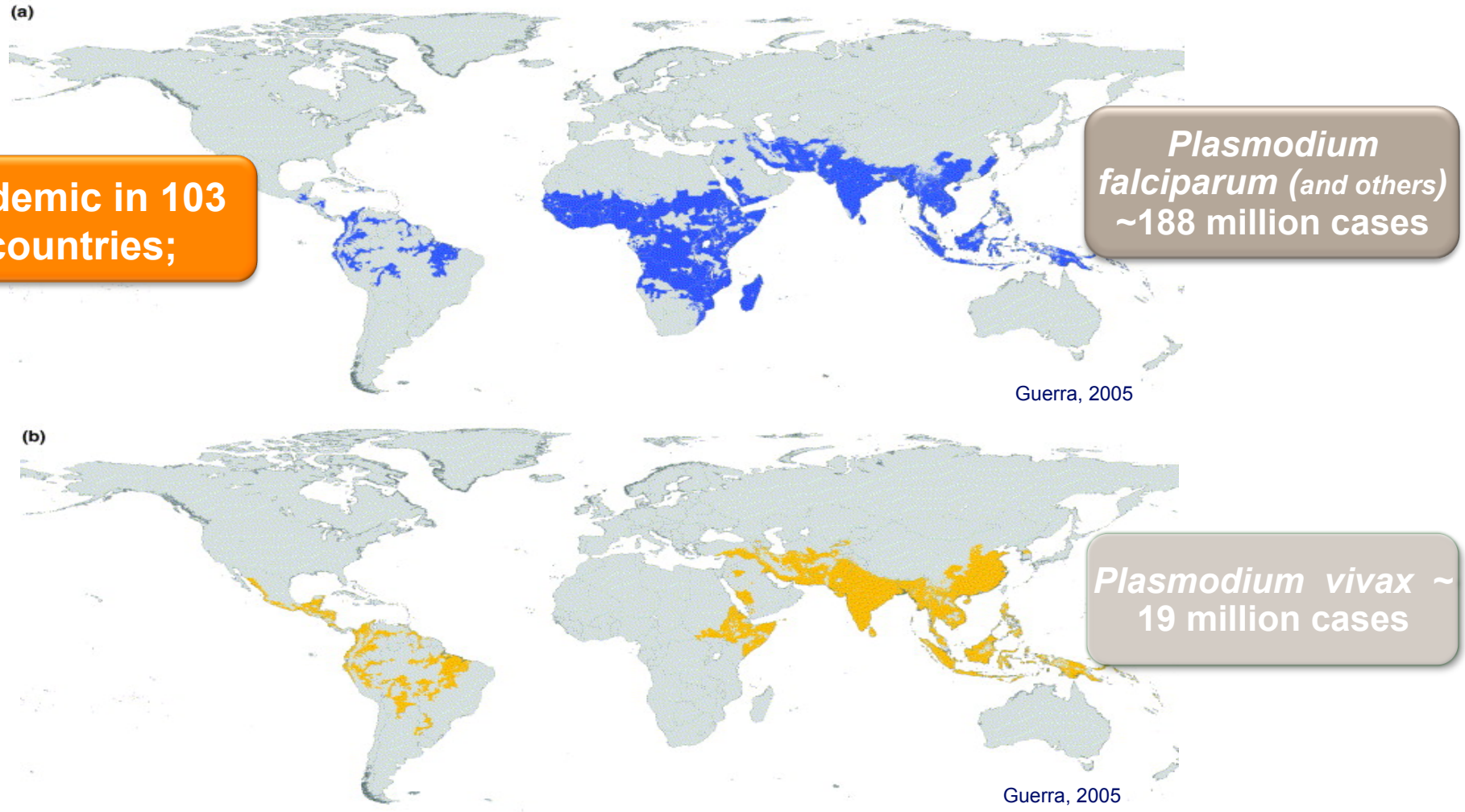
The overall burden of Malaria is still intolerable

Half of the global population is at risk, one death per minute



WHO World Malaria Report 2013

Malaria is caused by 5 *Plasmodium* strains, but only 2 with high global public health impact: *P. falciparum and vivax*



WHO World Malaria Report 2013

…and per continent…

Americas

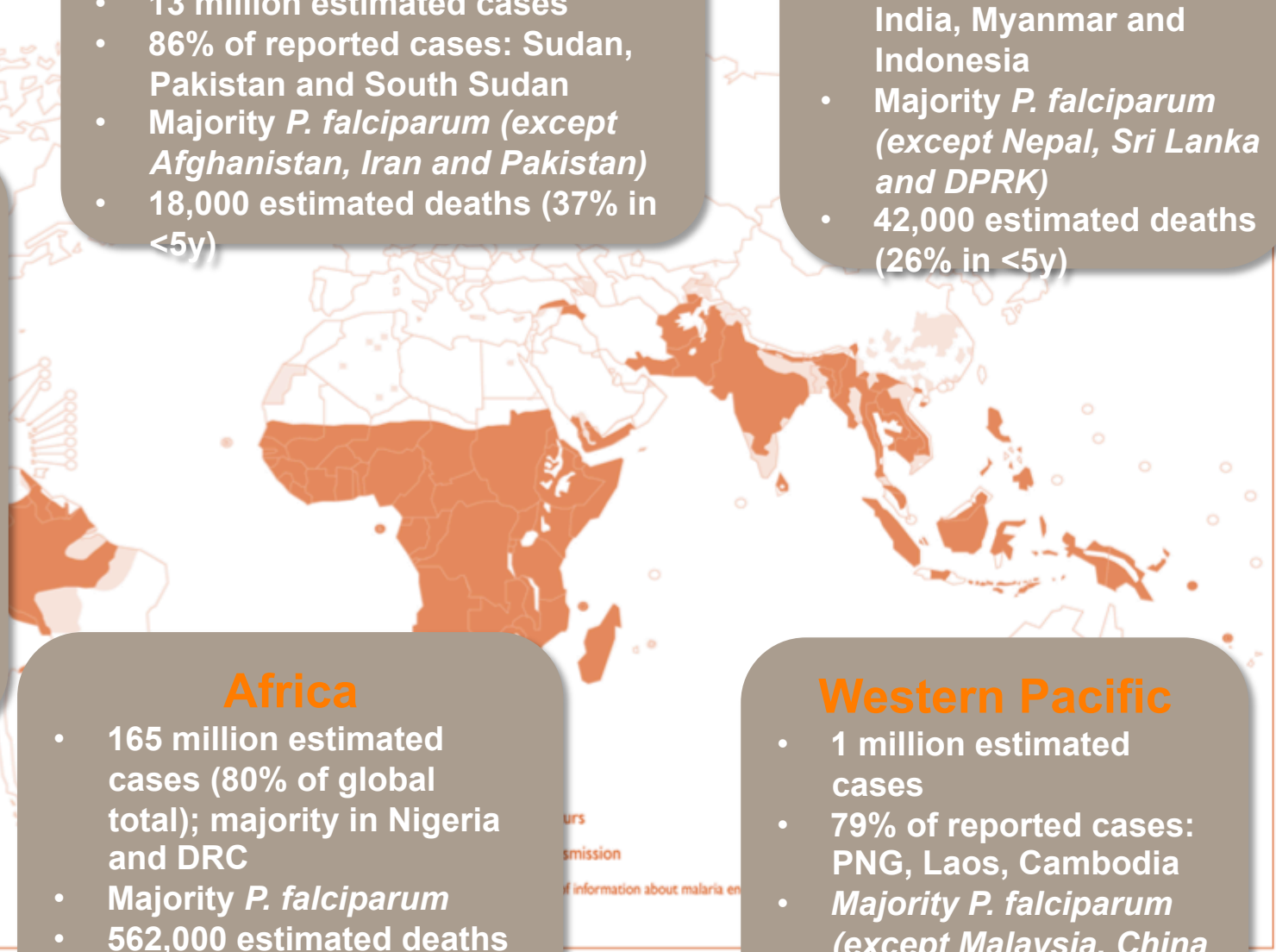
- 0.8 million estimated cases
- 76% of reported cases: Brazil, Colombia and Venezuala
- Majority *P. vivax (except Rep. Dom and Haiti)*
- 800 estimated deaths (27% in <5y)

E. Mediterranean

- 13 million estimated cases
- 86% of reported cases: Sudan, Pakistan and South Sudan
- Majority *P. falciparum (except Afghanistan, Iran and Pakistan)*
- 18,000 estimated deaths (37% in <5y)

SE Asia

- 27 million estimated cases
- 96% of reported cases: India, Myanmar and Indonesia
- Majority *P. falciparum (except Nepal, Sri Lanka and DPRK)*
- 42,000 estimated deaths (26% in <5y)



Africa

- 165 million estimated cases (80% of global total); majority in Nigeria and DRC
- Majority *P. falciparum*
- 562,000 estimated deaths (90% of global total) (82% in <5y)

Western Pacific

- 1 million estimated cases
- 79% of reported cases: PNG, Laos, Cambodia
- *Majority P. falciparum (except Malaysia, China and RoK)*
- 3,500 deaths (46% in <5y)

WHO World Malaria Report 2013

Key facts

- Half of the World Population remains at risk.
- 99 countries still have active Malaria transmission.
- The vast majority of estimated cases (80%) and deaths (91%) occur in sub-Saharan Africa.
- The vast majority of deaths (86%) occur in children <5 years of age.
- 80% of malaria deaths occur in just 14 countries and 80% of cases occur in 17 countries
- *Plasmodium vivax* is the most geographically widespread strain but *falciparum* remains the most deadly
  - Dormant liver stage of *P. vivax* (hypnozoïtes) that can be re-activated
    - 1 infection = multiple clinical episodes
    - dramatically increases the burden
  - Causes less deaths but frequently incapacity

WHO World Malaria Report 2012

High Risk Groups

Some population groups are at considerably higher risk of contracting malaria, and developing severe disease, than others. These include infants, children under five years of age, pregnant women, patients with HIV/AIDS, as well as non-immune migrants, mobile populations and travellers.

High Risk Group	
Pregnant women	Malaria in pregnancy increases the risk of maternal and fetal anaemia, stillbirth, spontaneous abortion, low birth weight and neonatal death.
Infants	Infants born to mothers living in endemic areas are vulnerable to malaria from approximately three months of age, when immunity acquired from the mother starts to wane.
Children under five	In high-transmission areas of the world, children under five years of age (including infants) are the most vulnerable group. Worldwide, over 85% of malaria deaths occur in children under five years of age.
HIV/AIDS patients	Co-infection and interaction between these two diseases have major public health implications. HIV infection increases the risk of malaria infection, severe malaria and death, while malaria may result in the worsening of clinical AIDS.
Migrants and mobile populations	Migrants, refugees and other mobile population groups often lack partial immunity to malaria, and have limited access to prevention, diagnostic testing and treatment services.

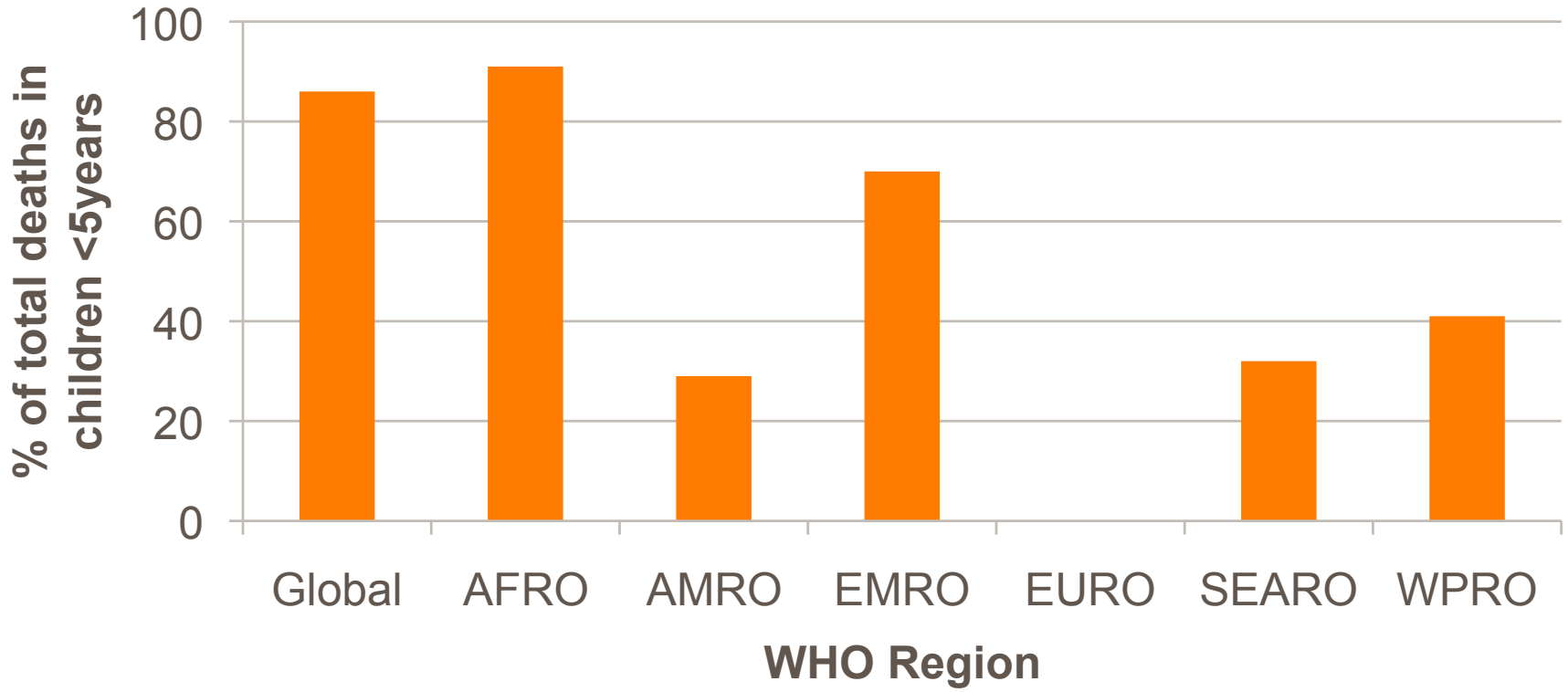
WHO World Malaria Report 2013

Peak incidence of malaria depends on intensity of transmission

- Infants are protected by maternal antibodies during the first 3 months of life.
- Natural immunity develops over time depending upon frequency and duration of parasite exposure (intensity of malaria transmission).
- **Natural immunity develops against clinical manifestations of malaria** (blood stage immunity). There is **no evidence of natural immunity against infection**.
- The age category with the highest malaria incidence depends on the speed of acquisition of natural immunity.

Snow RW et al. J Infect Dis 1998; 177:819-822

Age/Geography: proportion of Malaria deaths occurring in children <5y in different WHO-regions



- ~86% total malaria deaths in <5yrs
- High vs low burden settings
- Similar patterns in high burden regions in Asia as are seen in Africa

WHO Global Malaria Report 2012

Age – proportion *P. falciparum vs vivax*

Prevalence peak for *P. vivax* is younger than *P. falciparum* peak

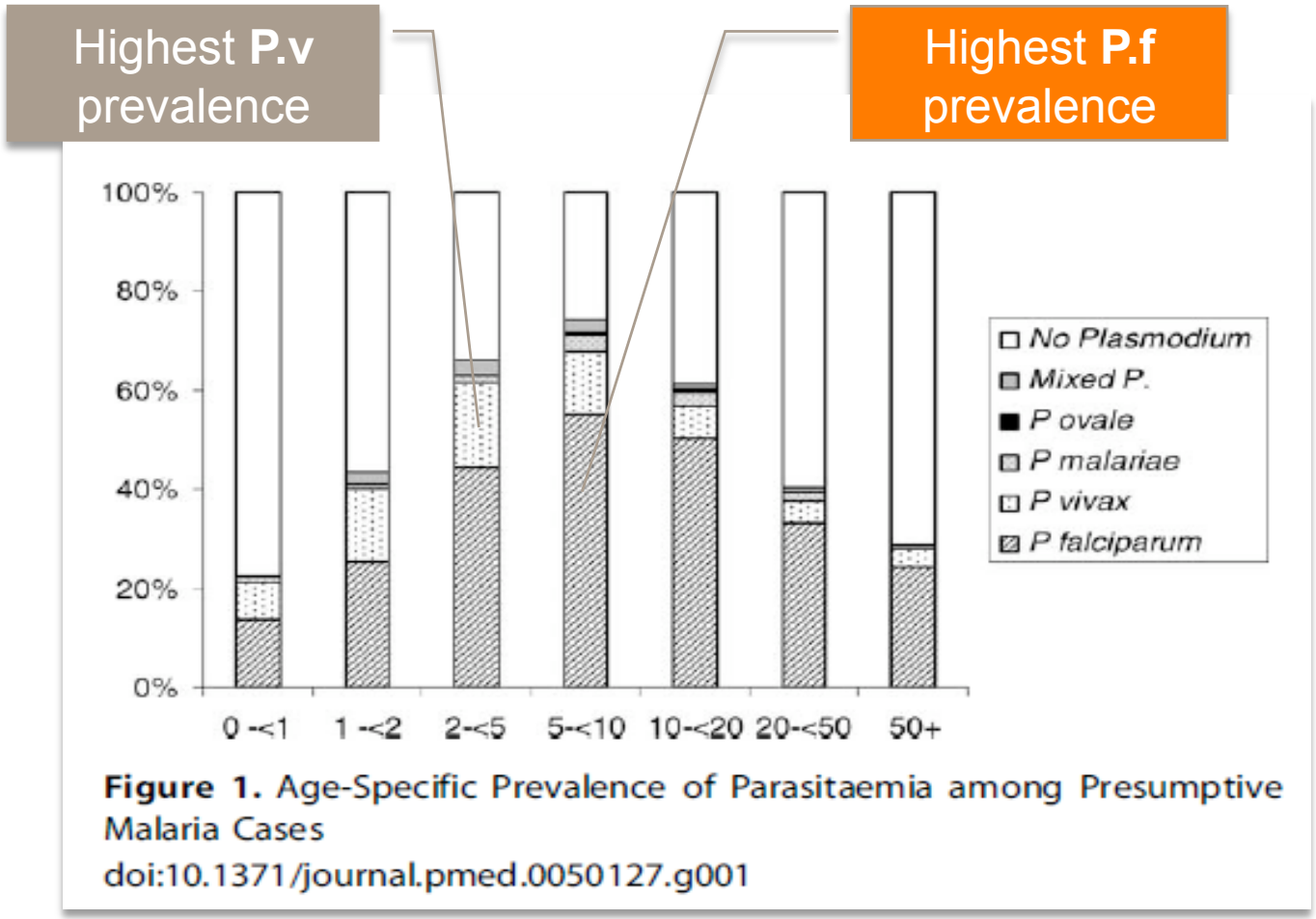


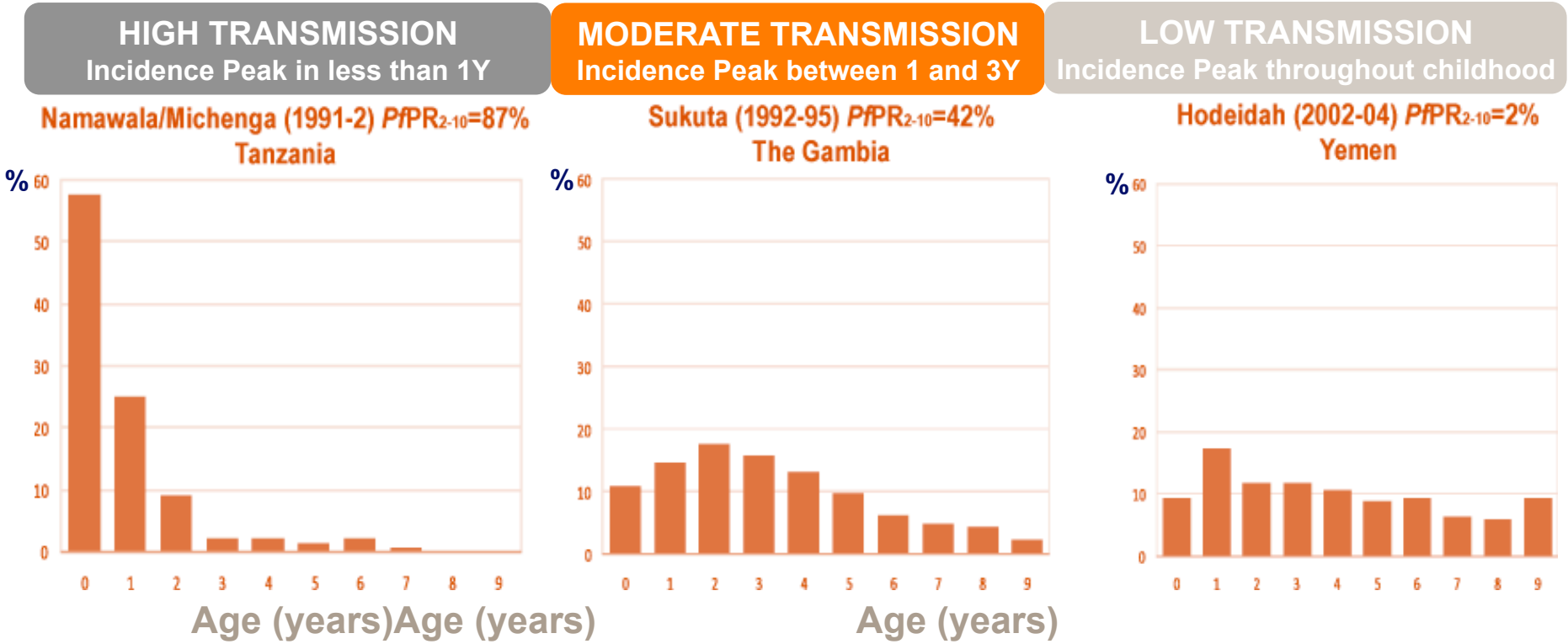
Figure 1. Age-Specific Prevalence of Parasitaemia among Presumptive Malaria Cases

doi:10.1371/journal.pmed.0050127.g001

WHO Global Atlas Database (2010)

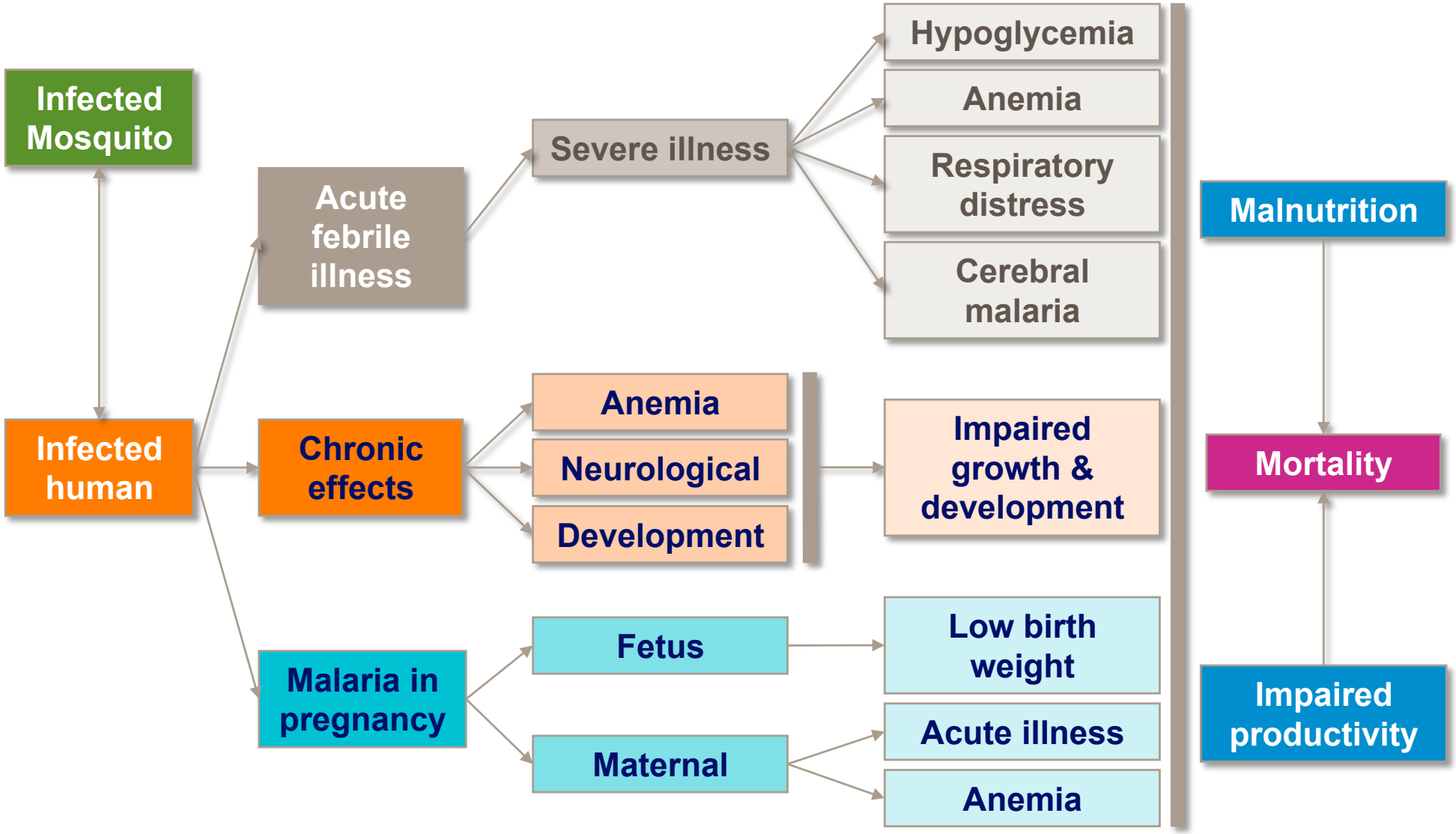
Intensity of malaria transmission and age of peak incidence

Age distribution of hospitalized malaria in children 0 to 9 years of age from three communities with different *P. falciparum* parasitaemia rates (PfPR)



Snow RW et al. J Infect Dis 1998; 177:819-822 - Mutabingwa TK et al. PLoS Med 2005; 2:e407
Okiro EA et al. Malar J 2009; 8:4 - Guinovart C et al. Malar J 2008; 7:36.

Clinical outcomes of malaria

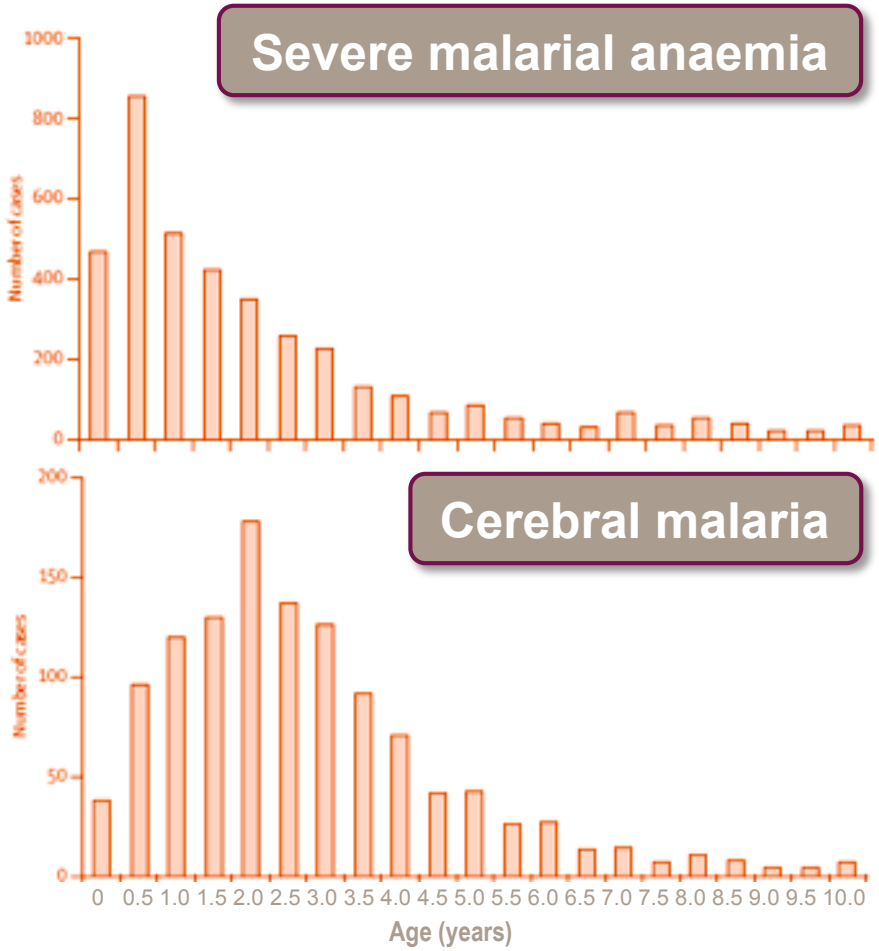


Breman JG. Am J Trop Med Hyg 2001; 64 (1-2 Suppl):1-11

Most frequent causes of hospitalisation due to severe malaria

- Younger children around 1 year old:
  - Severe anaemia
  - Respiratory distress

- Children between 2 and 3 years old:
  - Neurological manifestations, coma due to cerebral malaria
  - 20% case fatality rate



Bassat Q et al. *Malar J* 2008; 7:37 - O'Meara WP et al. *Lancet* 2008; 372:1555-1562.

Malaria control interventions available today

Preventive interventions

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

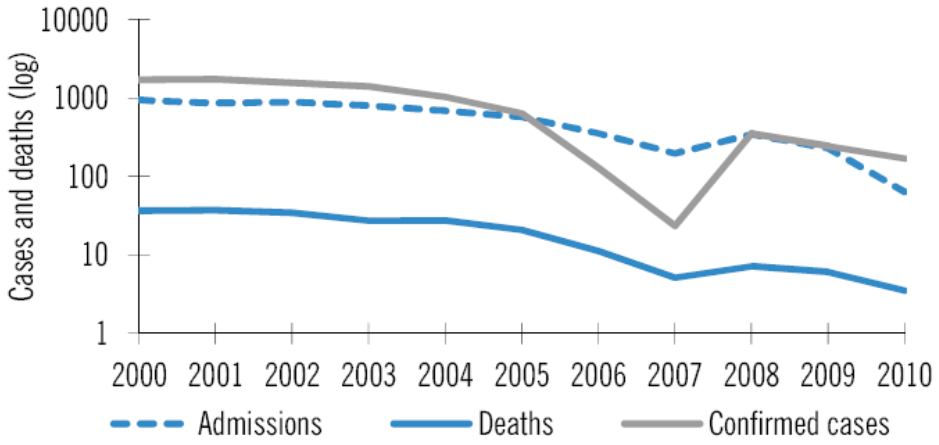
Curative interventions

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

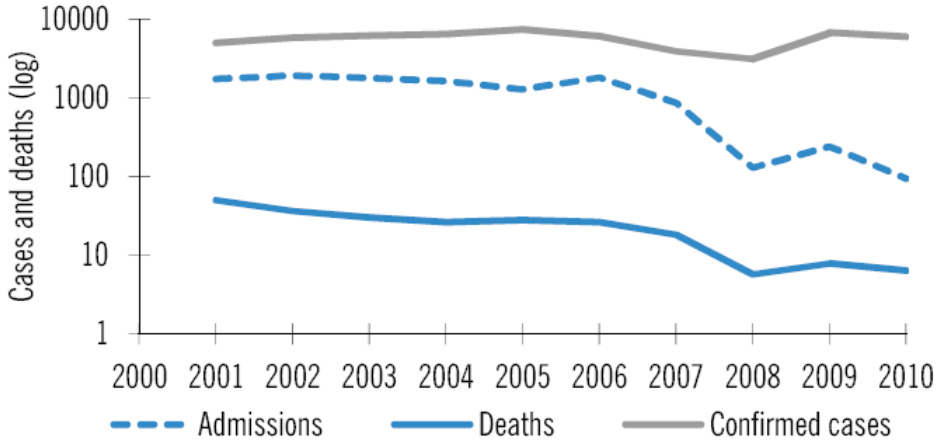
RBM Partnership web site. Global Malaria Action Plan, GMAP. Available from: <http://www.rbm.who.int/gmap/index.html> [Accessed: 15 June 2009]

Recent trends in malaria incidence

Zanzibar (Tanzania)



Rwanda



WHO World Malaria Report 2011

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)?

RDTs, Rapid Diagnostic Tests
LLIN Long-Lasting Insecticidal Nets
ACT Artemisinin Combinations Therapy

Trends

- Worldwide, mortality rates decreased by 45% in all age-groups and by 51% in the under 5 years old between 2000 and 2012 thanks to a tremendous expansion in financing and coverage of existing malaria control measures/programmes

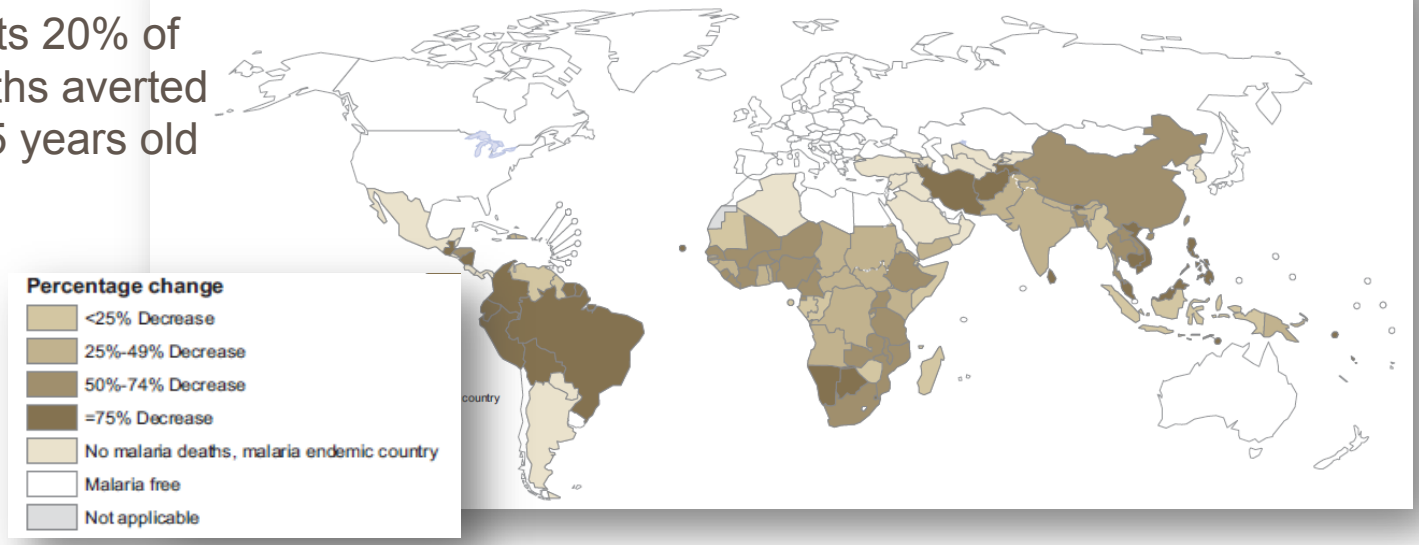
- 3,3 million deaths and 500 million cases averted between 2001 and 2012

  - ❑ 69% lives saved in the 10 countries with the highest burden in 2000

  - ❑ 3 million deaths averted in children under 5 years old in SSA (90%) and 3.08 million in Africa (93%)

  - ❑ which represents 20% of the 15 million deaths averted in children under 5 years old in SSA (MDG 4)

Figure 8.2 Percentage change in malaria mortality rates, 2000-2012



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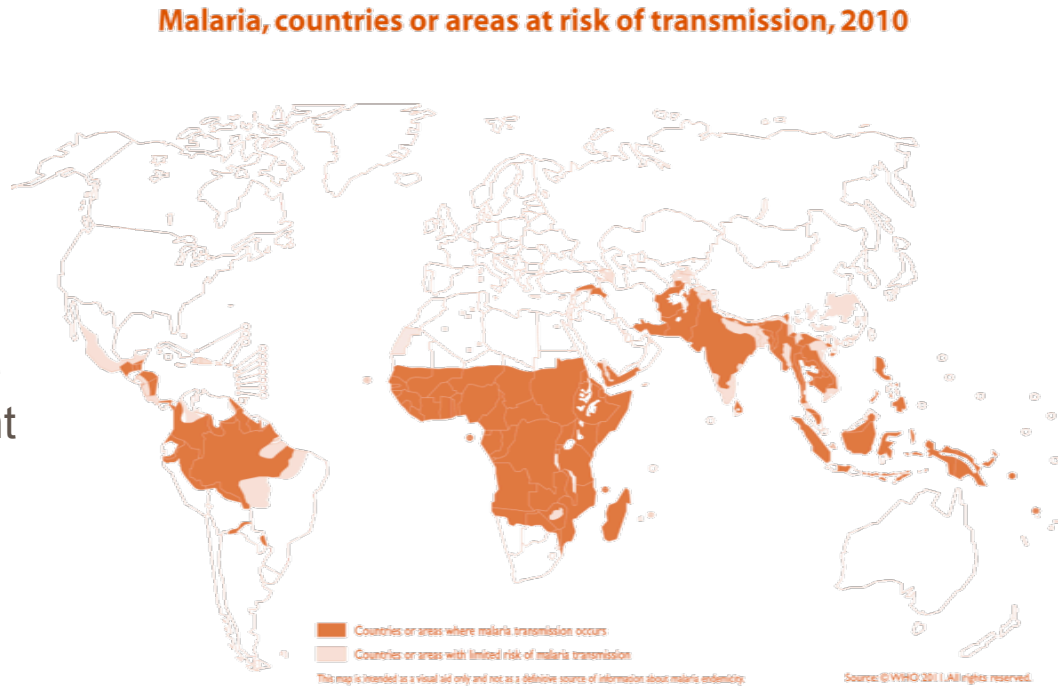
The intolerable burden of malaria

- **Malaria epidemiology:**
  - ~219 million cases/year, 80% of which are in sub-Saharan Africa
  - ~660,000 deaths/year, mostly in African children under five years
  - In Africa, malaria is the leading cause of death from a single infectious agent



- **Tools available today:**
  - Insecticide treated bednets
  - Indoor residual spraying
  - Improved case management
  - Rapid diagnosis and treatment (ACTs, Artemisinin Combination Therapies)

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

Agenda

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  - Epidemiology, clinical manifestations and prevention
  - **Principles of malaria vaccine development**
- RTS,S vaccine candidate
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  - Next steps

The need for a malaria vaccine

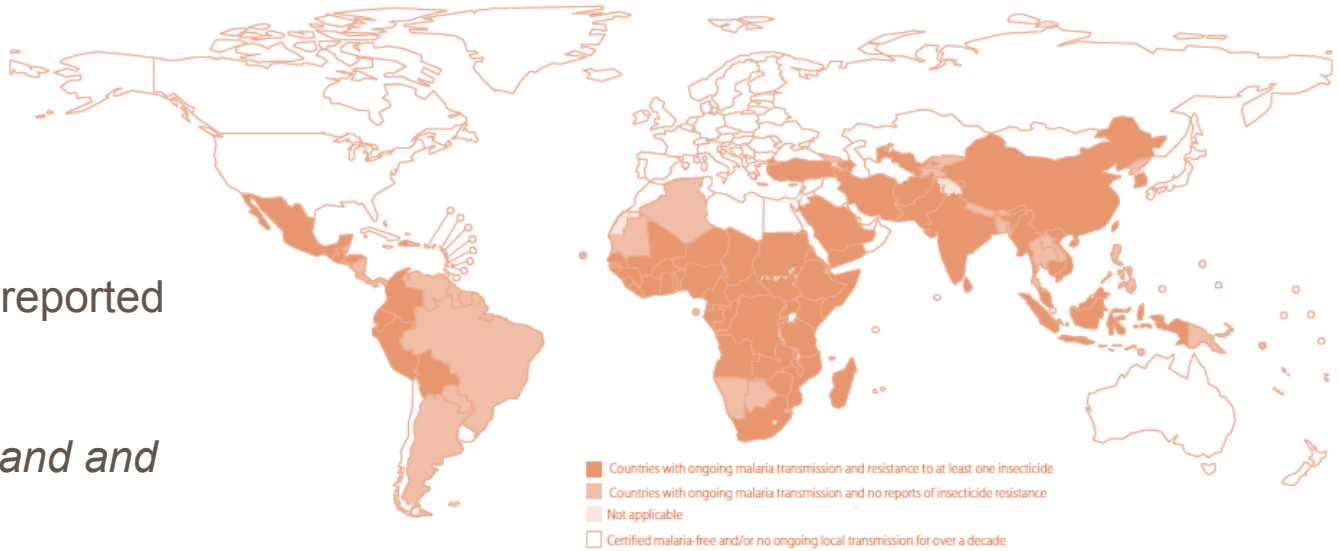
- Challenges to malaria control in the sub-Saharan Africa setting:
  - Parasite resistance to drugs
  - Mosquito resistance to insecticides
  - HIV co-infection
  - Climate change increasing suitable mosquito habitats
  - Inadequate infrastructure for delivery of control measures
  - Low compliance to protective measures
  - Long term sustainability of existing control measures
- Additional tools (such as a malaria vaccine channeled through national immunization programs) would help to meet public health policy goals and targets

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

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

Overall sustainability of Malaria Control remains at risk

Figure 4.7 Countries with ongoing malaria transmission where insecticide resistance has been identified in at least one of their major vectors



- Resistance to Artemisinins reported in **4 countries in SE Asia**: *Cambodia, Myanmar, Thailand and Viet Nam*
- Resistance to at least 1 insecticide used in ITNs or in IRS reported in **38 countries in Africa and 64 countries worldwide** (*77 countries have adopted policy recommendations to follow-up resistance progression in 2011)*
- **Funding** availability and sustainability uncertain (gap already exists).

WHO World Malaria Report 2012

The development of a malaria vaccine

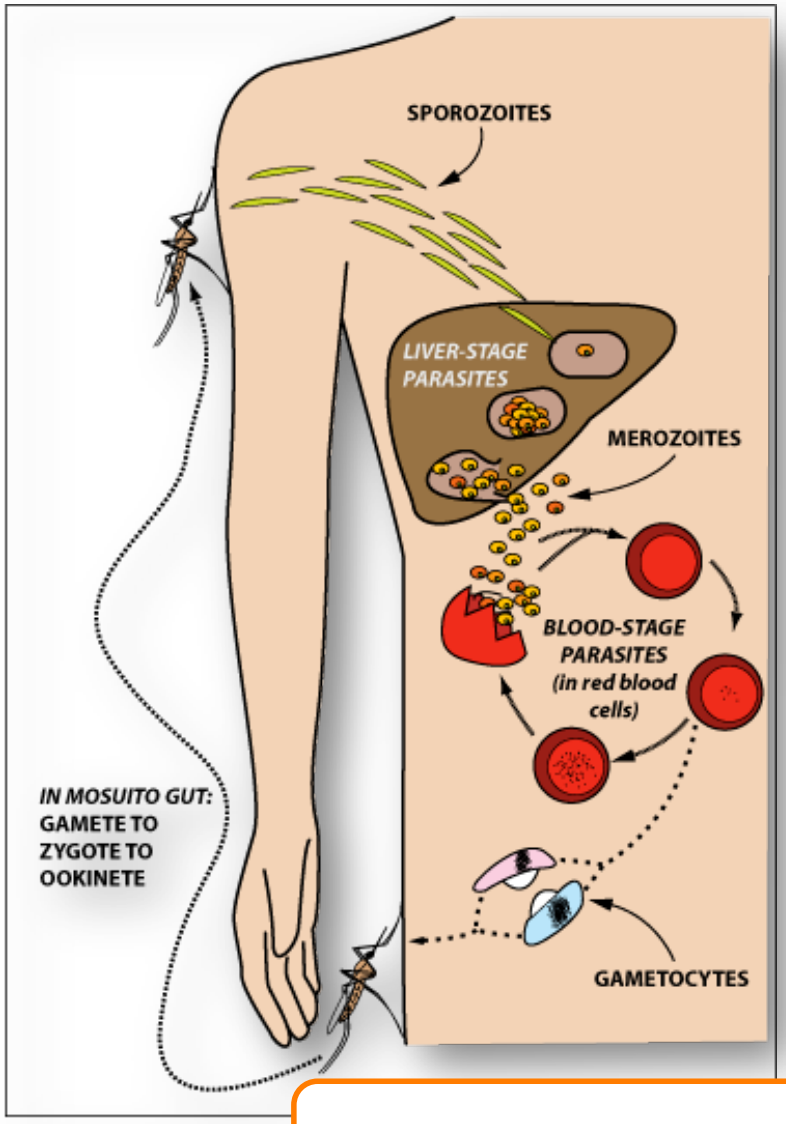
Challenging …

- 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



Pre-erythrocytic stage (= infection)

Asexual blood stage (resulting in disease)

Sexual blood stage (resulting in transmission)

⇨ **Stage specific antigens, immunity and vaccine approaches**

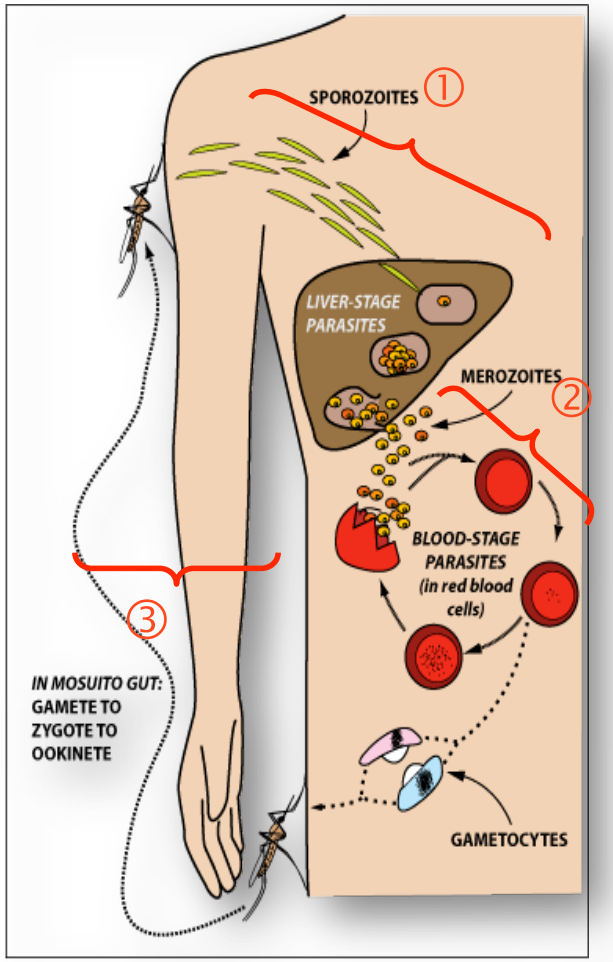
Parasite cycle & opportunities for vaccination

Three types of vaccines can be envisioned based on the Ag / parasitic stage they are targeting:

1) **Pre-erythrocytic vaccines**
    1) Targeting pre-erythrocytic antigen
    2) Potential to prevent or limit liver invasion or liver stage development
    3) ➥ impact on infection and disease incidence

2) **Blood stage vaccines**
    1) Targeting the asexual erythrocytic stages of the parasite
    2) Potential to reduce rate of asexual reproduction in the blood
    3) ➥ directly limit parasitemia and therefore clinical disease

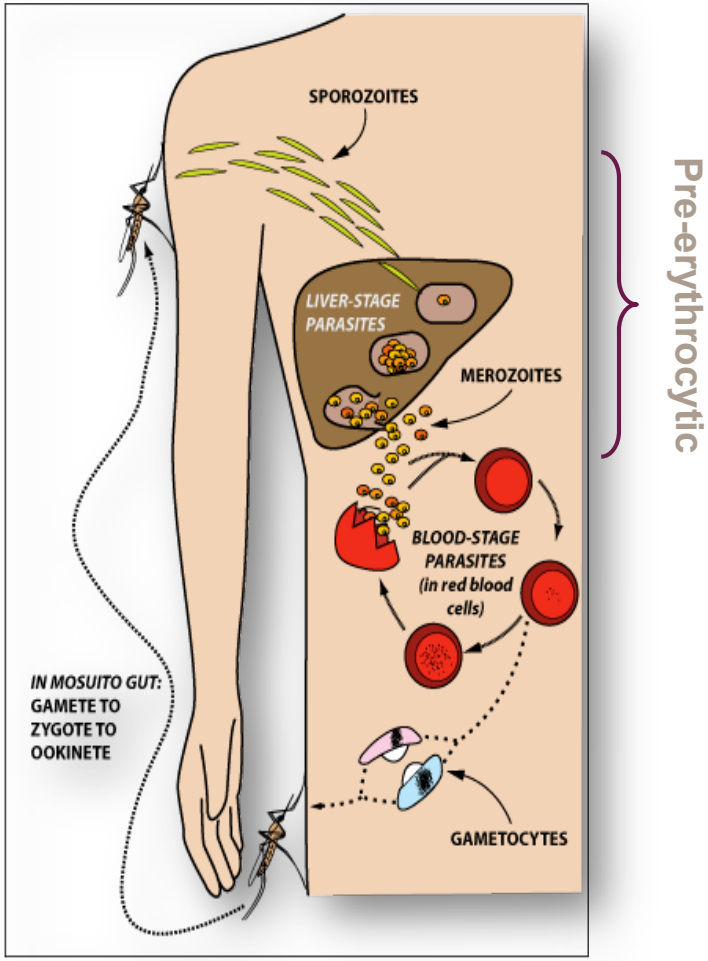
3) **“Transmission” blocking vaccines**
    1) Targeting the sexual erythrocytic stages of the parasite
    2) Potential to limit the development of the parasite cycle within the insect vector
    3) ➥ limit transmission of parasites to vectors



Pre-erythrocytic malaria vaccines

- Pre-erythrocytic malaria vaccines (sporozoites and intra-hepatic parasites): are aimed at **preventing infection and/or reduce incidence and severity of disease**
- Protection against pre-erythrocytic parasites requires:
  - Humoral antibody responses against sporozoites to block invasion of hepatocytes
  - Cellular $CD4^+$ (Th1) and $CD8^+$ (CTL) T lymphocyte responses to kill intra-hepatic parasites and/or destroy infected liver cells through IFN-γ secretion or via direct cytotoxicity

- ⇨ **Protection against infection**
- ⇨ **Impact on clinical disease**

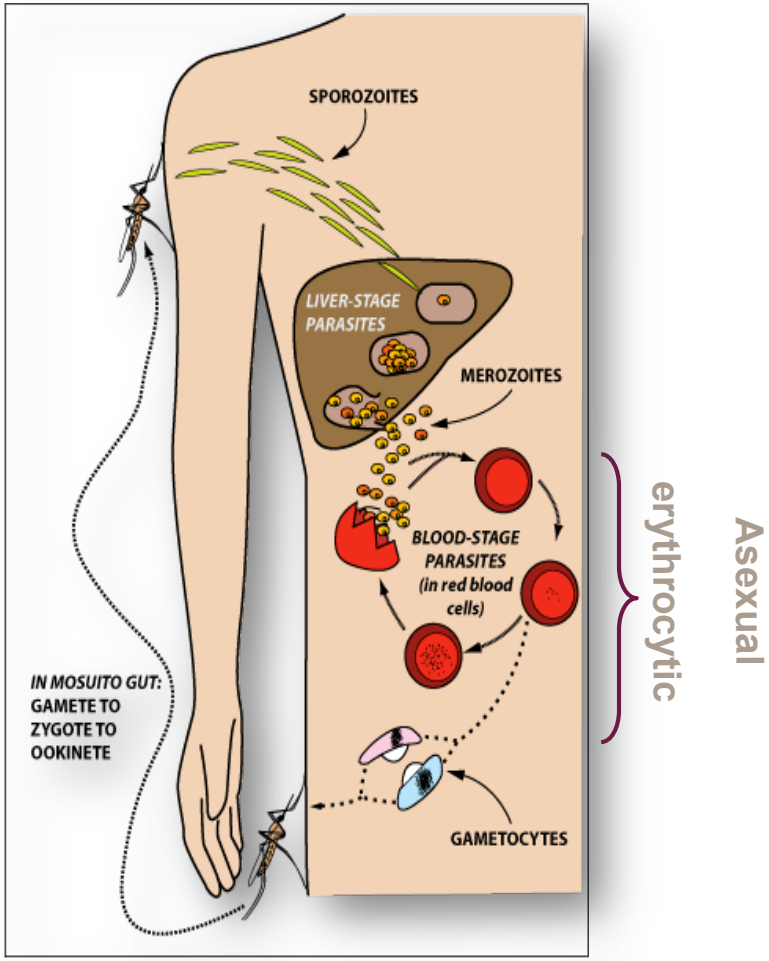


Asexual blood stage malaria vaccines

- Asexual blood stage malaria vaccines (free merozoites and parasitized RBCs): are aimed to **reduce disease incidence and severity**
- Protection against asexual blood stage parasites requires humoral antibody responses against merozoites, infected RBC surface proteins, or parasite toxins to:
  - Inhibit/neutralize infection of RBC
  - Inhibit intracellular parasite development
  - Prevent cyto-adherence
  - Neutralize disease-causing toxins

- ⇨ **Impact on clinical disease**

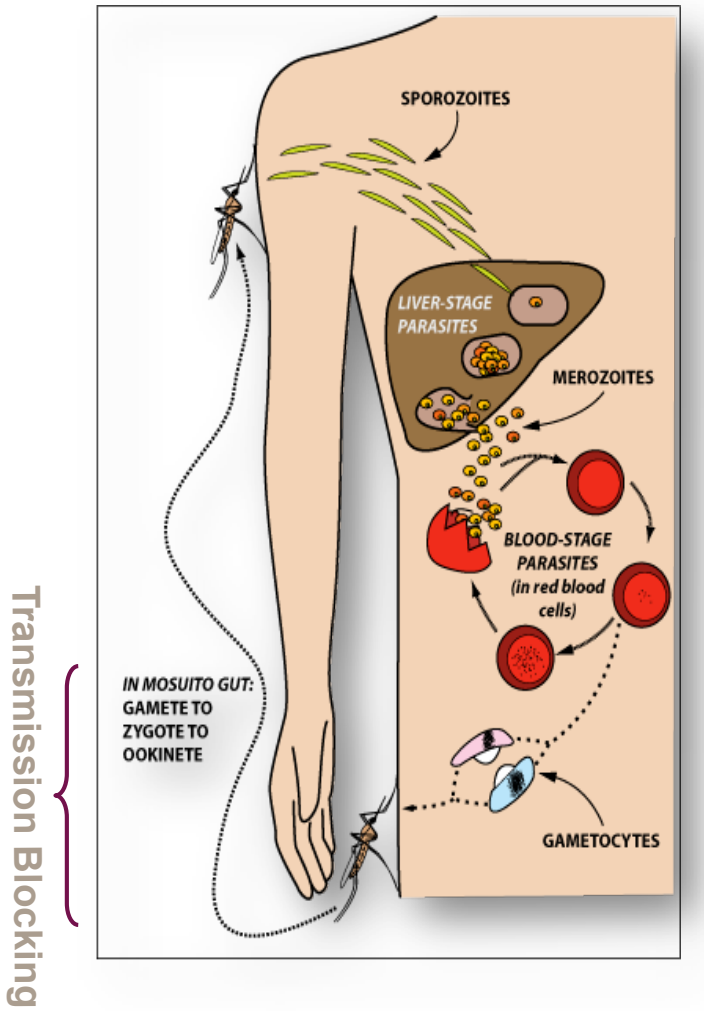
⇨ no impact on infection



Sexual blood stage malaria vaccines

- Sexual blood stage (transmission blocking, or altruistic) malaria vaccines (targeting gametocytes, gametes and/or zygotes): are aimed to **prevent man to mosquito transmission**
- Protection against sexual blood stage parasites (gametocytes) requires humoral antibody responses against surface exposed proteins of female and male gametes and zygotes to inhibit development of parasite within mosquitoes

- ⇨ **transmission-blocking vaccines**
  ⇨ no impact on disease



Potential malaria vaccine antigens

- More than 30 Antigens identified in various stages of *Plasmodium falciparum* life cycle as potential vaccine candidate, among them:

Pre erythrocytic	**Asexual blood stage**	**Sexual blood stage**
CSP	MSP1	Pfs230
TRAP/SSP2	MSP2	Pfs48/45
LSA1	MSP3	Pfs27/25
LSA3	SERA	Pfs28
PfEXP1	GLURP	Pfs25
STARP	AMA1	Pfs16
SALSA	RAP1/2	
	RESA	
	PfEMP1	
	HRP1	
	SEQUESTRIN	

Live attenuated vaccines based on irradiated/mutated sporozoites

Main Approaches to Malaria Vaccine Development

1. **Protein-adjuvant vaccines**
   - RTS,S/AS01
   - AMA1/ISA720
   - MSP1/Alum+CpG

antibodies

2. **Vectored vaccines**
   - Fowlpox-MVA
   - Adenovirus-MVA
   - DNA-Adenovirus

cellular immunity

3. **Whole parasite vaccines**
   - Irradiated sporozoites
   - Genetically attenuated parasites
   - Low dose blood-stage parasites

both to multiple antigens

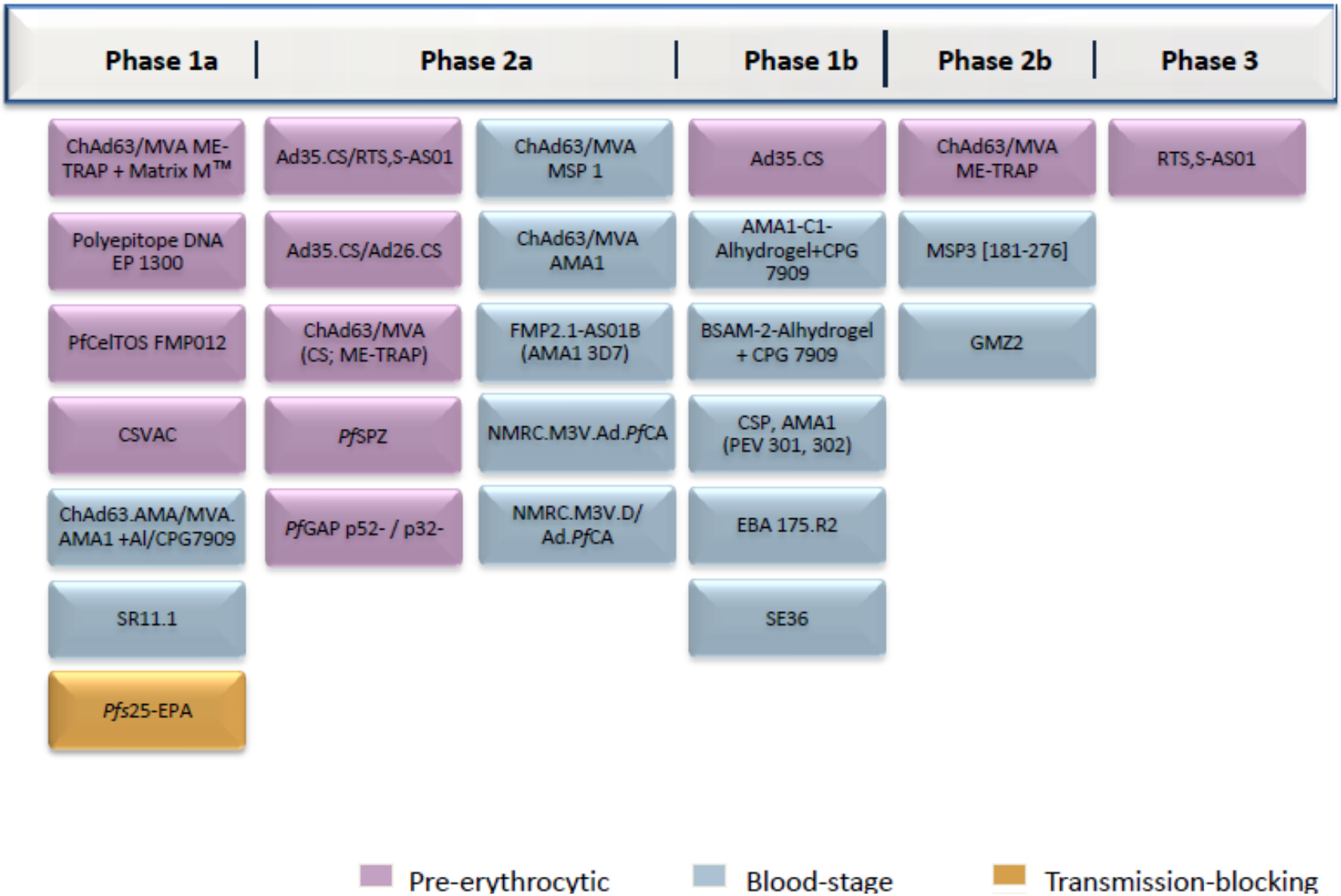
Courtesy of Adrian Hill, Jenner Institute UK, Oxford

Multi-Component Malaria Vaccine Strategy

- A Four-Stage High Efficacy Modular Vaccine against *P. falciparum* malaria
  - Sporozoite Stage: CSP (R21)
  - Liver Stage: TRAP
  - Blood Stage: PfRH5
  - Mosquito Stage: Pfs25

Courtesy of Adrian Hill, Jenner Institute UK, Oxford

Global malaria vaccine pipeline



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

WHO Rainbow Table : phase 2b and 3 studies

Vaccine Clinical Phase		Reference
Pre-erythrocytic Projects		
RTS,S/AS01E Phase 3	RTS,S consists of sequences of the circumsporozoite protein and the hepatitis B surface antigen (HBsAg). The vaccine contains AS01E adjuvant	Ballou 2009 Parasite Immunol Cohen 2010 Hum Vaccin Agnandji 2010 J Infect Dis Agnandji 2011 NEJM 2012 NEJM
ChAd63/MVA **ME-TRA**P Phase 2b	ME-TRAP is a pre-erythrocytic fusion antigen comprising B-cell, CD4+ and CD8+ T-cell epitopes from 6 P. falciparum antigens fused to TRAP pre-erythrocytic Antigen – Prime Boost strategy	Reyes-Sandoval 2010 Infect Immun Bakshi et al 2010 Human Vaccines F.M.Ndungu et al.2012 PNAS Imoukhuede, 2012 International Innovation
Blood-stage Projects		
GMZ2 Phase 2b	GMZ2 is a fusion protein of P. falciparum merozoite surface protein 3 (MSP3) and glutamate rich protein (GLURP) that mediates an immune response against the blood stage of the parasite	Mordmuller 2010 Vaccine Belard 2011 Plos One
MSP3 [181-276] field Phase 2b	Malaria merozoite surface protein 3 (MSP3) - believed to induce immunity through cytophilic antibodies that disrupt the process of erythrocytes invasion by merozoites	Sirima 2007 Vaccine Lusingu 2009 Malar J Nebie 2009 Parasite Immunol Sirima 2009 PlosOne

Web site accessed Dec 20 2012 http://www.who.int/vaccine_research/links/Rainbow/en/
Salvador et al. Expert Reviews Vaccines 11(9): 1071-1086, 2012,

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Objectives of the RTS,S malaria vaccine candidate development program

- **Develop a vaccine that will help to protect infants and children residing in malaria endemic regions from clinical disease and severe malaria resulting from *Plasmodium falciparum* infection***
- **Acceptable safety and tolerability profile**
- **Compatible with co-administration with routine EPI vaccines**
- **Implementable through national immunization programs**
- **Complements existing malaria control measures**

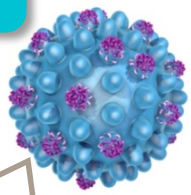
* Primarily in Sub-Saharan Africa where more than 80-90% of malaria cases and deaths occur mainly in children under five years of age and caused by *P falciparum*. (WHO 2012)

The malaria candidate vaccine composition

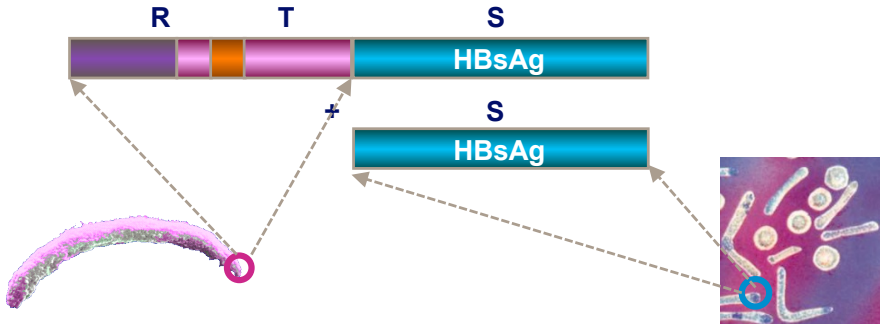
Vaccine
Mosquirix™

Antigen
RTS,S (powder)

Specificity of the immune response



Co-express in yeast

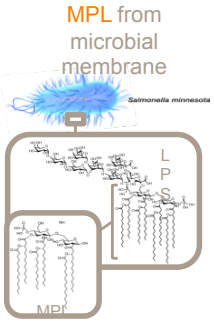


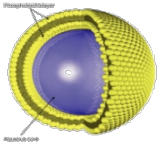
Regions from the major surface protein of the *P. falciparum* circumsporozoite

Hepatitis B virus surface Antigen

Adjuvant System
AS01 (liquid)

Enhances the immune response to vaccine antigen





Liposome

Saponin QS21

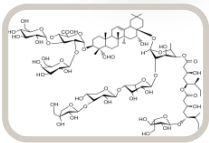
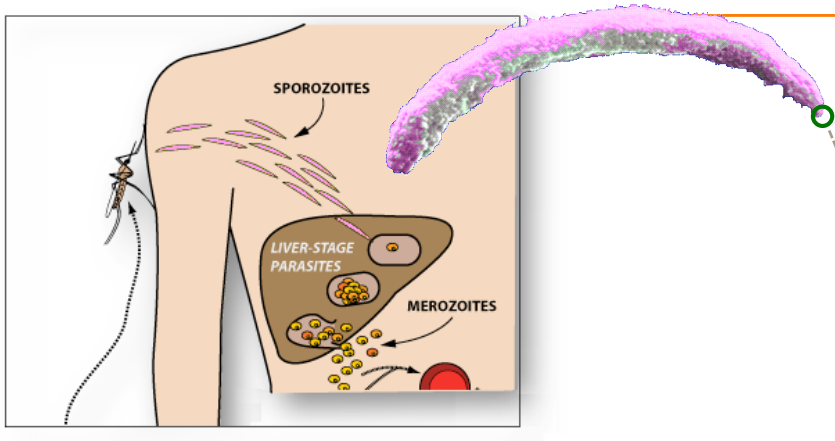


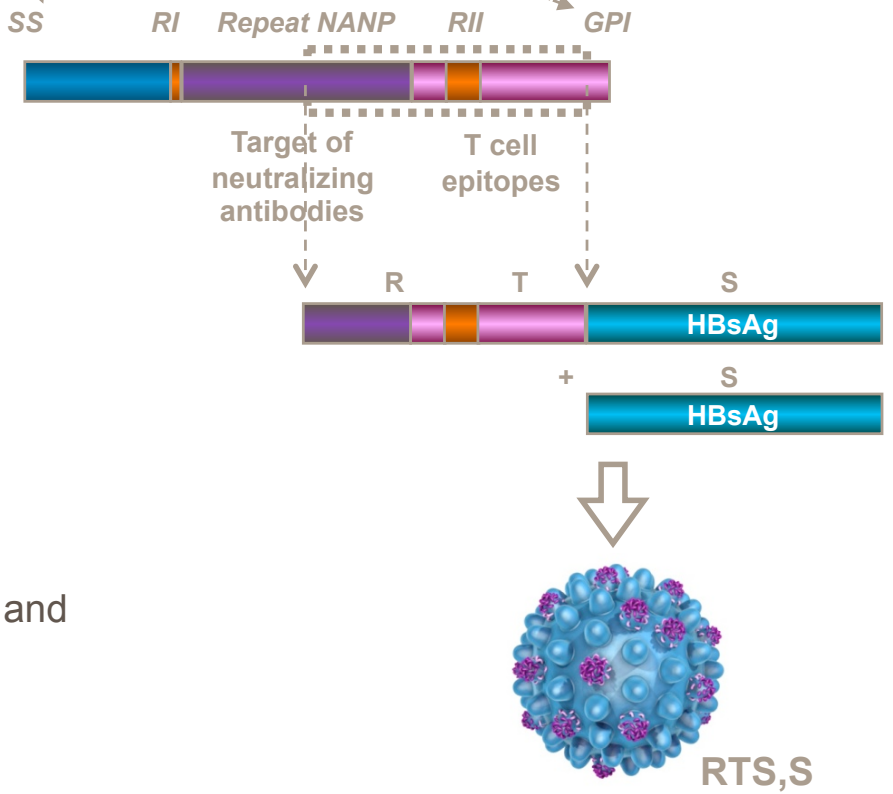
Illustration by Franz Eugen Köhler

Vekemans J et al. *Vaccine* 2009: 27:G67-G71; Vekemans J et al *Expert Review Vaccines* 2008: 7(2): 223-240

The RTS,S pre-erythrocytic antigen



- The **circumsporozoite protein**:
- is the major surface protein of the sporozoite
  - helps the parasite bind to liver cells



- The **RTS,S** vaccine particles:
- The **R** and **T** regions from CSP are fused to the Hepatitis B **S**urface Antigen (HBsAg)
- The fusion protein is co-expressed with HBsAg in yeast (*Saccharomyces cerevisiae*) where they spontaneously assemble into mixed particles

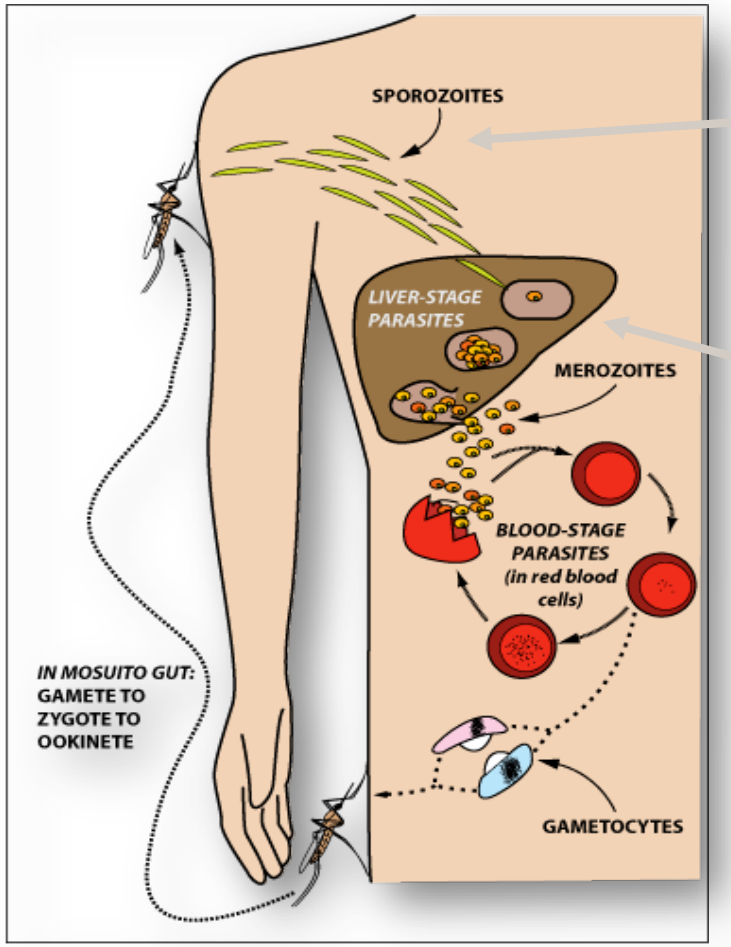
- The **AS01** adjuvant system:
- Adjuvant system designed to induce strong antibody and Th-1 cell-mediated immune responses
- Consists of MPL, QS21* and liposomes

Gordon et al. *J Infect Dis* 1995;171:1576–85

* QS-21 Stimulon® adjuvant licensed from Antigenics Inc, a wholly owned subsidiary of Agenus Inc. (NASDAQ: AGEN)

The scientific approach behind the RTS,S/AS01 malaria vaccine candidate

Induces strong and persisting immunity against the early stage of the malaria parasite life cycle in human.



Antibodies
to block infection

T cells
to kill intra-hepatic parasites and eliminate infected hepatocytes

Protection against Infection

Impact on Incidence and Severity of Disease

Agenda

- Malaria
  - Epidemiology, clinical manifestations and prevention
  - Principles of malaria vaccine development
- **RTS,S vaccine candidate**
  - RTS,S vaccine design
  - **Summary of early development**
  - Status of ongoing Phase III
  - Next steps

Partnership is a key factor for successful development

The development of the RTS,S malaria vaccine candidate is an example of a successful partnership between public and private stakeholders.

Phase III program

Research capacity building in SSA

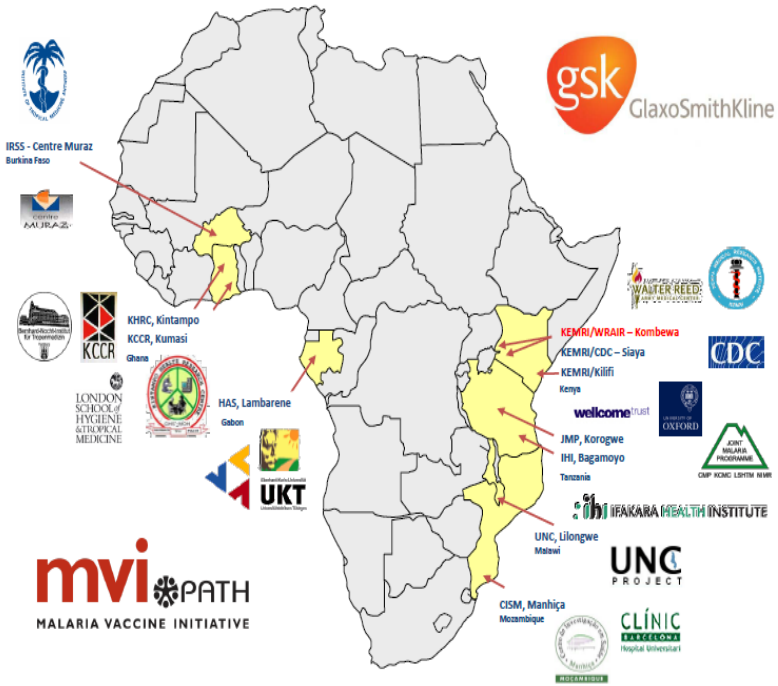
Product development

CTPC 2013

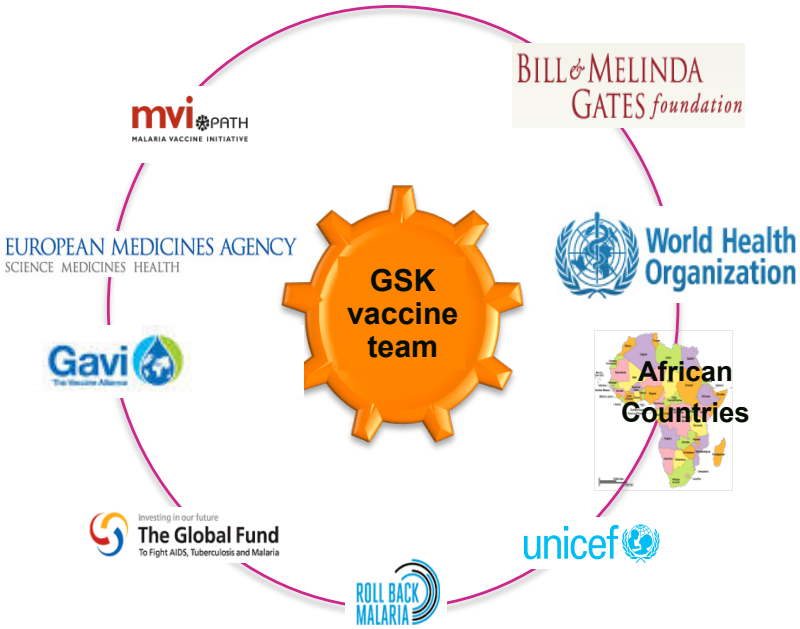
Malaria Clinical Trials Alliance

Northern research partners

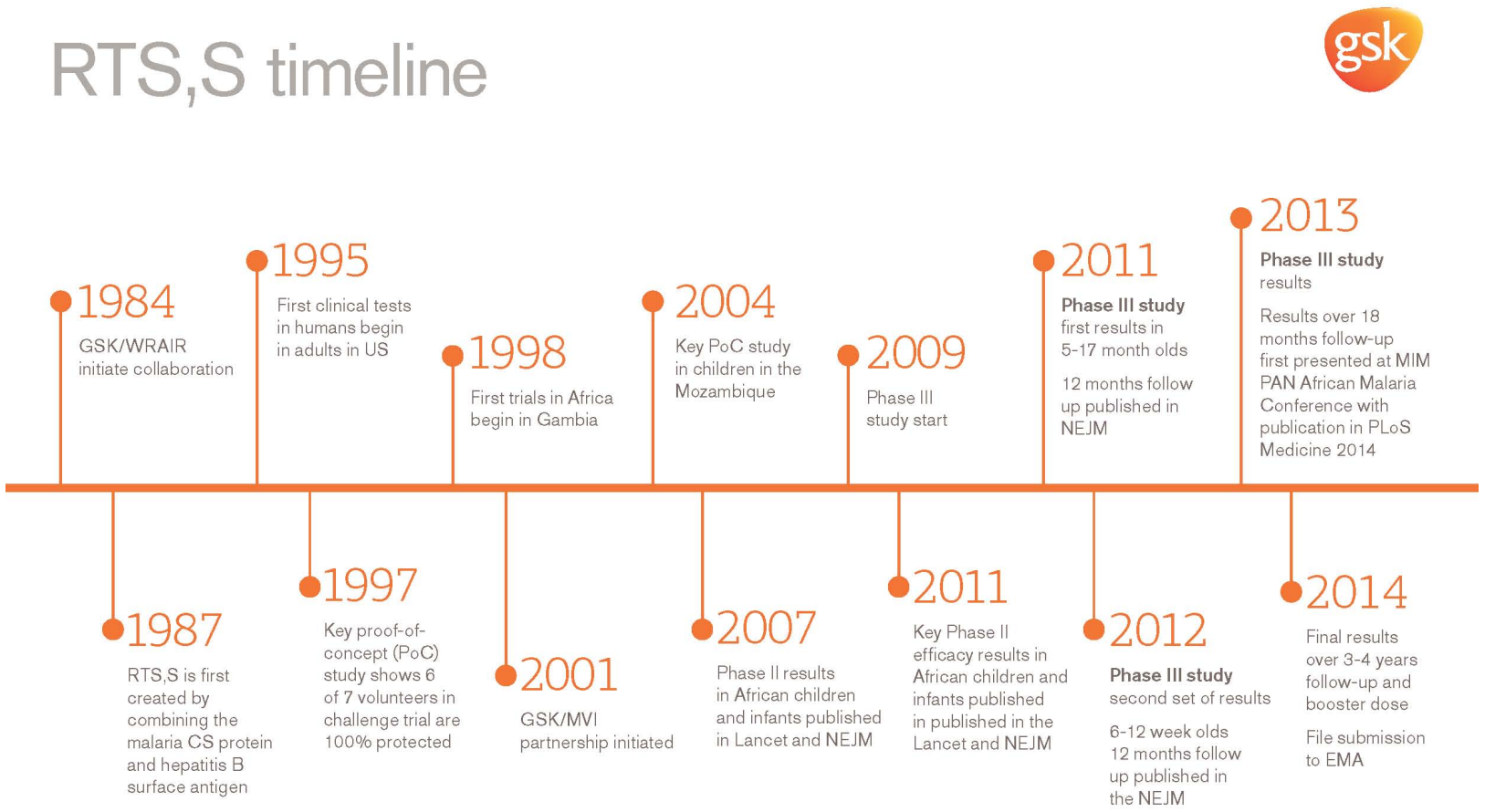
RTS,S Phase III Research Study Centers



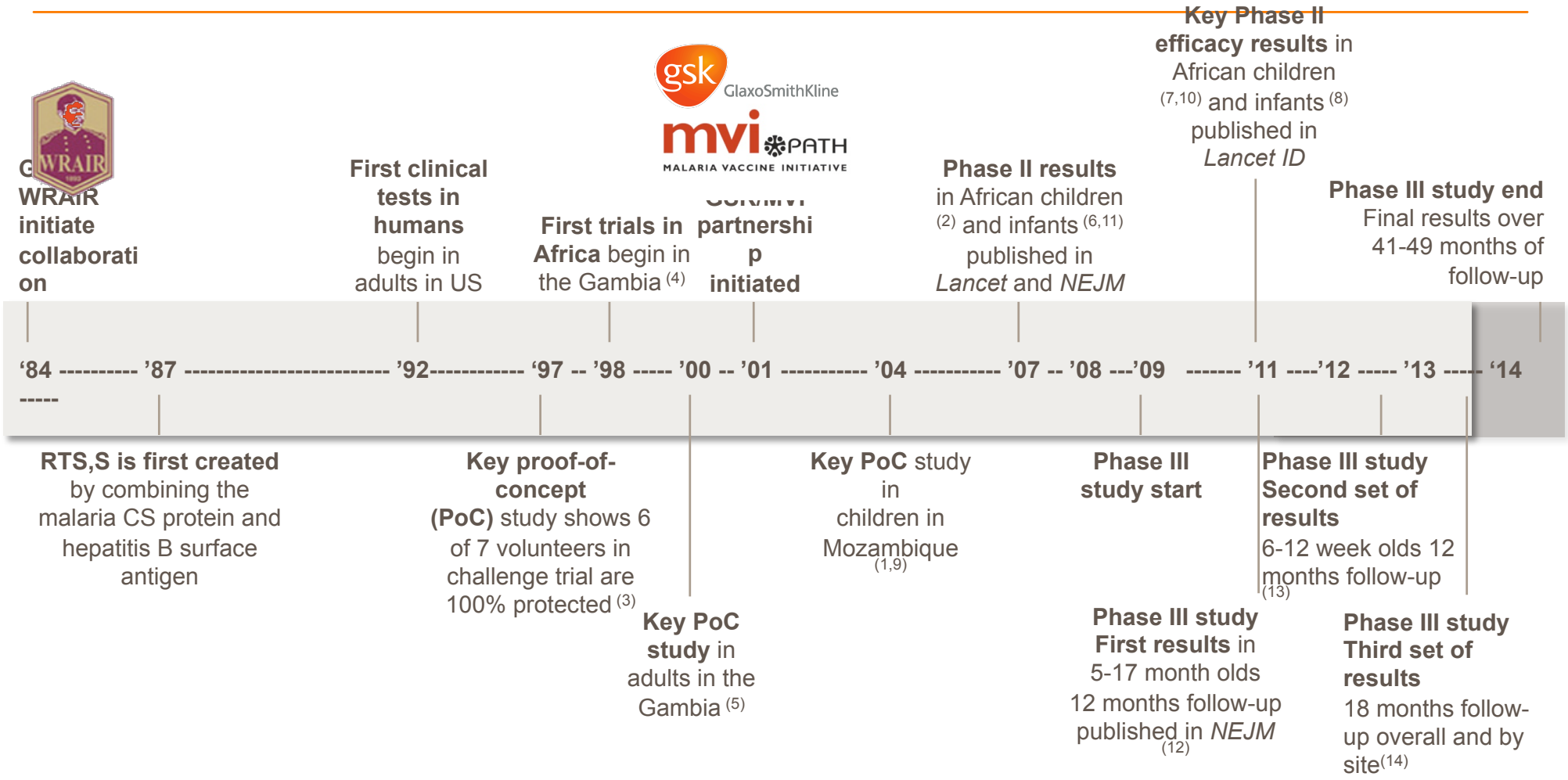
Ensure timely access



The RTS,S malaria vaccine development program: A 30-year effort



More than 27 years of RTS,S/AS01 development history



(1) Alonso P. et al. Lancet 2004; 364: 1411-20. (2) Aponte J. et al. Lancet 2007; 370: 1543-51. (3) Stoute J. et al. NEJM 1997; 336: 86-91. (4) Doherty J. et al. AJTMH 1999; 61: 865-8. (5) Bojang K. et al. Lancet 2001; 358: 1927-34. (6) Bejon P. et al. NEJM 2008; 359: 2521-32. (7) Olotu A. et al. Lancet ID 2011; 11: 102-09. (8) Asante KP. et al. Lancet ID 2011; 11: 741-9. (9) Sacarlal J. et al. JID 2009; 200: 329-36. (10) Agnandji S. et al. JID 2010; 202: 1076-87. (11) Abdulla S. et al. NEJM 2008; 359: 2533-44. (12) The RTS,S Clinical Trials Partnership. NEJM 2011; 365: 1863-1875 . (13) The RTS,S Clinical Trials Partnership. NEJM 2012; 367: 2284-95. (14) Otieno L. MIM 2013, Oct 8th

Summary of Phase II findings

- **Consistent efficacy** (40-50%) in different malaria transmission settings in Kenya, Mozambique, Tanzania, Gabon & Ghana:
  - Trend toward higher efficacy in younger children (with less natural immunity)
  - Trend toward higher efficacy against severe forms of disease
  - Beneficial effect on clinical disease up to 42 months after the last vaccine dose
- **Acceptable safety profile**, with reactogenicity pattern comparable to control vaccines (including EPI vaccines) and 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

1) Alonso P. et al. Lancet 2004; 364: 1411-20. 2) Alonso P. et al. Lancet 2005, 366: 2012-18 . 3) Sacarlal J. et al. JID 2009; 200: 329-36. 4) Bejon P. et al 2008 NEJM 359; 24: 2521-32 . 5) Aponte J. et al. Lancet 2007; 370: 1543-51. 6) Abdulla S. et al. NEJM 2008; 359: 2533-44. 7) Agnandji S. et al. J Infect Dis 2010; 202:1076-87. 8) Kester K. et al. JID 2009; 200: 337-46. 9) Olotu A. et al. Lancet ID 2011; 11: 102–09 . 10) Asante K. et al. Lancet ID 2011; 11: 741-9

Agenda

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  - Epidemiology, clinical manifestations and prevention
  - Principles of malaria vaccine development
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  - RTS,S vaccine design
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  - **Status of ongoing Phase III**
  - Next steps

RTS,S: Phase III double-blind randomized controlled efficacy trial

Trial design

Efficacy against clinical malaria
over first 12 months of follow-up

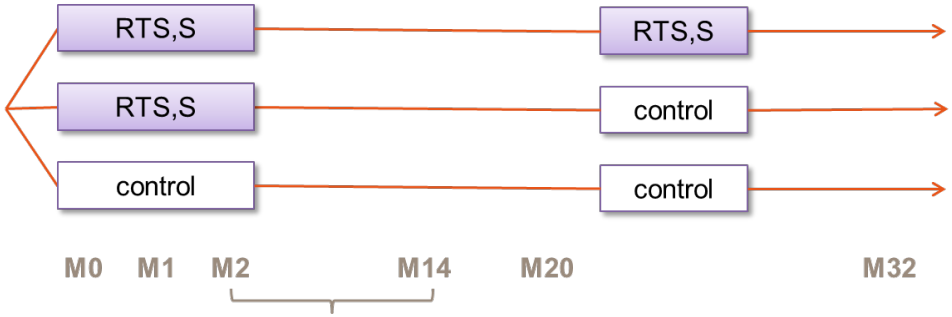
- Booster dose at 18 months

15,460 children:

- Children aged 5–17 months
- Infants aged 6–12 weeks, RTS,S co-administered with EPI vaccines

Control vaccines:

- Rabies vaccine in 5-17 month old children
- MenC-conjugate vaccine in 6-12 week old infants (and at booster)

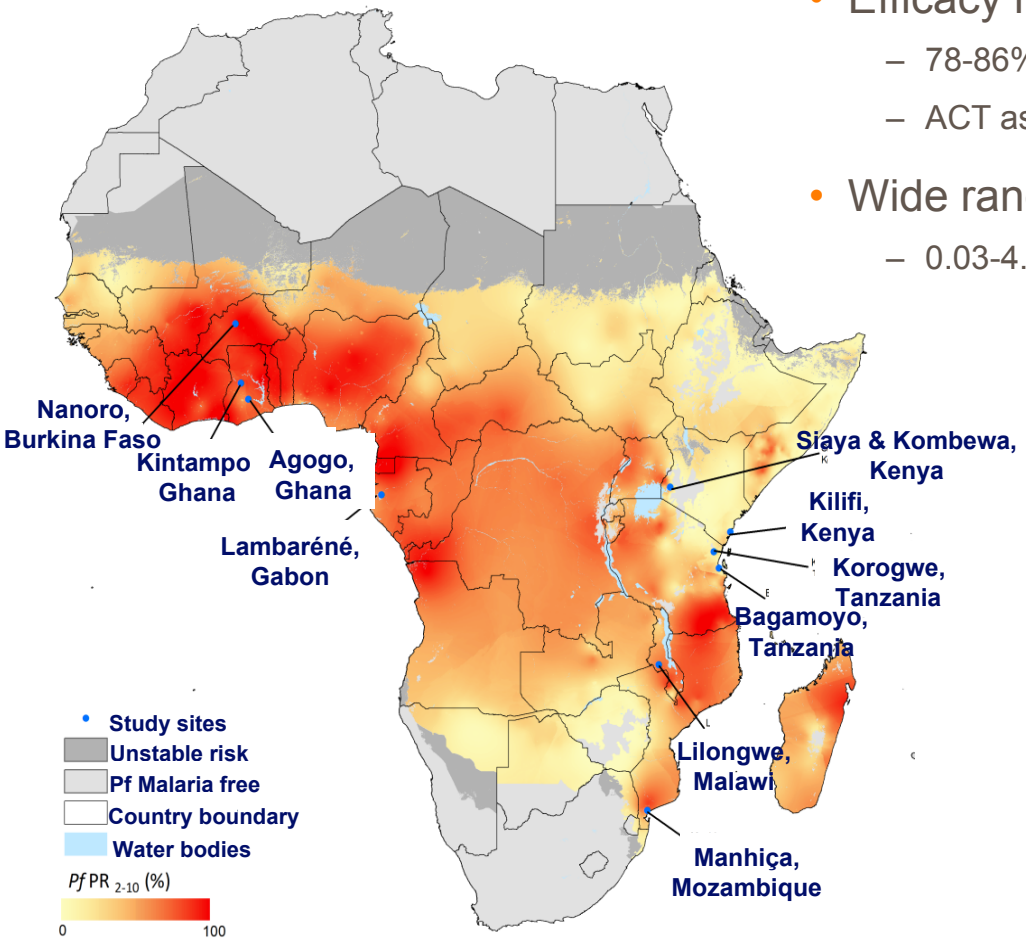


- Trial standardization of clinical care and study procedures
  - Overall good quality
  - Close clinical follow-up, high standard of care
- Designed in collaboration with PATH-MVI and the CTPC (Clinical Trials Partnership Committee) with feedback from WHO, FDA, EMA and NRAs

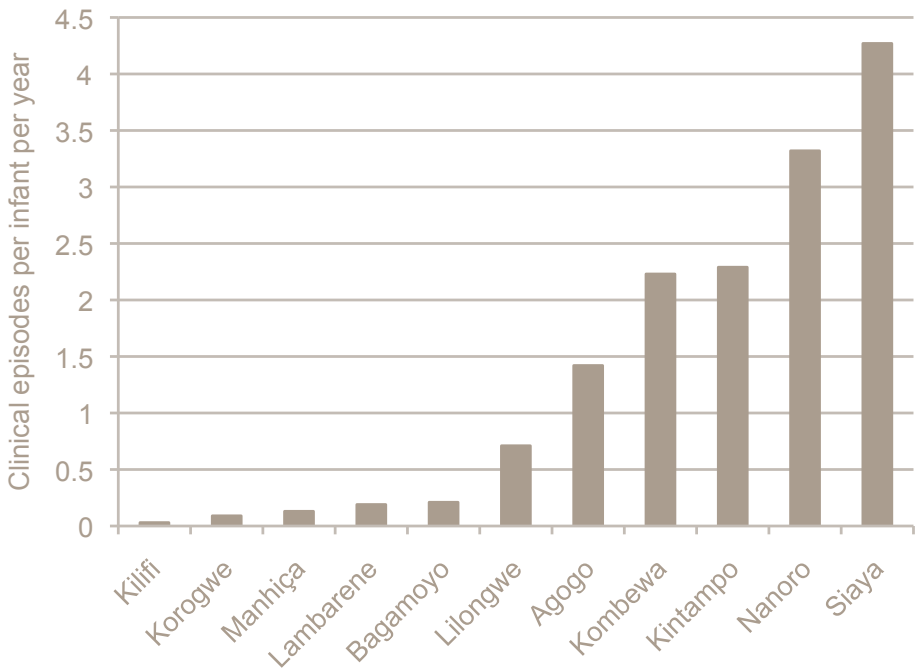
Leach A., et al. Malaria J 2011, 10:224

RTS,S: Phase III double-blind randomized controlled efficacy trial

Malaria environment



- 11 centers in 7 African countries
- Efficacy measured on top of other malaria interventions
  - 78-86% insecticide-treated bed net use overall
  - ACT as first-line treatment
- Wide range of malaria transmission intensities
  - 0.03-4.27 clinical episodes per infant per year



The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

Capacity building for Phase III

- Standardization of evaluation of clinical cases, blood slide and X-ray reading, laboratory methods and QA processes

- Challenges: different capacity building needs at each of the sites to be fixed within short timelines:
  - 3 research centers, 3 labs and 1 teaching center have been built,
  - Many wards and primary health care facilities have been refurbished,
  - Lab equipment has been provided as well as generators to provide uninterrupted power supply,
  - 10 of the 11 sites were equipped with satellite terminal installations.

- Thanks to partnership between the PATH Malaria Vaccine Initiative (MVI), Malaria Clinical Trials Alliance (MCTA) and GlaxoSmithKline (GSK), CLS (Contract Laboratory Services, SA) and the staff at each of the individual study sites.

Clinical development conducted in partnership

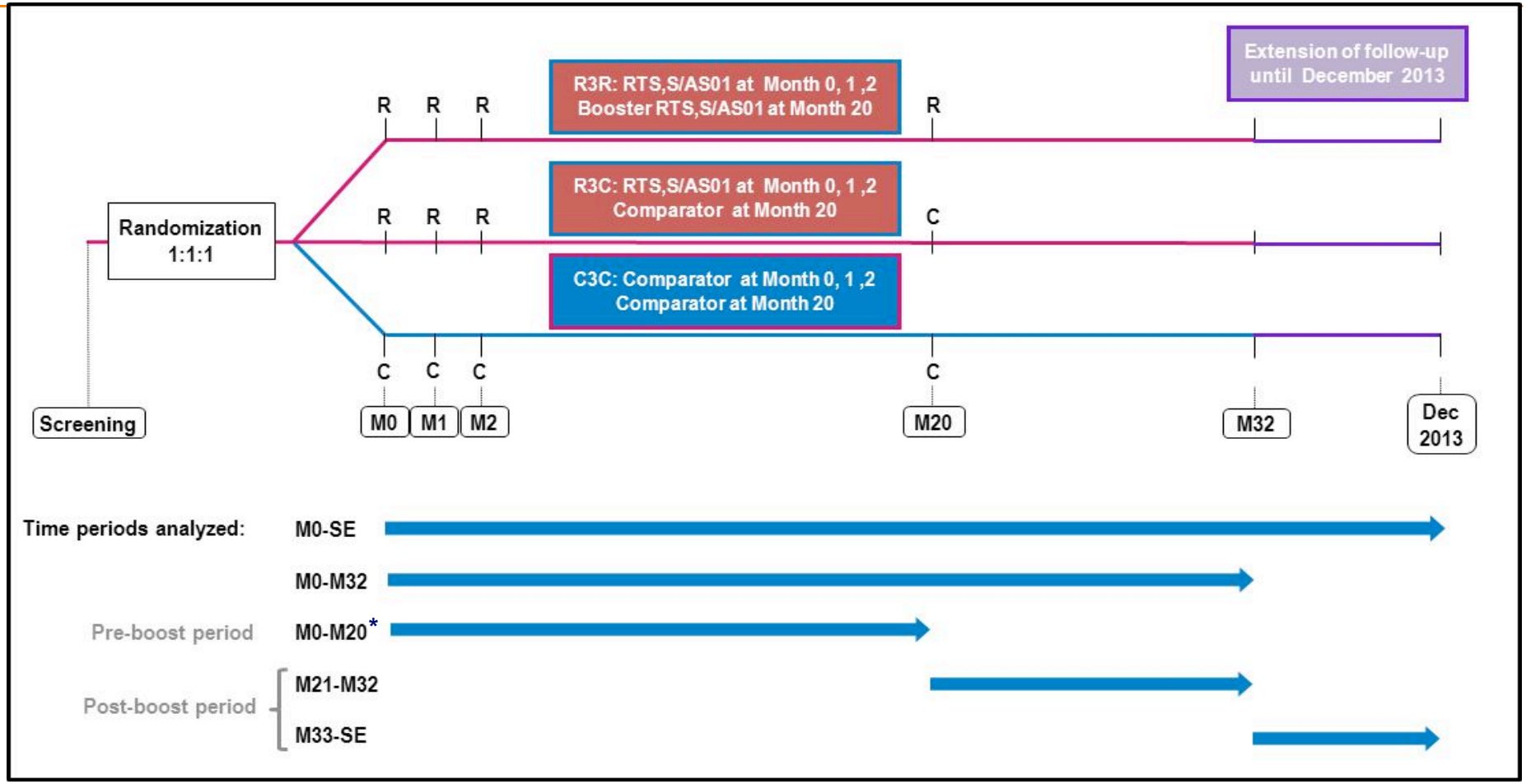
PATH-Malaria Vaccine Initiative (MVI), GSK and …

- **African Research Institutes:**
- Institut de Recherche en Science d
  Santé, Nanoro, **Burkina Faso**
- Kumasi Centre for Collaborative Re
  School of Medical Sciences Kumas
- Kintampo Health Research Centre,
- Albert Schweitzer Hospital, **Gabon**
- KEMRI-Walter Reed Project, **Keny**
- KEMRI-Wellcome Trust Research
  Programme, **Kenya**
- KEMRI/CDC Research and Public
  Collaboration, **Kenya**
- University of North Carolina Project
- Centro de Investigação em Saude de Manhiça, **Mozambique**
- Ifakara Health Institute, **Tanzania**
- National Institute of Medical Research, **Tanzania**

- **Academic partners:**
- Prince Leopold Institute of Tropical Medicine, **Belgium**
- University of Copenhagen, **Denmark**
- University of Tuebingen, **Germany**
- University of Barcelona, **Spain**
- Swiss Tropical Institute, **Switzerland**
- London School of Hygiene & Tropical Medicine, **UK**
- Centers 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

MARA & ARMA web site. Maps. Map adapted from "Duration of Malaria Transmission Season": http://www.mara.org.za/ [Assessed: 11 June 2009]

Phase III Study design



M = study month

M0-M20: both groups receiving RTS,S primary vaccination pooled (*), reported in *PLoS Medicine* 2014

SE = study end

M0-SE: median 48 months in children, 38 months in infants

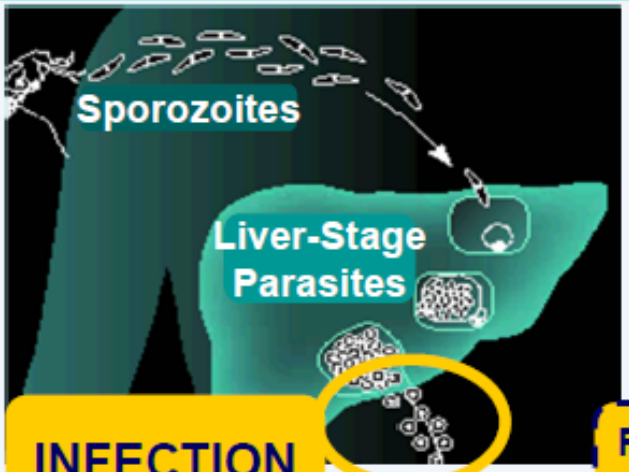
Leach A., et al. Malaria J 2011; 10:224

Study design pivotal RTS,S efficacy trial

- Primary endpoints: **Efficacy against clinical 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
  Infants received the study vaccine co-administered with EPI vaccines
- **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

Leach A., et al. Malaria J 2011; 10:224

Vaccine Efficacy Estimates depend on the Endpoint Considered



INFECTION

Release of the Parasites from the Liver

Clinical Symptoms | No Clinical Symptoms

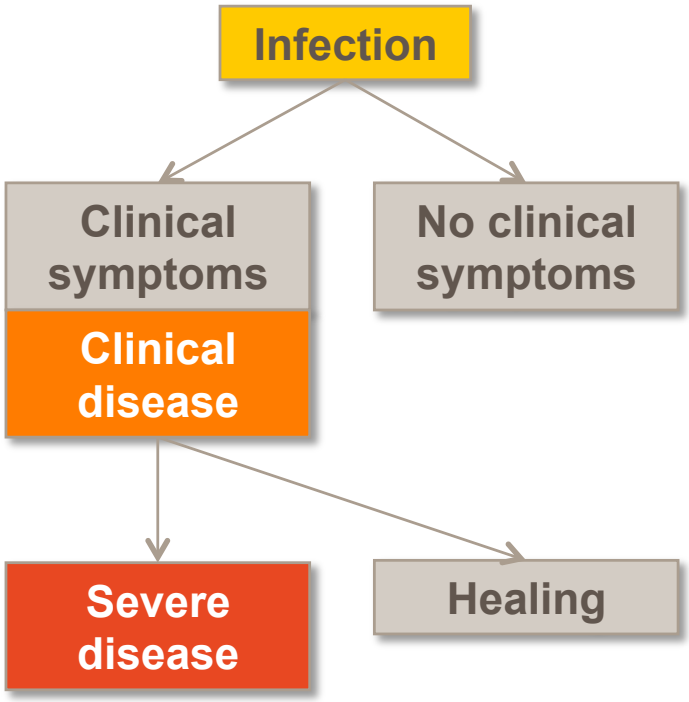
CLINICAL DISEASE

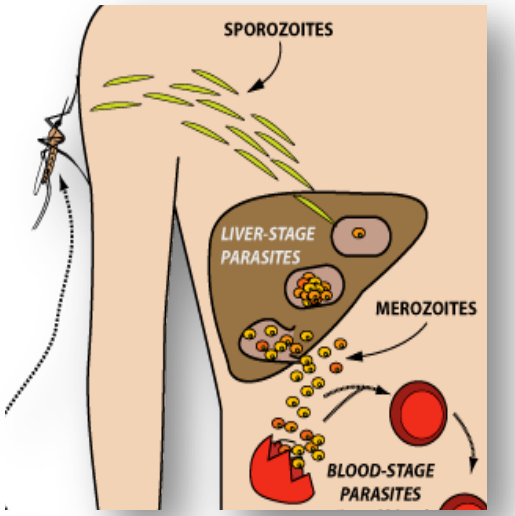
Patient presents with Fever and Parasitemia* for example

SEVERE DISEASE | Healing

Patient presents with Anemia for example

Vaccine efficacy estimates depends on the endpoint considered





Release of parasites from the liver

Patient presents with eg fever and parasitaemia

Patient presents with eg anemia

Case definition of clinical malaria

Primary case definition

- *P. falciparum* parasitemia > 5,000/µL
- **AND** fever ≥ 37.5°C at time of presentation
- **AND** child unwell and brought for treatment (i.e. passive case detection)

OR

- Malaria meeting the primary case definition of severe malaria disease

Rationale

- A single case definition used across all sites to facilitate pooling of data
- Parasite density threshold value defined to ensure minimum 80% specificity at all sites
- Case detection by passive surveillance at health facilities as outcome measure of public health relevance
- To ensure that high proportion of cases are captured, access to and high quality of health care will be assured

(1) Moorthy V, Reed Z, Smith PG; WHO Study Group on Measures of Malaria Vaccine Efficacy. Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine. 2007;25(28):5115-23.

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Case definition: severe malaria

Parasite positive *P. falciparum* > 5,000 parasites per µL

AND with one or more marker of disease severity

- Prostration
- Respiratory distress
- Blantyre score ≤ 2
- Seizures 2 or more
- Hypoglycemia < 2.2 mmol/L
- Acidosis BE ≤ -10.0 mmol/L
- Lactate ≥ 5.0 mmol/L
- Anemia < 5.0g/dL

AND without diagnosis of a co-morbidity

- Radiographically proven pneumonia
- Meningitis on CSF examination
- Bacteremia on blood culture
- Gastroenteritis with dehydration

Cases associated with HIV and malnutrition will not be excluded

(1) Moorthy V, Reed Z, Smith PG; WHO Study Group on Measures of Malaria Vaccine Efficacy. Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine. 2007;25(28):5115-23.

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RTS,S: Phase III double-blind randomized controlled efficacy trial

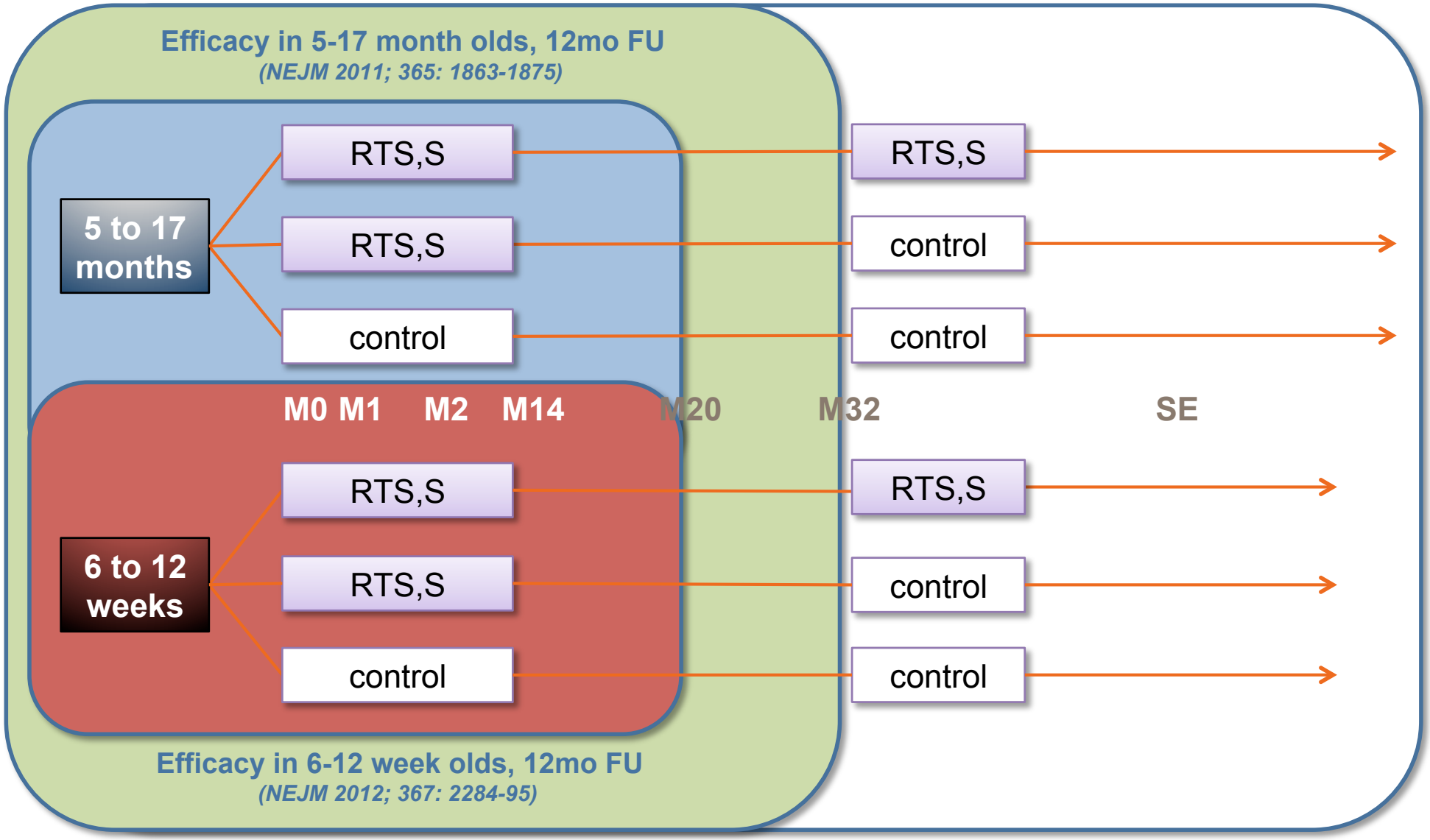
Case definitions and surveillance

Criterion	Primary definition [specific]	Secondary definition [sensitive]
P. falciparum asexual parasitaemia	>5,000 parasites/μL	>0 parasites/μL
Fever	Temperature ≥37.5°C	≥37.5°C OR history of fever within 24 h of presentation
Other	OR algorithm defined case of severe malaria	

- Data on **malaria episodes** and **serious adverse events** [SAE] were collected by **passive surveillance**.
- In each clinical trial site, **anti-circumsporozoite [anti-CSP] antibodies** were measured in the first **200 participants**, in each age-category at enrollment and 1 month after dose 3.

Leach et al. Malaria Journal 2011, 10:224

Different analyses of the Malaria-055 efficacy trial



Context of Phase III efficacy trial

- Efficacy measured in presence of other malaria control measures:
  - ACT first line treatment of malaria in all sites
  - ITN usage documented in 78% 5-17 months and 86% 6-12 weeks age categories
  - IRS was used in only 4 sites Bagamoyo, Kintampo, Lambaréné, Manhiça (2%-30%) IRS use was low or absent in the other sites
- Research centers selected to cover a wide range of malaria transmission intensities and incidences of clinical disease
- Close clinical follow-up, high standard of care:
  - Very low case fatality rate in hospital
  - Low overall mortality rate
- Trial conducted according to protocol with overall good quality
- Trial conduct under CTPC* guidance; standardization of clinical care and study procedures

*CTPC: Clinical Trials Partnership Committee

RTS,S : Key efficacy results against clinical malaria

Over 12 months	%VE (with 95%CI)	
	5-17 mo*	6-12 wk
First episode of clinical malaria (ATP, adjusted, co-primary endpoint)	**56%** (51; 60)	**31%** (24; 38)
All clinical malaria episodes	**55%** (51; 59)	**33%** (26; 39)

*First 6000 children enrolled

NEJM 2011; 365: 1863-1875

NEJM 2012; 367: 2284-95

Over 18 months	%VE (with 95%CI)	
	5-17 mo**	6-12 wk
All clinical malaria episodes	**46%** (42;50)	**27%** (20;32)
VE across sites	Significant variation (range 40 to 77%)	Not statistically different (range -56 to 48%)
Cases prevented per 1000 vaccinees (ITT)	**829** (range 37; 2365)	**449** (range -10;1402)

** All children enrolled

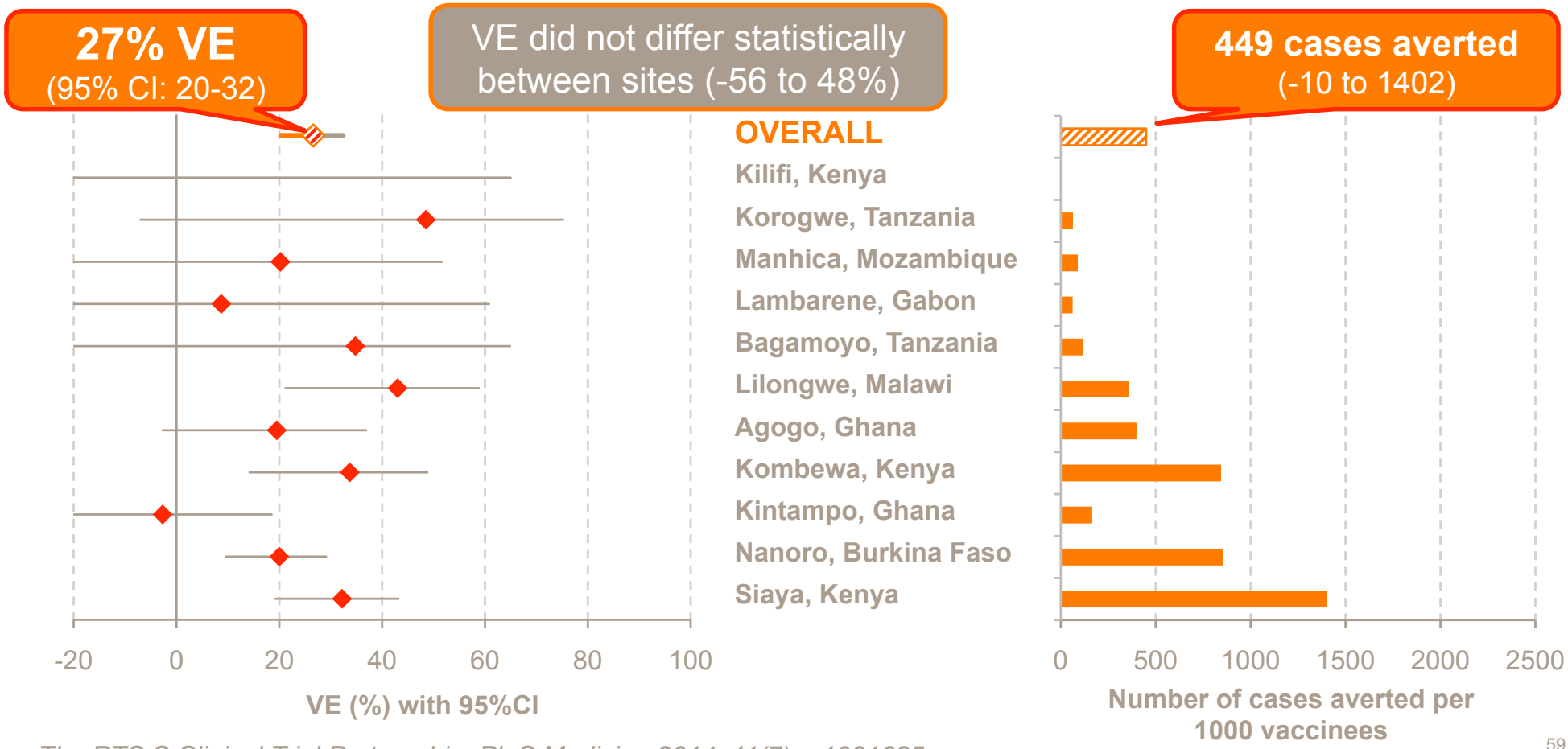
The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

RTS,S: Vaccine efficacy and impact against clinical malaria

Infants 6-12 weeks

Over the first 18 months of the Malaria-055 trial, RTS,S

- reduced by a quarter the number of cases of clinical malaria in infants
- prevented more than 1000 malaria cases for every 1000 vaccinated infants living in areas with highest malaria transmission.[1]



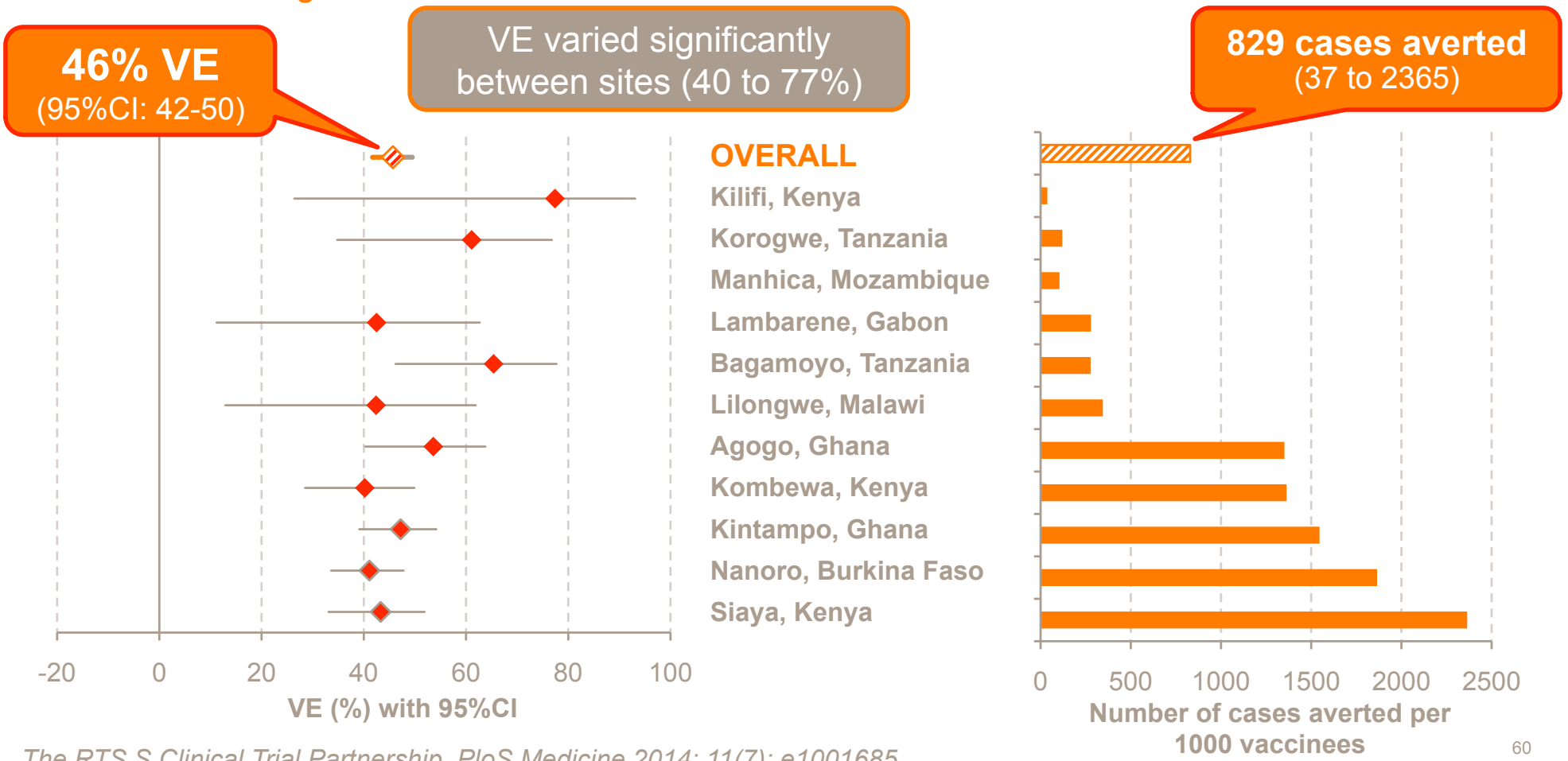
The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

RTS,S: Vaccine efficacy and impact against clinical malaria

Children 5-17 months

Over the first 18 months of the Malaria-055 trial, RTS,S

- almost halved the number of clinical malaria cases in young children
- prevented more than 2000 malaria cases for every 1000 vaccinated children living in areas with highest malaria transmission.



The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

RTS,S: Evolution of protection over time

- VE varied over time, being highest close to vaccination (Schoenfeld residuals $p<0.001$) but it persisted throughout the observation period.

Clinical malaria per 6-month period (Malaria-055)	**%VE** (with 95%CI)	
	5-17 mo	**6-12 wk**
Months 1 to 6 post dose 3	**68%** (64;72)	**47% (39;54)**
Months 7 to 12 post dose 3	**41%** (36;46)	**23%** (15;31)
Months 13 to 18 post dose 3	**26%** (19;33)	**12%** (1;21)

- In infants, a statistically non-significant increase in the incidence of severe malaria was observed in RTS,S/AS01 recipients in the last 6 months of follow-up (p= 0.17)

The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

RTS,S: Other efficacy endpoints

Severe malaria, hospitalization and mortality

Over 18 months (Malaria-055)	**%VE** (with 95%CI)	
	5-17 mo	**6-12 wk**
Severe malaria over 18 months (ATP, adjusted)	**36%** (15;51)	**15%** (-20;39)
Malaria hospitalization	**42%** (29;52)	**17%** (-7;36)
All-cause hospitalization	**19%** (9;28)	**6%** (-7;17)
Prevalent parasitemia	**31%** (17;42)	**13%** (-8;29)
Severe malaria cases prevented per 1000 vaccinees (ITT)	**18** (range -1; 49)	**6** (range -13; 37)

- Case fatality rate was low and vaccine efficacy was not demonstrated against malaria mortality , all-cause mortality, hospitalized pneumonia, septicemia or prevalent anemia
- No detectable effect on childhood nutritional status or growth

The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

RTS,S: Other efficacy endpoints

Severe malaria, malaria hospitalization and all-cause hospitalization

Over 12 months	%VE (with 95%CI)	
	5-17 mo*	6-12 wk
Severe malaria over 12 months	**47%** (22; 64)	**37%** (5; 58)

*First 6000 children enrolled

NEJM 2011; 365: 1863-1875

NEJM 2012; 367: 2284-95

Over 18 months	%VE (with 95%CI)	
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The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

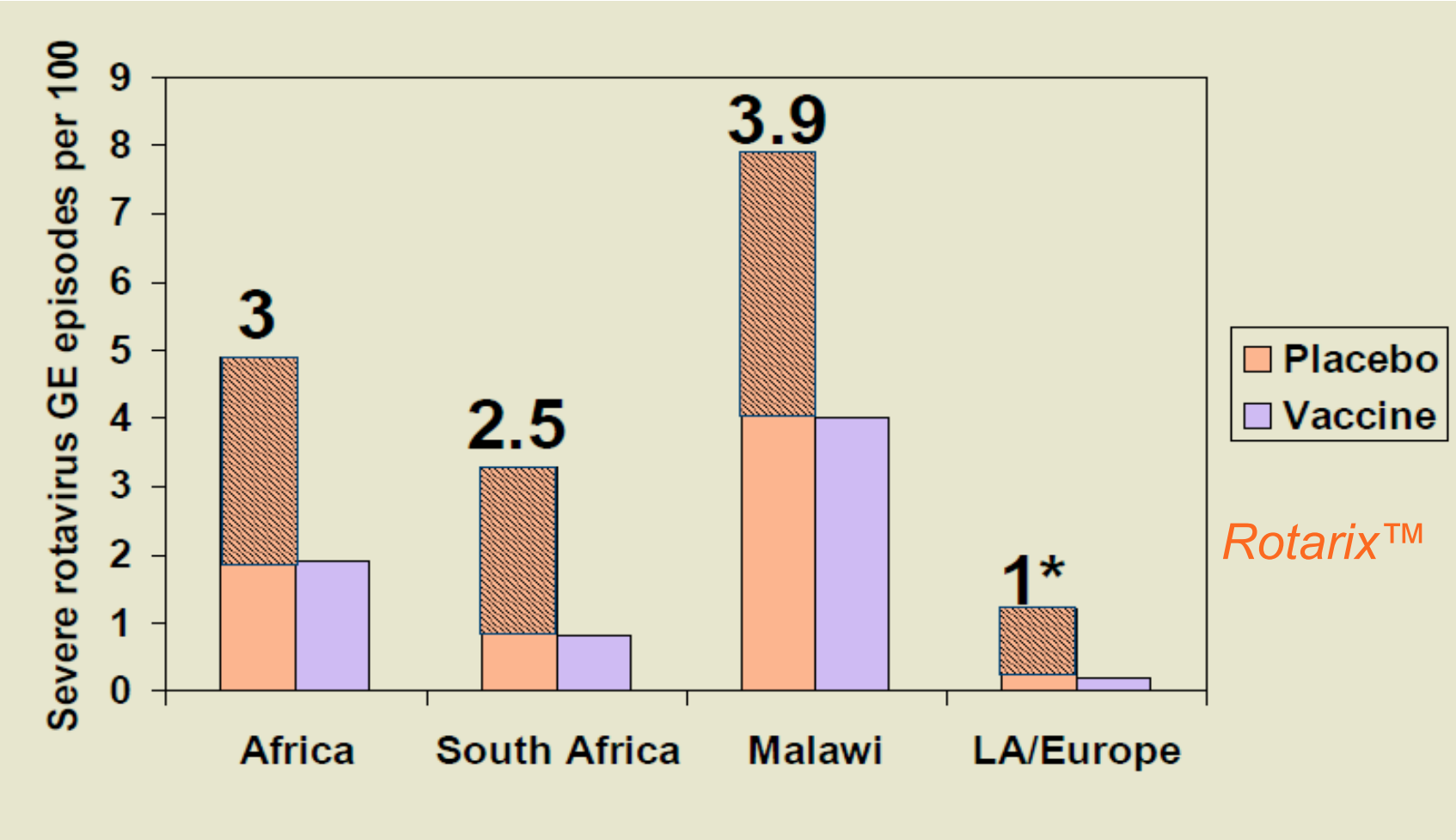
RTS,S : Conclusion on efficacy

- This phase 3 trial has confirmed the efficacy of the RTS,S malaria vaccine candidate in infants 6 to 12 weeks of age and in children 5 to 17 months of age at the time of first vaccination
- VE was statistically significant over 18 months of follow-up
- VE was higher in children than in infants
- In children VE against clinical malaria was significant in each setting but varied significantly between sites [range 40 to 77%]
- This variation in VE could not be explained by differences in malaria transmission intensity, nor by differences in anti-CS antibody responses between sites.
- The evolution of efficacy over time and the role of a booster dose will provide the evidence-base to determine the potential and role of the RTS,S malaria vaccine candidate for malaria control

The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

Example : Burden of Rotavirus potentially prevented in Africa

Severe Rotavirus gastroenteritis episodes prevented per 100 children – comparison with Latin America and Europe



Ruiz-Palacios GM NEJM 2006; 543: 11-22; Cunliffe et al, ESPID 2009, abstract 449

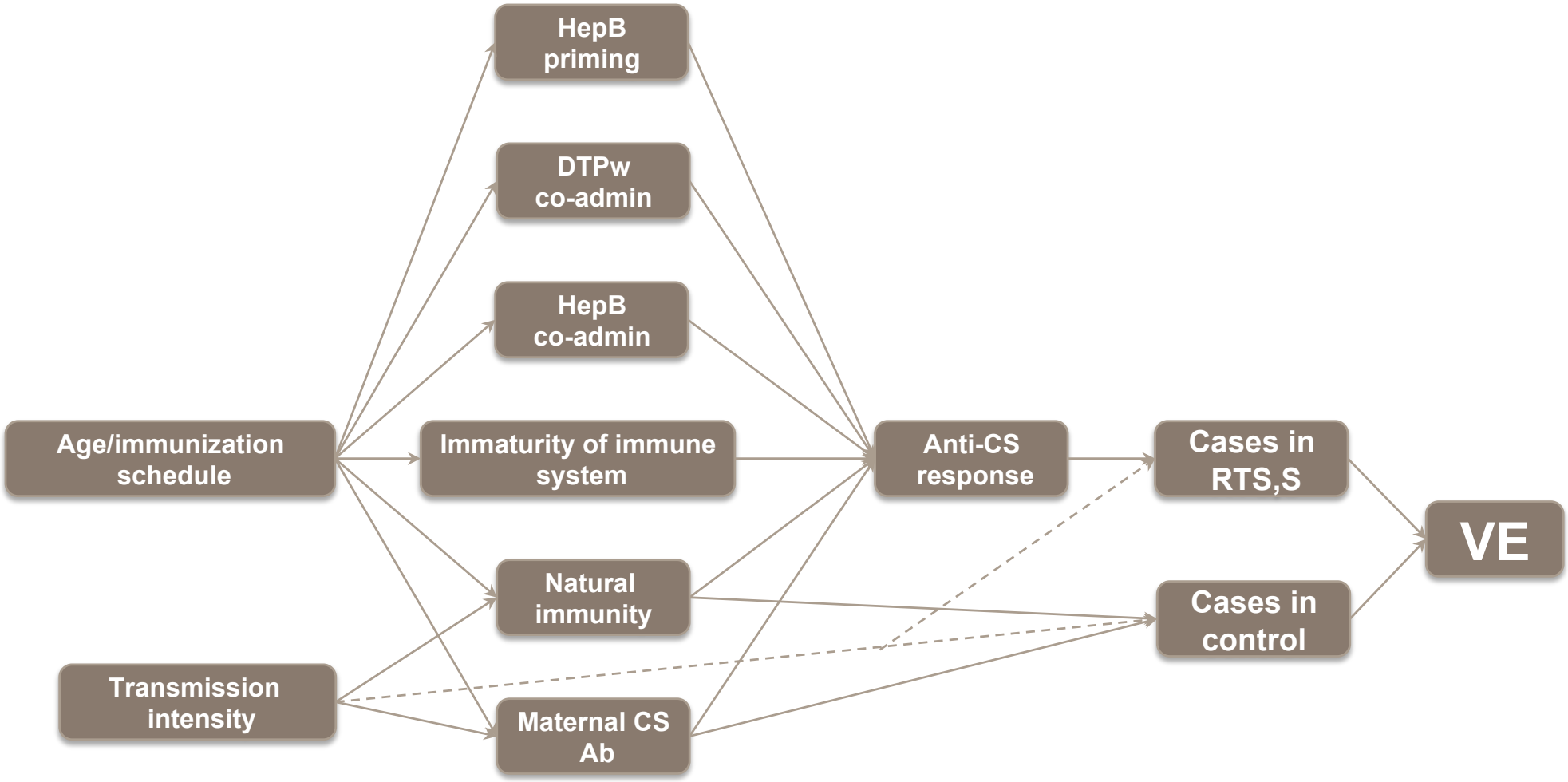
Points to consider on efficacy results

- RTS,S/AS01 induced significant vaccine efficacy over 18 months across different transmission settings
- Vaccine efficacy decreased over the 18 months follow-up period
- Higher efficacy in 5-17 months age category compared to 6-12 weeks age category could be due to:
  - Younger age, meaning / resulting in:
    - Immaturity of immune system
    - Interference with maternal antibodies
    - Less exposure to *P. falciparum* and reduced natural priming
  - Co-administration of DTPw-HepB/Hib and OPV vaccines
  - HepB priming did not seem to have an influence on VE
- The added value of a booster dose given 18 month after dose 3 will be evaluated in the Malaria-055 study

The RTS,S Clinical Trial Partnership, PloS Medicine 2014; 11(7): e1001685

Summary of factors that could drive vaccine response

(non exhaustive)



Key differences between 6-12 weeks and 5-17 months age categories

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

Reactogenicity and safety profile of the RTS,S malaria vaccine candidate

- The malaria vaccine candidate was more reactogenic than the control vaccines, (injection site reactions and fever), but only few reactions were of severe intensity. RTS,S was less reactogenic than the pentavalent EPI vaccine in infants.[1,2]
- Febrile seizures within 7 days following vaccination were observed more frequently in the 5-17 month age category in the RTS,S group occurring at 1/1000 doses.[1]
- Overall reporting in SAEs was comparable between the RTS,S recipients and the control vaccine groups. [1,2]
- Fatal SAEs were balanced between groups. None were considered causally related to study vaccines. [1,2]
- Meningitis signal previously reported remained and meningitis cases will be followed closely in all trials with RTS,S. [1,3]
- No other safety signals were identified. [1,2,3]

1) NEJM 2011; 365: 1863-1875; 2) NEJM 2012; 367: 2284-95; 3) PloS Medicine 2014; 11(7): e1001685

Conclusion

- This phase 3 trial has confirmed the efficacy of the RTS,S malaria vaccine candidate in infants 6 to 12 weeks of age and in children 5 to 17 months of age at the time of first vaccination.
- Vaccine efficacy was statistically significant over 18 months and over different malaria transmission settings
- Vaccine efficacy was higher in the children than in the infants category.
- The duration of efficacy and the role of a booster dose will provide the evidence-base to determine the potential and role of the RTS,S malaria vaccine candidate for malaria control.

Agenda

- Malaria
  - Epidemiology, clinical manifestations and prevention
  - Principles of malaria vaccine development
- **RTS,S vaccine candidate**
  - RTS,S vaccine design
  - Summary of early development
  - Summary of ongoing Phase III
  - **Next steps**

Next steps

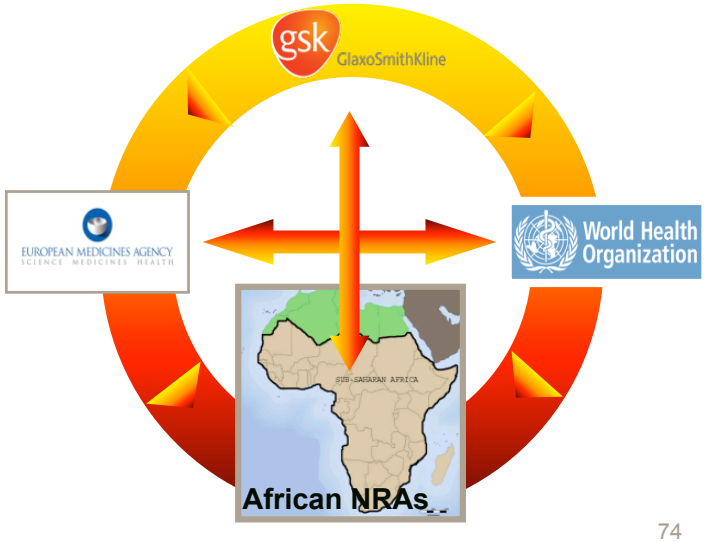
- Final results of efficacy trial in 2014, including 3-4 years follow-up, and effect of the booster dose given 18 months post dose 3.
- Regulatory file submitted in June 2014 to the European Medicines Agency (EMA)
  - Article 58 (candidate manufactured, but not for use in European Union) for review in collaboration with WHO
- A positive scientific opinion from EMA on the quality, safety and efficacy of RTS,S would pave the way for:
  - WHO recommendation, possibly end 2015
  - WHO prequalification
  - Marketing Authorisation Applications to National Regulatory Authorities (NRAs) in sub-Saharan Africa.
- Discussions with WHO and other stakeholders are ongoing to define how this potential additional malaria control intervention could best be used to provide public health benefit to children in malaria endemic areas in SSA.

Innovative, streamlined regulatory strategy

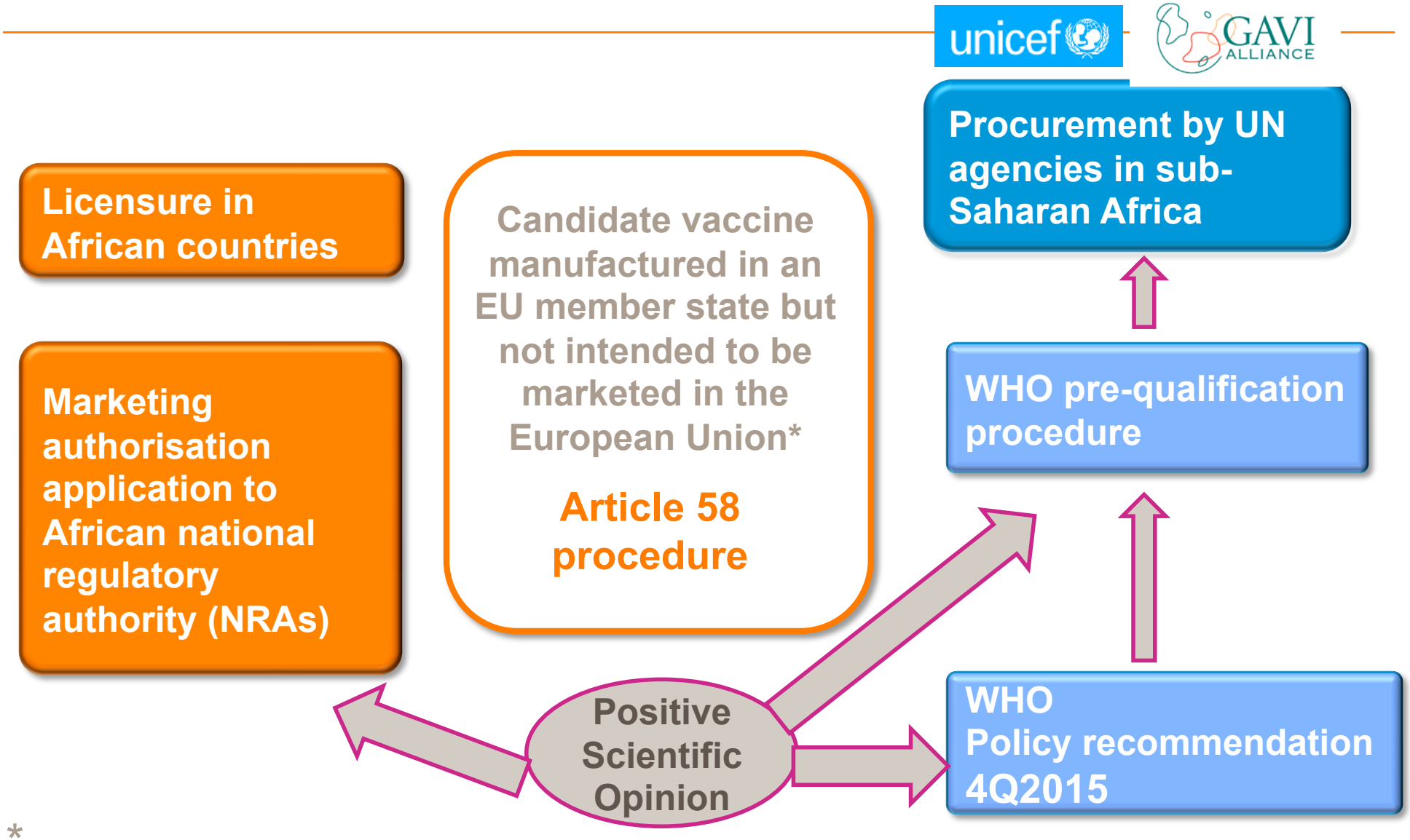
GSK, European & African Regulatory Authorities, WHO

Common Goal = make a malaria vaccine available to African children as soon as possible

- Strong PATH-MVI / GSK partnership to lead clinical development.
- Regular consultations with WHO (SAGE, GACVS, JTEG, ECBS).
- Early EMA involvement (3 Scientific Advices in 2007, 2009 and 2011).
- Registration pathway: use of EU "**Article 58**" procedure.
- Post-licensure commitments to be expected:
  - ➔ early feedback on post-approval plan (phase IV) required from EMA, WHO and NRAs to allow adequate preparation.



Regulatory Filing in 2014 and after



*Mosquirix is not a traveller's vaccine and malaria is not endemic in Europe

Beyond regulatory approval...

"A medicinal product is authorized on the basis that, in the specific indication(s), at the time of authorisation, the benefit-risk is judged positive for the target population."*

- **Regulatory requirement to establish post-authorization plans including:**
- monitoring vaccine effectiveness, and
- pharmacovigilance activities
- in order to ensure the continued re-assessment of the benefit-risk relationship of the vaccine in real life setting

**Guideline on the conduct of pharmacovigilance for vaccines for pre- and post –exposure prophylaxis against infectious diseases. (EMEA/CHMP/PhVWP/503449/2007)*

Conclusions

- First Phase III results showed that **RTS,S candidate vaccine allows to reduce malaria burden by half in children** aged 5-17 months and **by one quarter in infants** aged 6-12 weeks over 18 months of follow-up.
- The RTS,S malaria vaccine candidate is being developed through a **Public Private Partnership** between GSK, PATH-MVI and leading African research institutes, with the support of the Gates Foundation.
- The RTS,S candidate vaccine is the **first and only malaria vaccine candidate to date to demonstrate it can help protecting young children and infants** exposed to malaria transmission against infection and disease due to *Plasmodium falciparum*.
- If licensed by regulatory authorities and implemented **in addition to existing malaria interventions**, the candidate vaccine could have a **major societal, economic and public health impact** in malaria-endemic regions in Africa.
- **Implementation in sub-Saharan Africa** will require timely policy recommendations and financing mechanisms.

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Malaria Clinical Trials Alliance

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