OPTIMUNIZE Stakeholder Meeting Accra 2016

The RTS,S vaccine trials: further evidence for NSE or other explanations?

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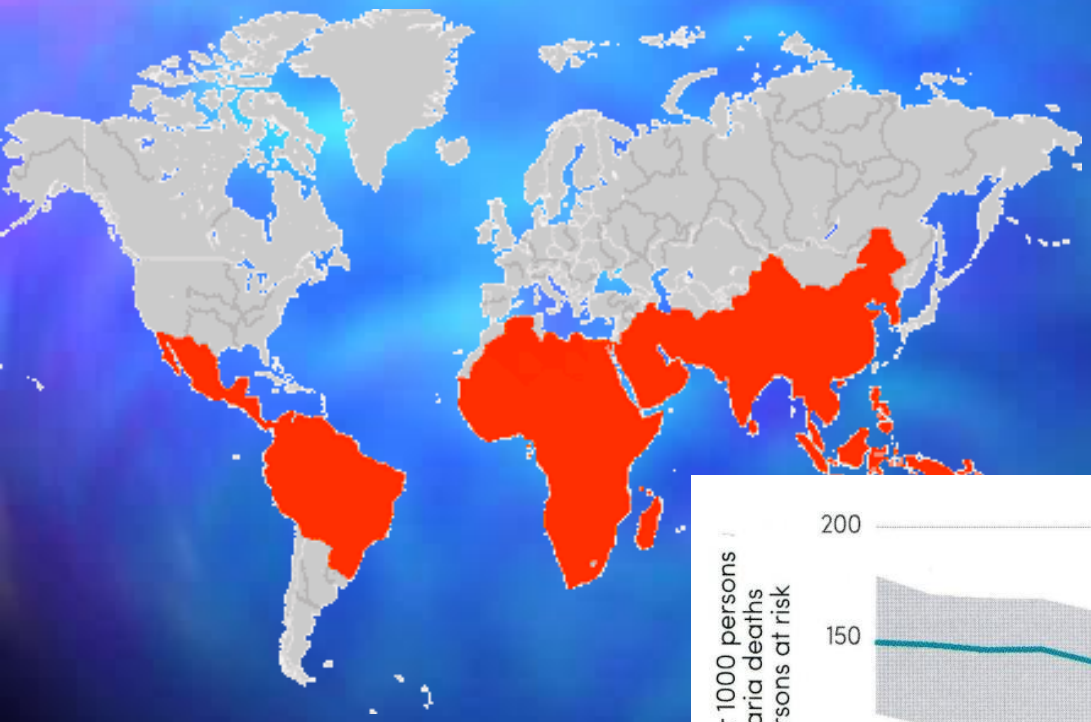
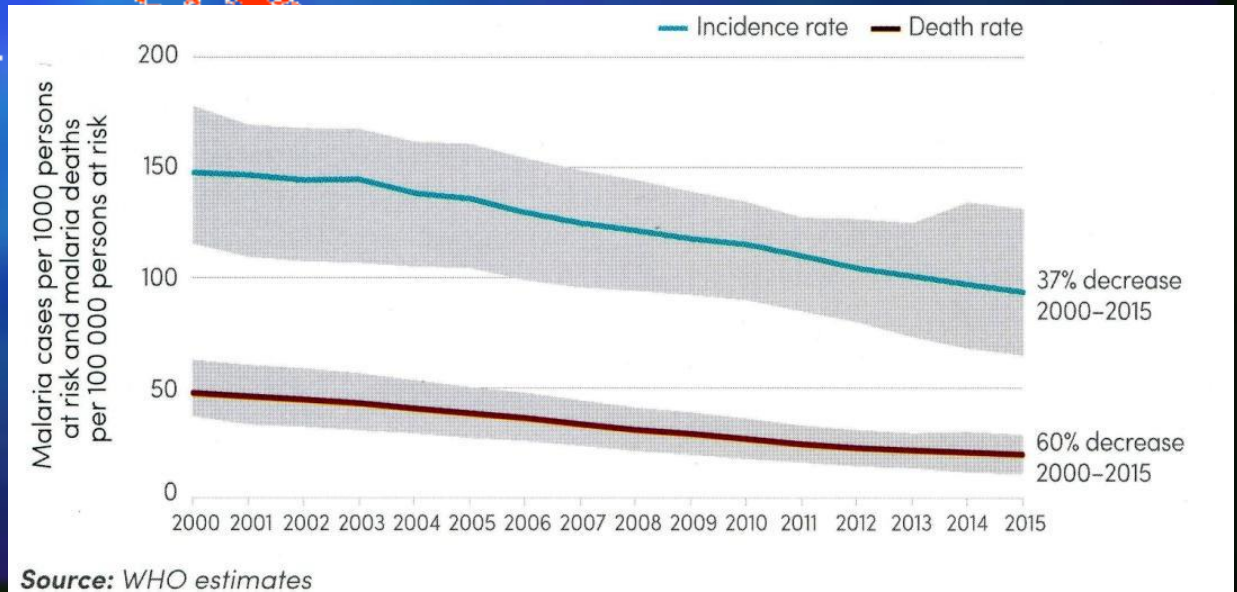
Global malaria burden today

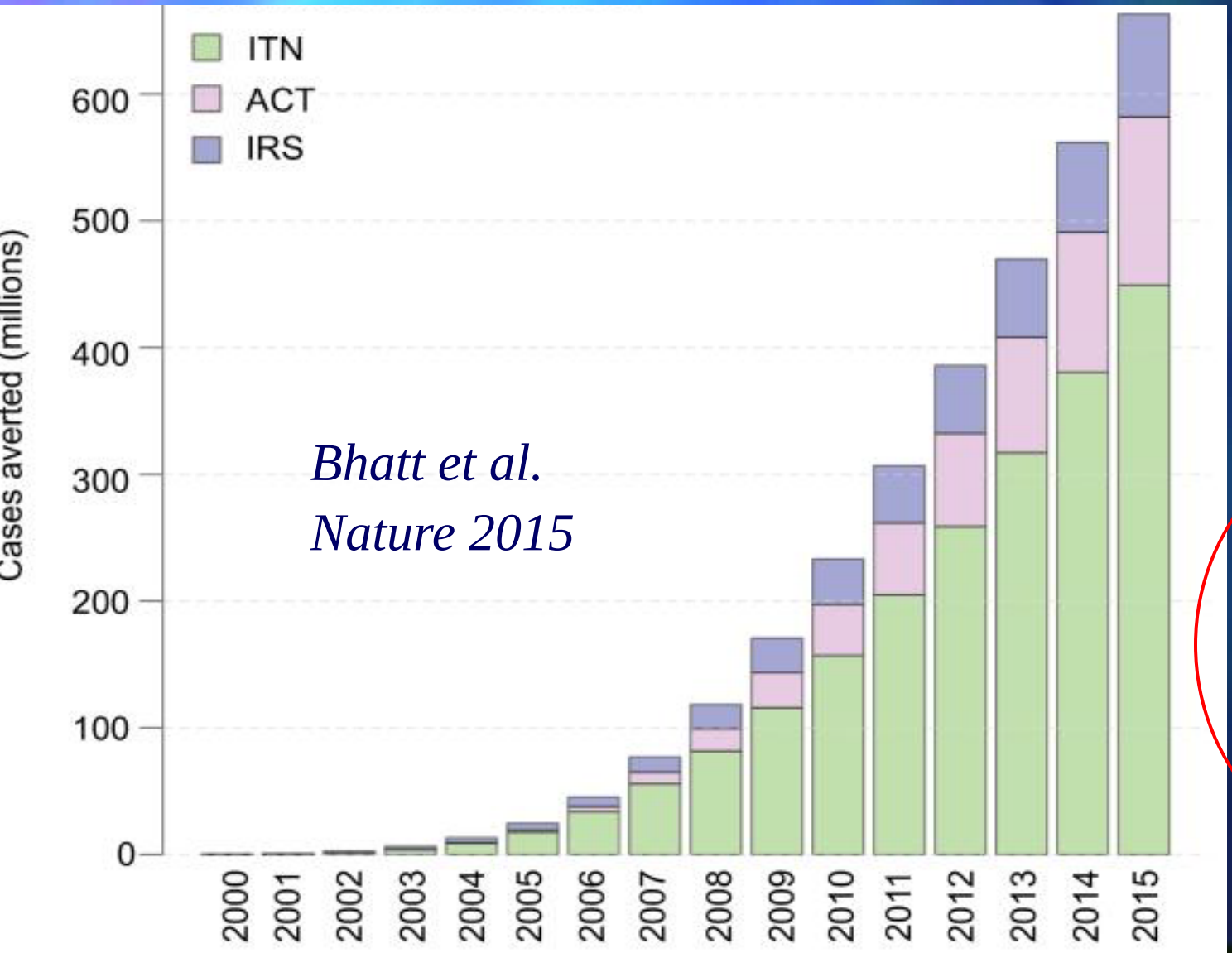


150 – 300 mio malaria cases/year, resulting in 300.000 – 600.000 deaths/year
(WHO 2015)

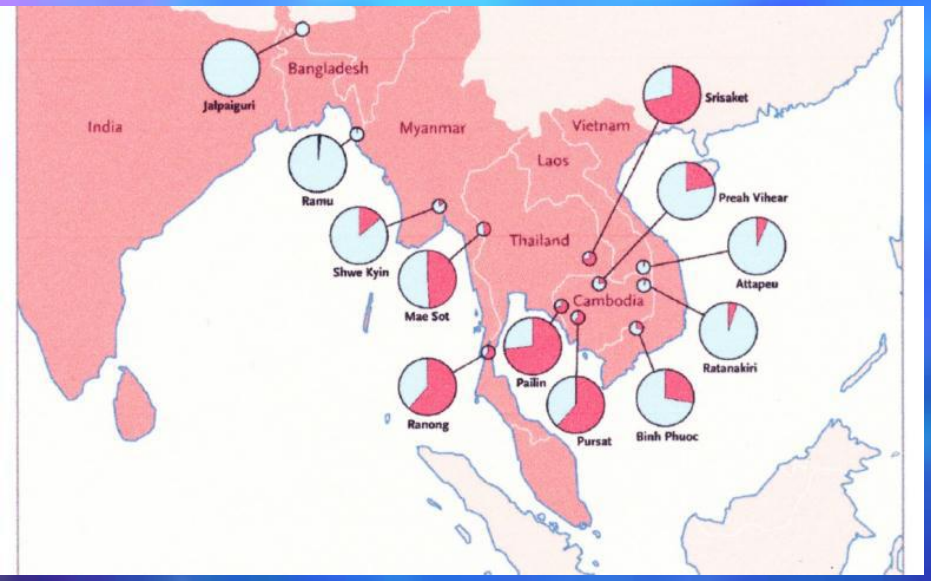


Source: *WHO estimates*

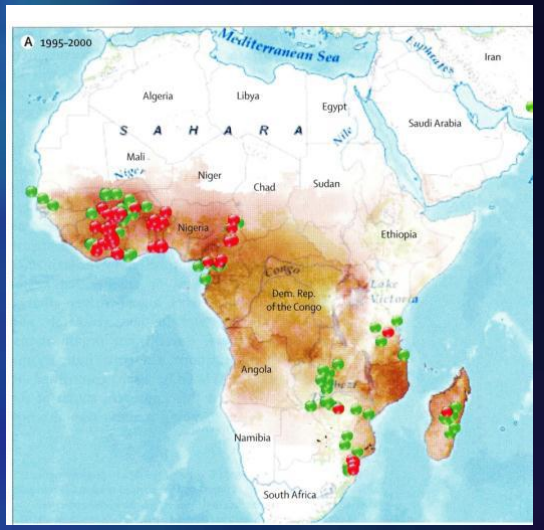
Impact of malaria control tools



Threats by drug & insecticide resistance development



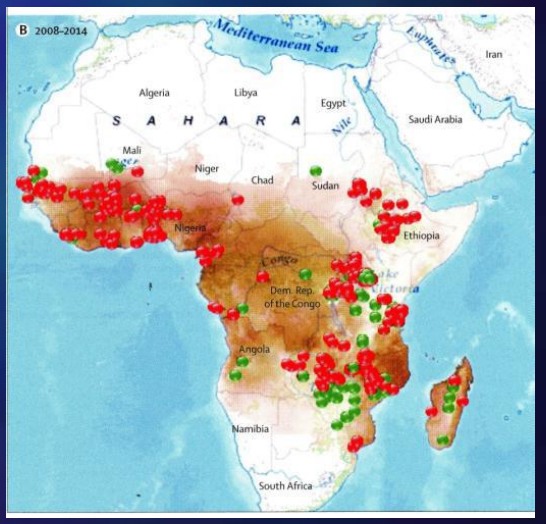
1995-2000



Artemisinin resistance

Ashley et al. NEJM 2014

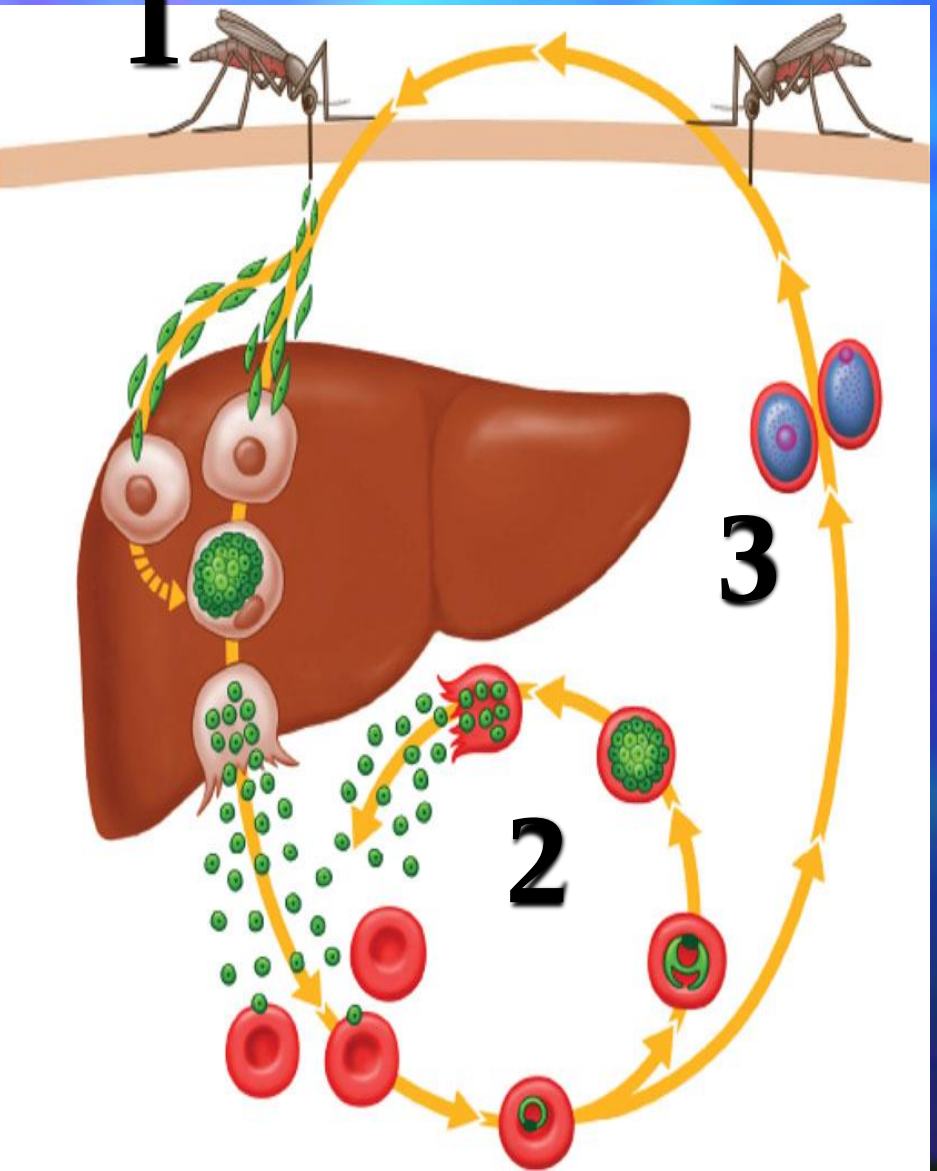
2008-2014



Pyrethroid resistance

Hemmingway et al. Lancet 2016

Need for malaria vaccines



Vaccine types:

1 = Pre-erythrocitic vaccines
2 = Blood stage vaccines
3 = Transmission blocking vaccines

Subunit vaccines (e.g. RTS,S)

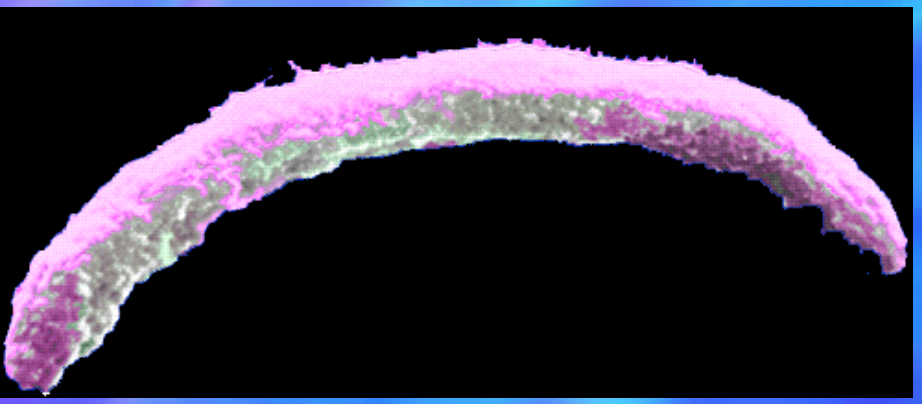
Whole attenuated parasite approaches (e.g. sporozoites from y-irradiated mosquitoes; immunization-treatment-vaccination, genetically attenuated sporozoites)

Challenges for malaria vaccines

- There is **no vaccine against a human parasite** until today.
- Although **natural immunity** to malaria develops in endemic areas, this generally **takes some years** of exposure and is **imperfect**.
- Extensive **immuno-epidemiological studies** have provided limited insight into what the best antigens for a vaccine might be.
- No good **animal models** for human malaria parasites.

Nick White, Manson Tropical Diseases: *„Despite considerable effort and expense, a generally available and highly effective malaria vaccine is still unlikely in the future.“*

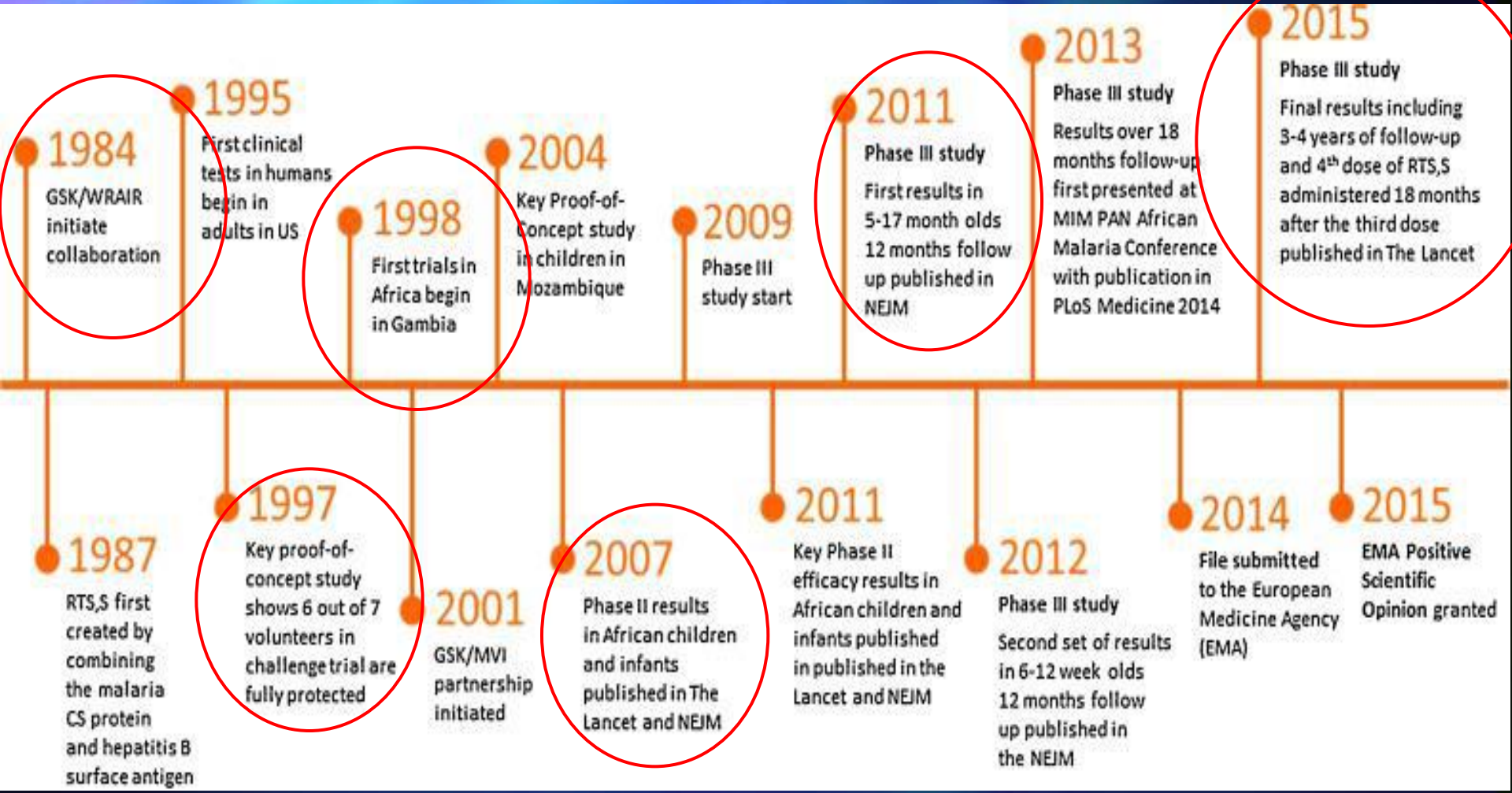
RTS,S



The Circumsporozoite Protein (CSP)

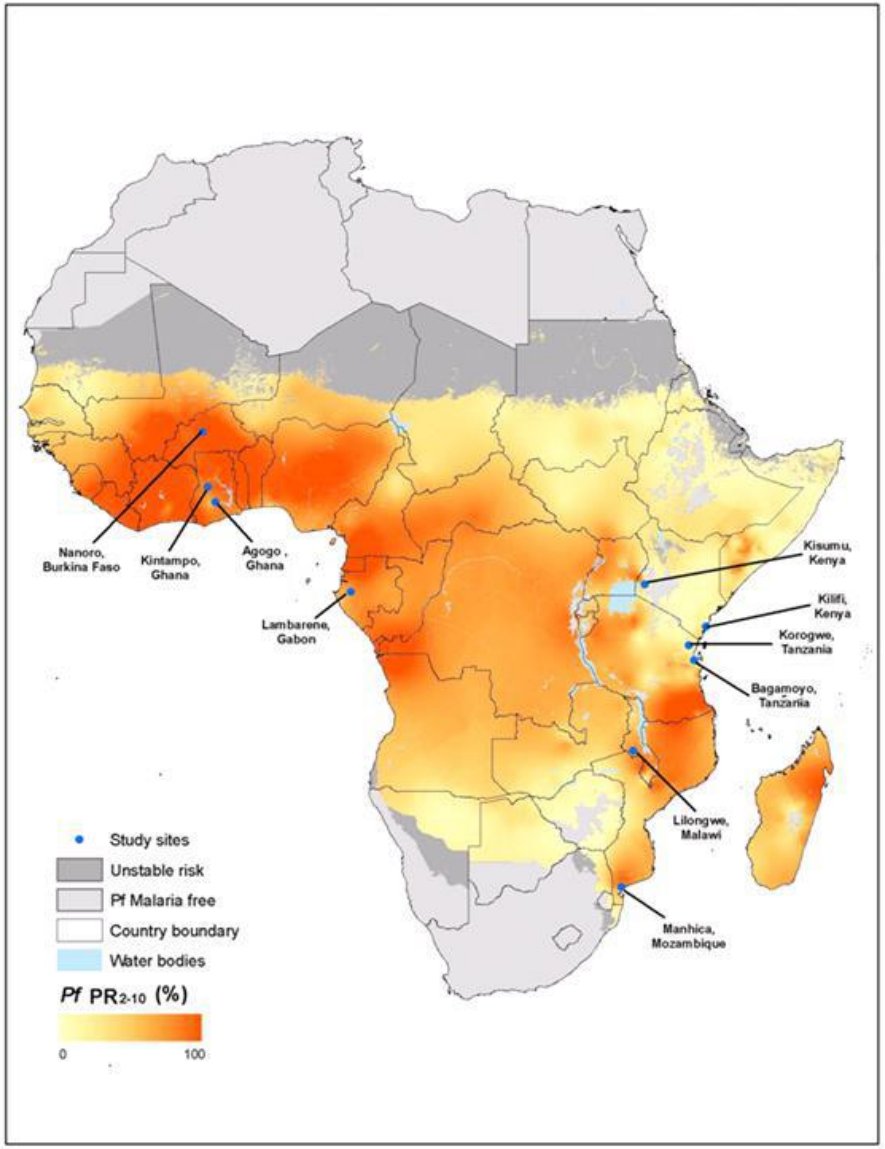
- It results from a collaboration, commenced in the 1980s, between the US **Walter Reed Army Institute and GSK**.
- A **hybrid protein**, formulated in an **adjuvant** named **AS01**.
- Initial vaccine constructs of **CSP** showed very low-level efficacy, but expressing the central repeat (‘**R**’) fused to the C-terminal region known to contain T cell epitopes (hence ‘**T**’) fused in turn to the hepatitis B surface antigen (‘**S**’) yielded a yeast-expressed protein RTS. To generate immunogenic particles, the RTS protein needed to be co-expressed with the ‘**S**’ protein to yield RTS,S.

History of RTS,S development



Kaslow & Biernaux Vaccine 2015

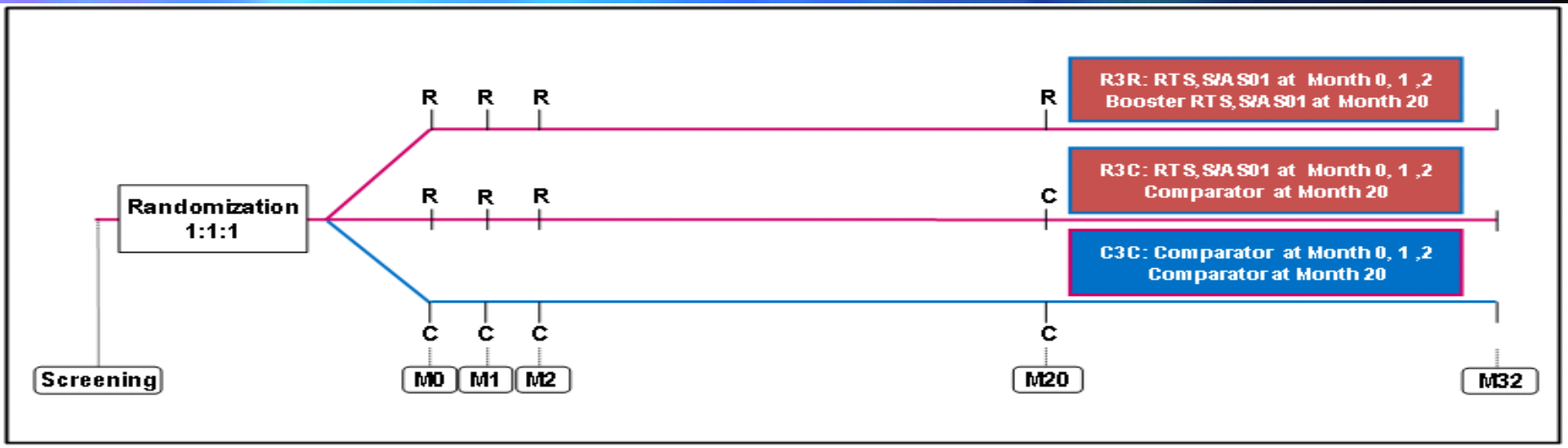
RTS,S phase III trial



Eleven study centres in 7 SSA countries (enrolment 03/2009 – 01/2011; follow-up until 01/2014)

- 6537 **infants** (6-12 weeks)
- 8922 **children** (5-17 months)
- **Primary endpoint** was the occurrence of malaria (passive case detection) after dose 3

Phase III study design



Infants (6-12 wks): RTS,S or comparator with EPI vaccines (3 arms)

Children (5-17 mo): RTS,S or comparator (3 arms)

- Arm 1: Three times RTS,S + booster dose at 20 months
- Arm 2: Three times RTS,S + comparator at 20 months
- Arm 3: Comparator vac. (infants – meningococcal, children - rabies)

Final RTS,S trial results
- efficacy -

- **Vaccine efficacy (VE) was 31% in infants, and 66% in children** *(12 months after dose 3)*

- With and without booster dose, **VE was 26% and 18% in infants and 36% and 28% in children** *(38/48 months after dose 1)*

- **VE against severe malaria reached 32%** in boostered children.

- **VE became negative after prolonged follow-up** in children exposed to higher transmission levels *(5-7 years after dose 1)*

RTS,S. NEJM 2011/2012, PLoS Med 2014, Lancet 2015, NEJM 2016

Final RTS,S trial results
- adverse events -

RTS,S-specific:

- **Increased risk for febrile convulsions** (infants and children)
  - roughly 2/1000 RTS,S doses, 0.5/1000 comparator doses -

- **Increased risk for meningitis** (only children)
  - 21 cases in the two RTS,S groups, 1 in the control group –

- **Increased risk for mortality, females** (infants and children)
  - 123 cases in the two RTS,S groups, 33 in the control groups –

RTS,S Clinical Trial Partnership. Lancet 2015

Final RTS,S trial results

- mortality -

	R3R	R3C	C3C	Risk Ratio
Infants	51	55	42	1.26 (0.89-1.80)
Children	61	46	46	1.22 (0.87-174)
Total	112	106	88	1.24 (0.97-158)
Males	50	45	55	0.84 (0.61-1.17)
Females	62	61	33	1.91 (1.30-2.79)

Klein et al. mBio 2016; 7 e00514, modified by Greenwood 2016

Final RTS,S trial results
- adverse events -

Associated with successful malaria control:

- **Increased malaria incidence over time**
- **Increased incidence in cerebral malaria (only in children)**

  - 54 cases in the two RTS,S groups, 16 in the control group –

"Rebound malaria" = An increase in malaria incidence after malaria control has been achieved above that which would have occurred without the intervention.

RTS,S Clinical Trial Partnership. Lancet 2015

Olotu et al. NEJM 2016; Greenwood UK, 2016

RTS,S – conclusions

- RTS,S provides only **modest and short-lived protection**.
- **Increased AEs** and **increased mortality** are unexplained issues; reasons are unclear **(different NSE of RTS,S/comparators?!)**
- Malaria vaccines in young children may lead to **rebound morbidity (and probably mortality)** in older age groups.
- Because of these **residual questions about programmatic feasibility, preventive effect, and safety,** the WHO recommended that more evidence be generated in **pilot** implementation **studies (only 4 dose regimen in children)** in 3-5 SSA countries with moderate-to-high levels of malaria transmission.

Müller et al. Lancet 2015, Gessner et al. Lancet 2016