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First malaria vaccine: true?

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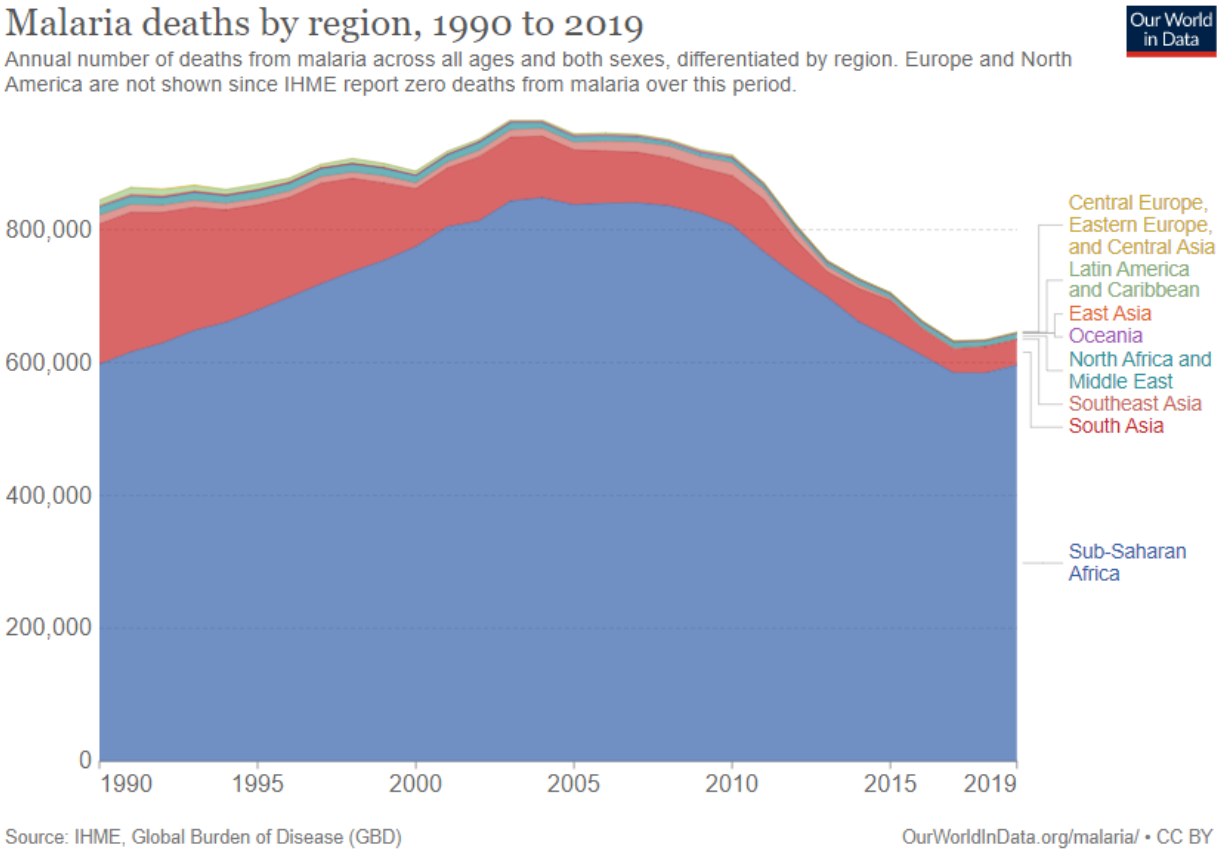
Policlinique de médecine tropicale, voyages et vaccinations

Why is malaria vaccine development not as easy and quick as COVID?..

- Ab against SARS-CoV-2 act constantly against the virus, before entering the cell, when expressed out of the cell, during the disease course…
- Ab of CSP only target the parasite before entering the liver (10-15 mn)…

A malaria vaccine why?



A malaria vaccine: why?

- Increase of resistance :
  - Parasite to drugs
  - Mosquito to insecticides

- Difficult to eliminate P vivax malaria
- Complementary tool for elimination/eradication

Menu

- Malaria vaccines
  - Vision – roadmap
  - Challenges
- First generation vaccine: RTS’S
  - Results of Phase 1-3 trials
  - Potential impact
  - Usefulness
  - Combined strategies : Vaccine + ?
- Other vaccines: SPZ, R1-CSP, pregnancy

Updated Vision

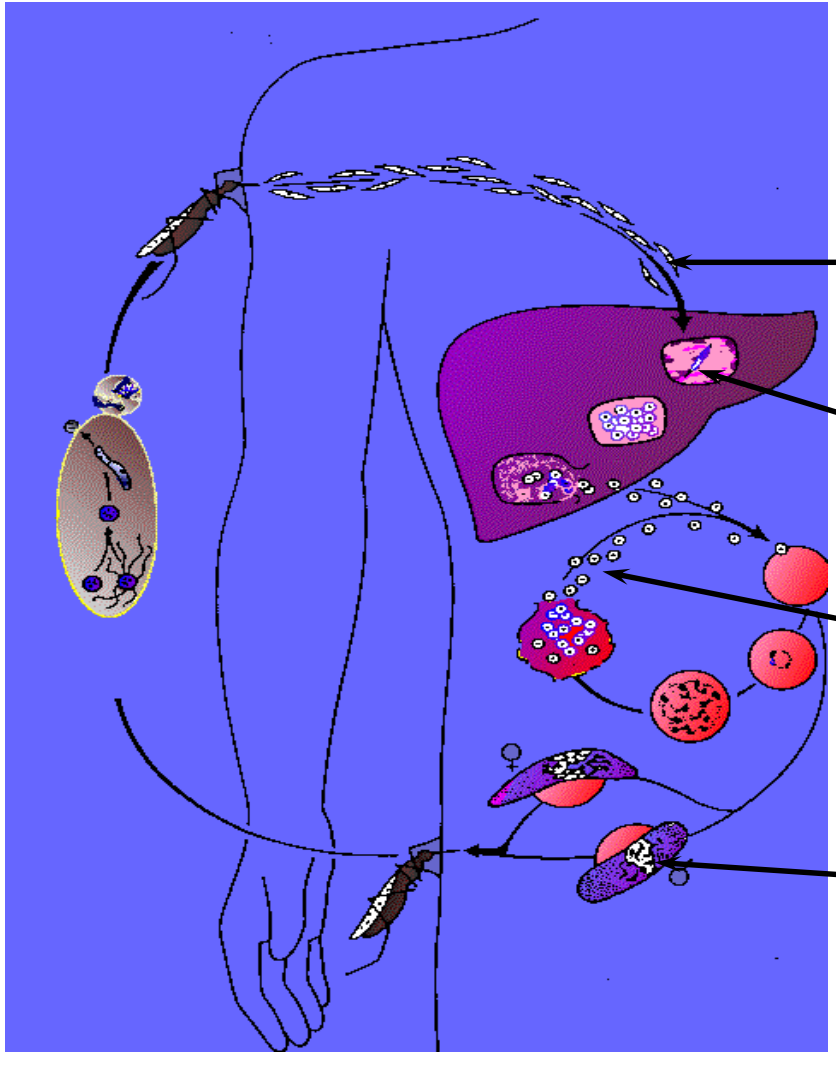
- Safe and effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax* that prevent transmission, disease and death to enable malaria eradication.

Updated Strategic Goals

- By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* and encompassing the following two goals, for use by the international public health community:
  - *Malaria vaccines with a protective efficacy of at least 70-80% against clinical malaria, suitable for administration to appropriate at-risk groups in malaria-endemic areas.*
  - *Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings.*

Malaria vaccine development challenges

- >5’000 proteins of Plasmodium, 5 species
- No good immune correlate of protection
- Not good animal model
- Antigenic diversity
- Different desired immune responses need different technology platforms
- Time to conduct safety and efficacy trials
- Long-term impact difficult to assess



Vaccine targets and mechanisms

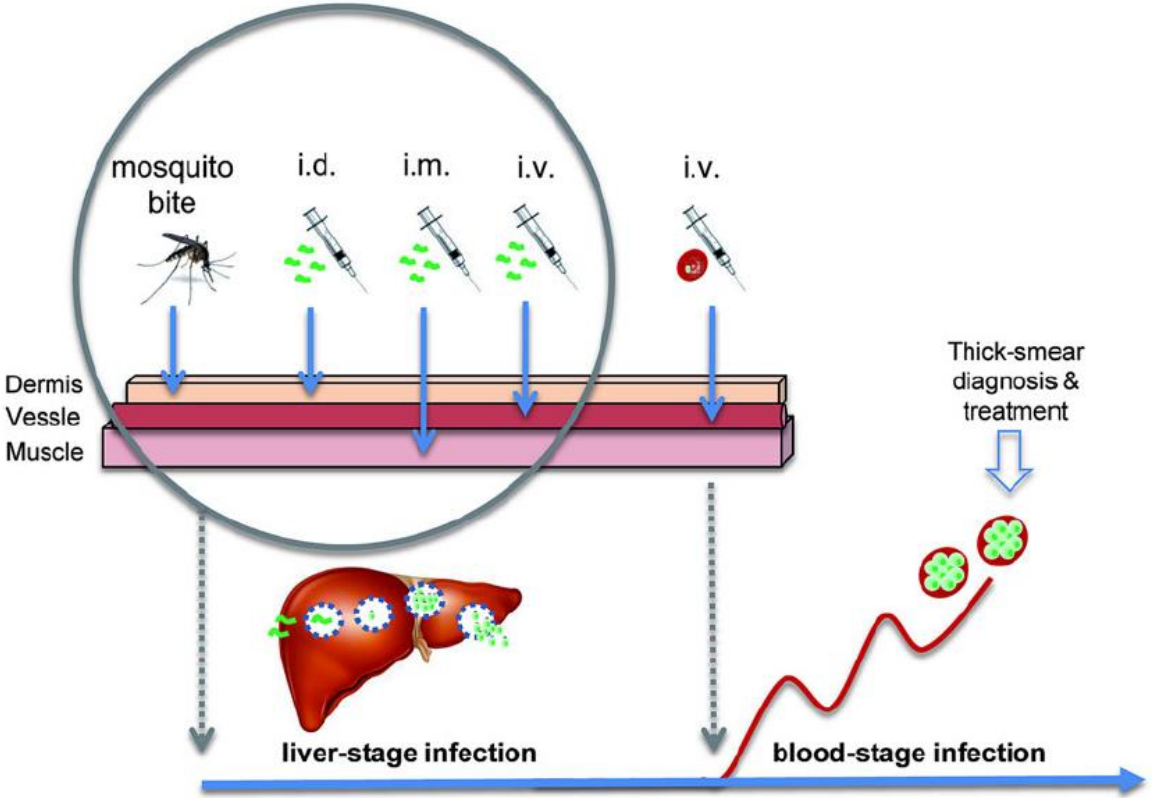
sporozoite stage
- High Ab titers
- Long lived memory B cells

hepatic stage
- High CD8
- Th1 helper cell response

merozoite stage
- High Ab titers
- Macrophage mediated clearance

gametocyte stage
- High Ab titers
- Long lived memory B cells

No good correlate of protection =>
Controlled Human Malaria Infection (CHMI): major advance



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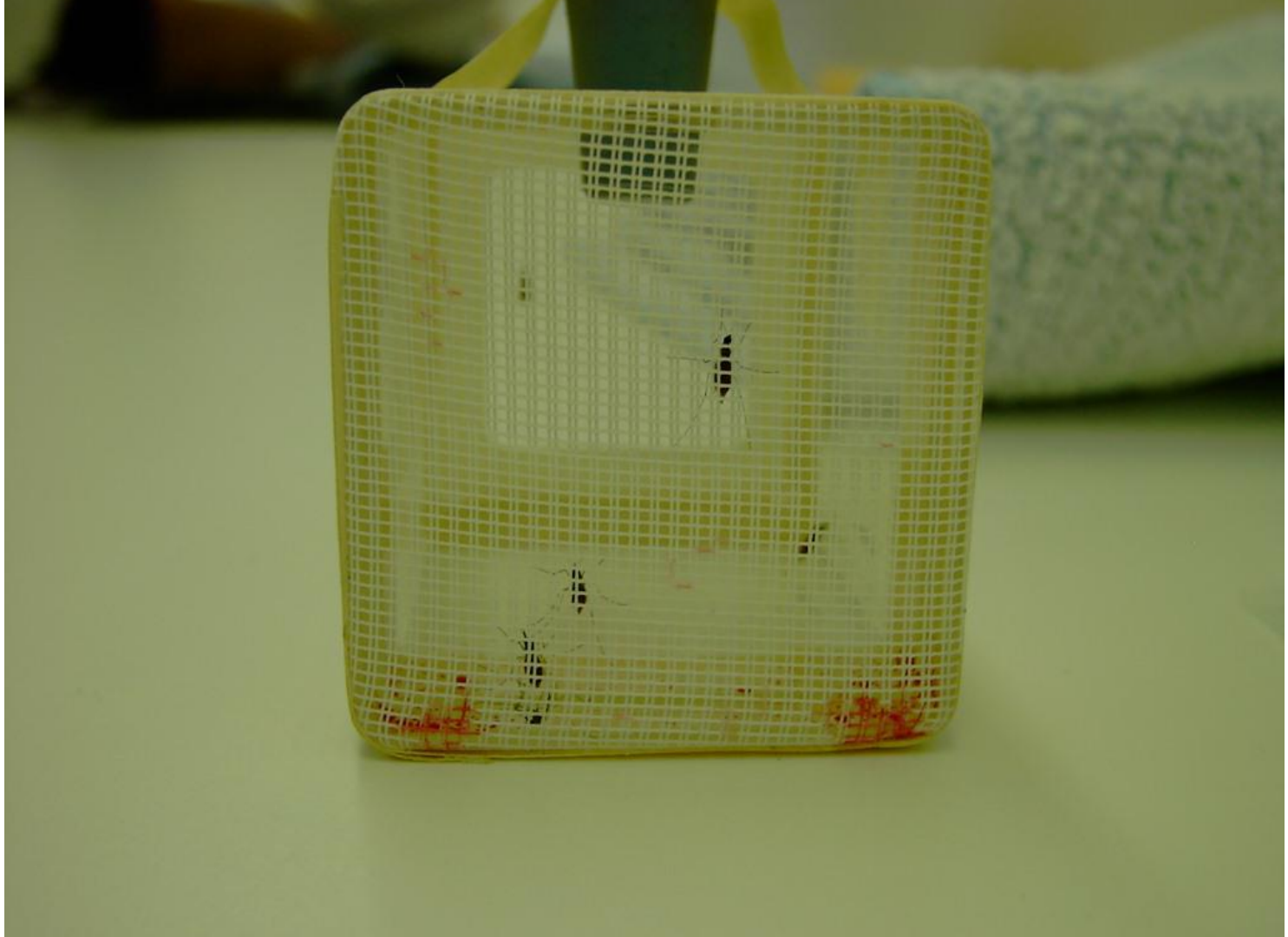

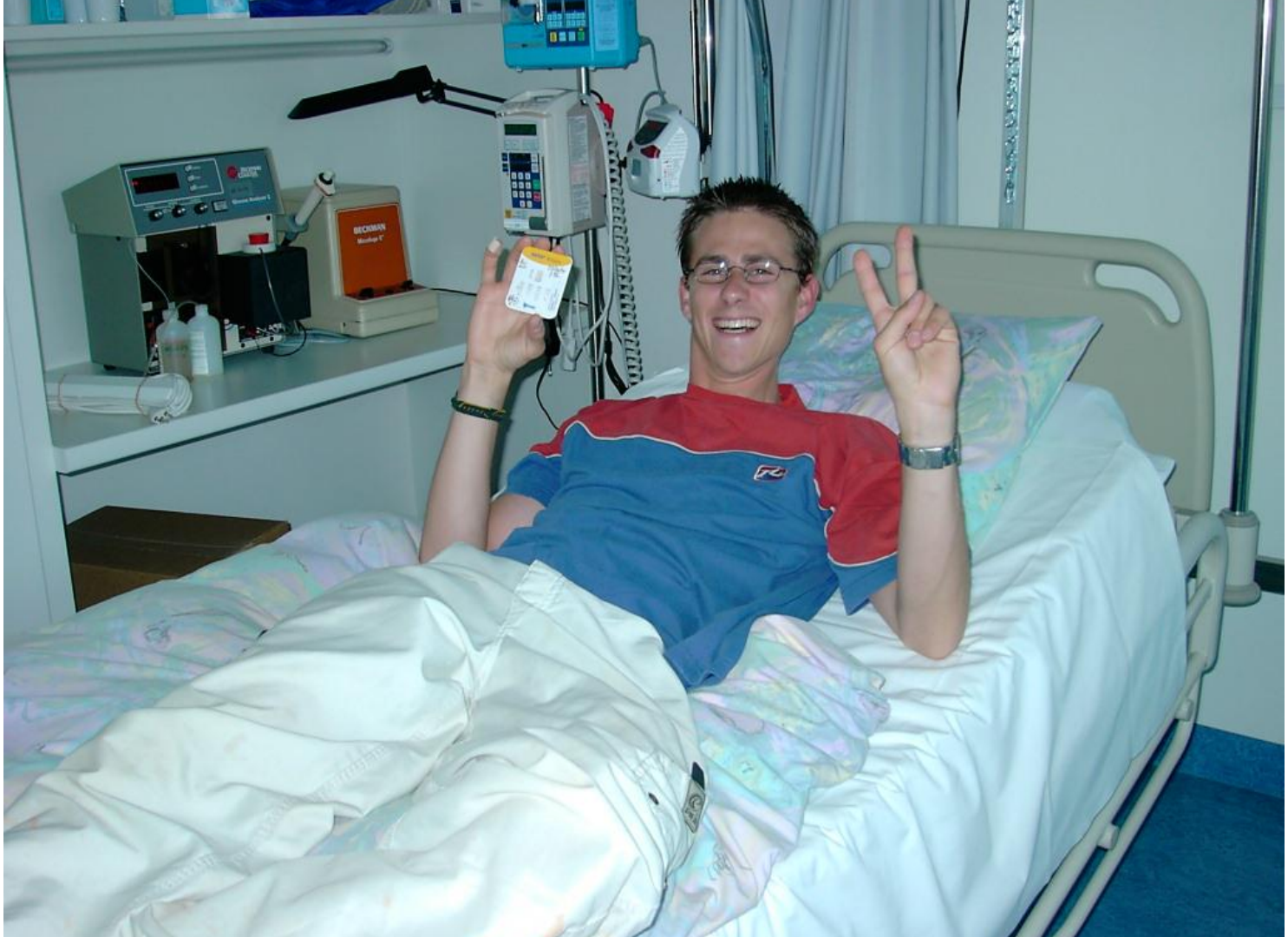
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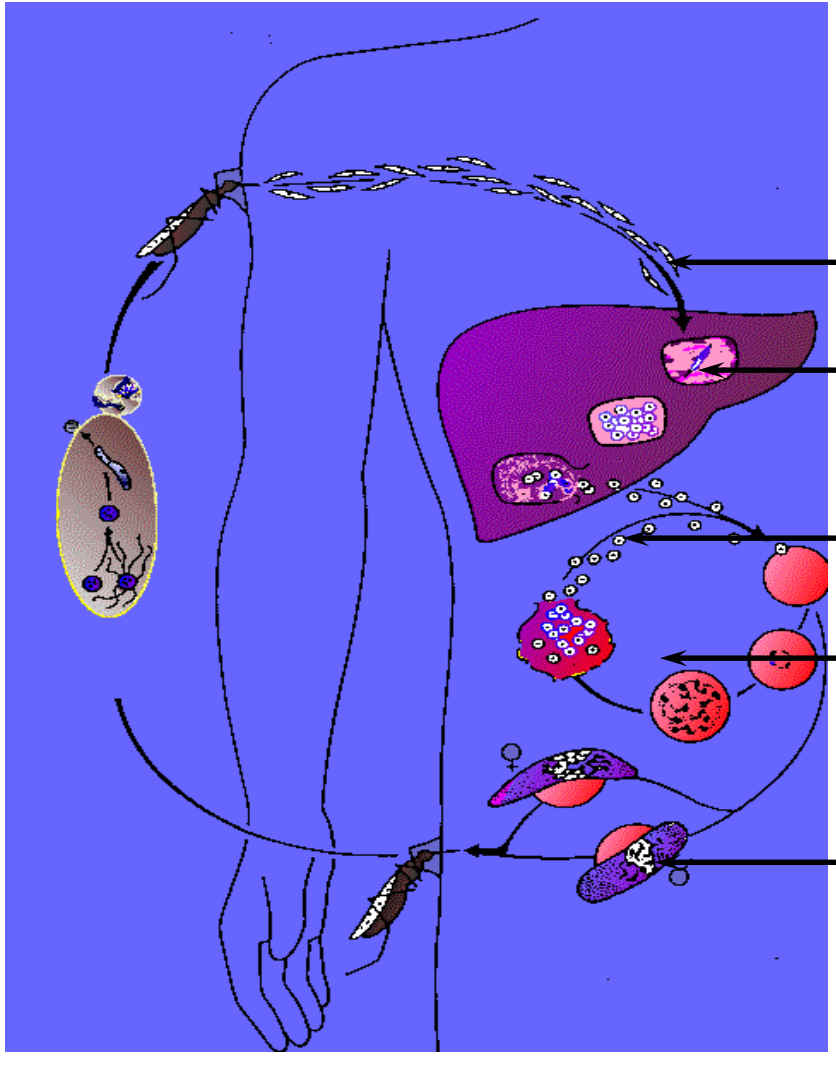


Vaccine targets

sporozoite stage

hepatic stage

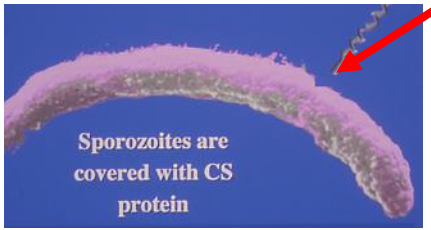
merozoite stage

parasite toxins

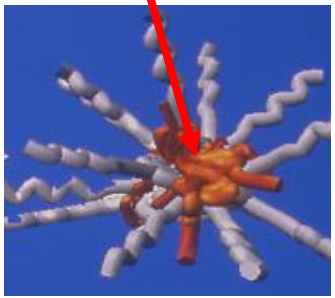
gametocyte stage

- RTS'S/ASO1 vaccine

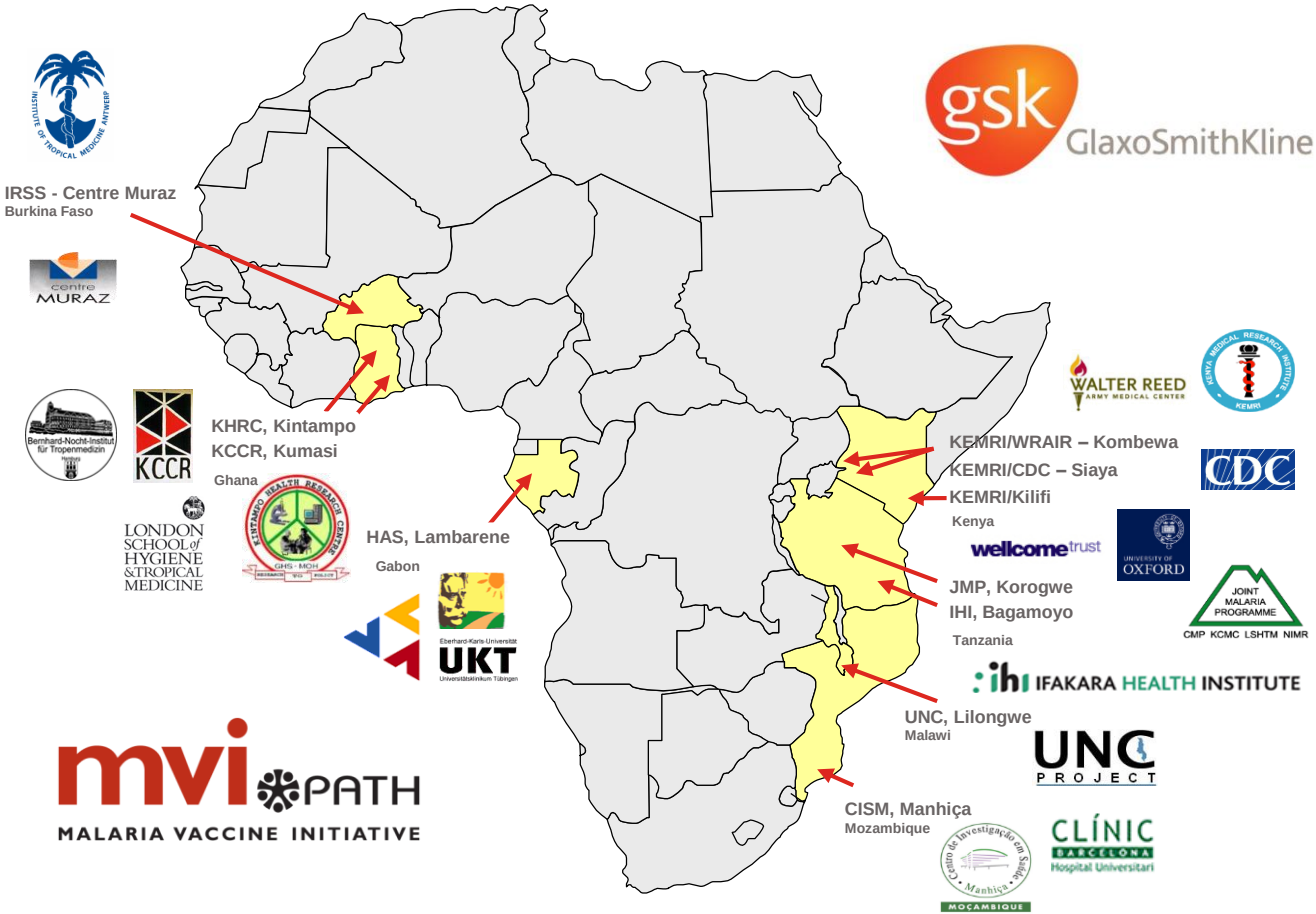
Circumsporozoite protein



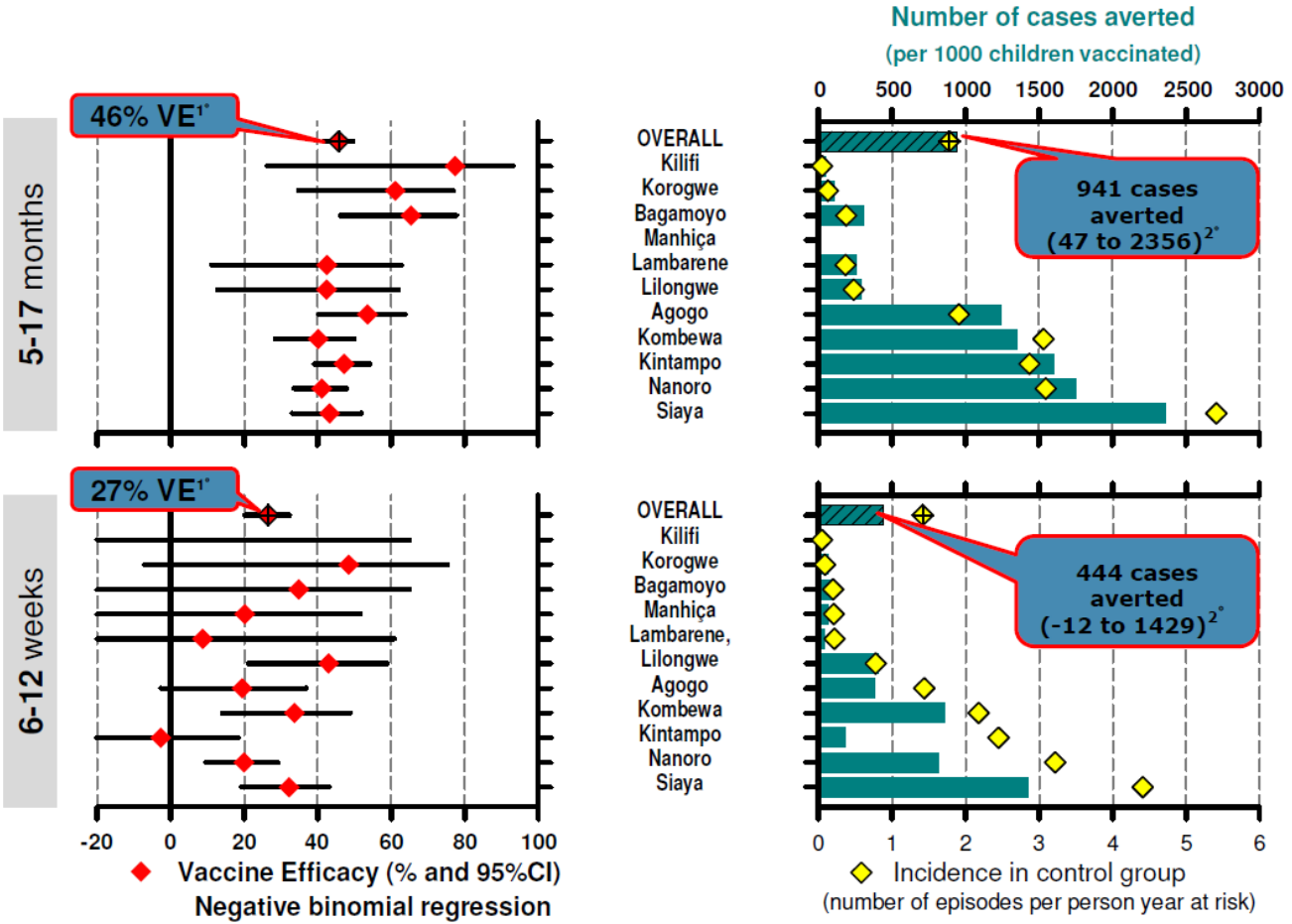
Hep B surface protein



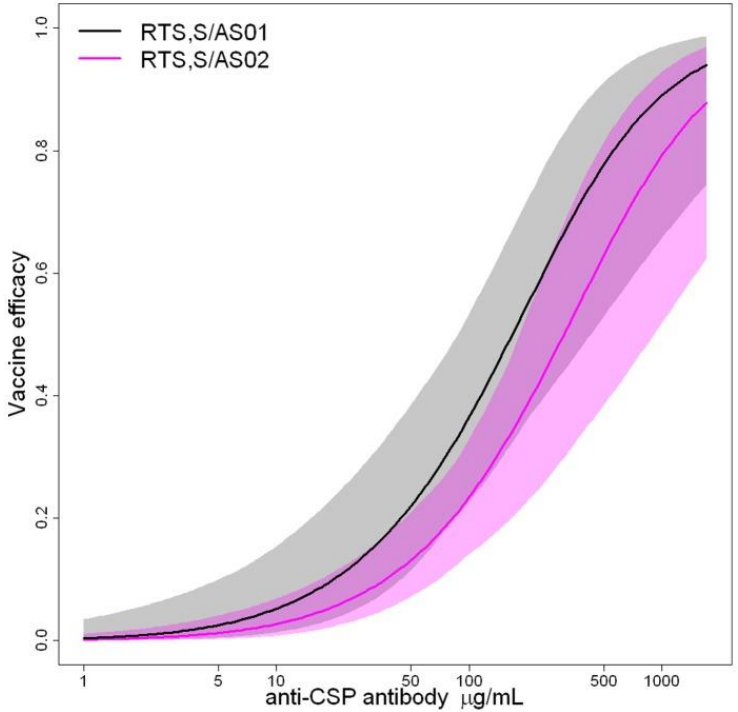
RTS,S/ASO1E: Phase III pivotal trial



Impact of RTS'S on clinical malaria (18 month FUP)

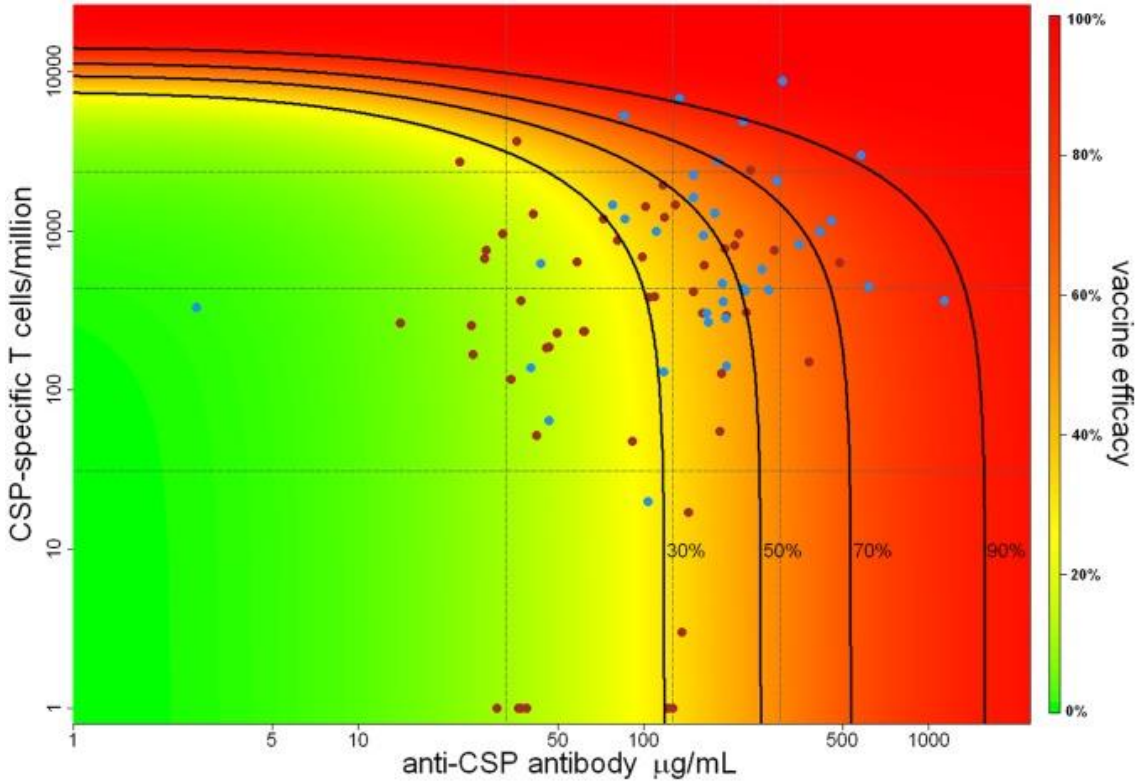


Modeling efficacy against infection as a function of anti-CS Ab in absence of CD4 cells



White et al Plos One 2013

Modeling efficacy against infection as a function of anti-CS Ab and CS-specific CD4 cells



White et al Plos One 2013

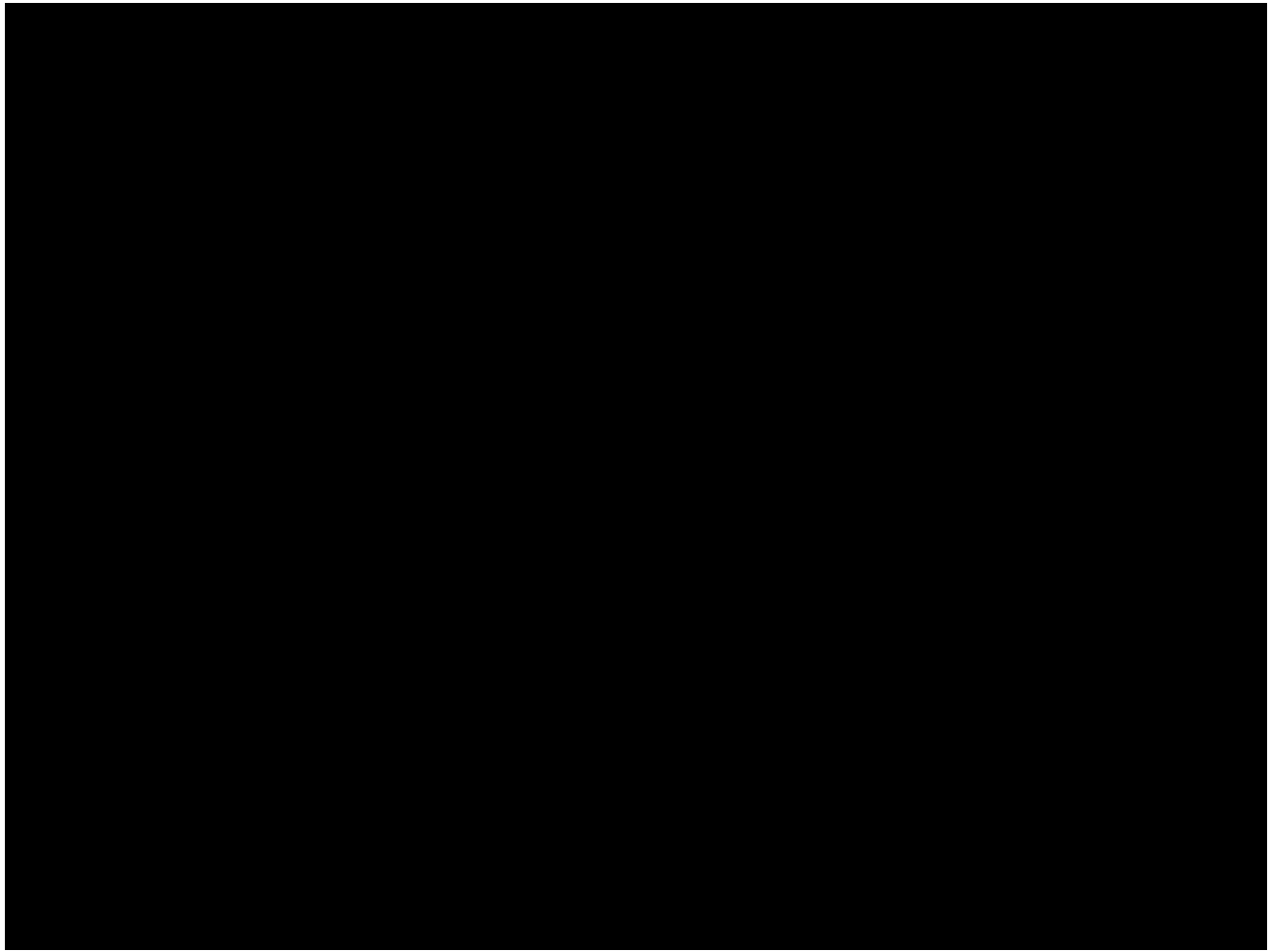
RTS,S/ASO1E: Phase 3 pivotal trial
Efficacy over 36-48 median follow-up

3 doses		
Vaccinees age	*5-17 months*	*6-12 weeks*
Clinical malaria	28% [23 - 33]	18% [12 - 24]
Severe malaria	1% [-23 - 21]	10% [-18 – 32]
Booster dose		
Clinical malaria	36% [32 - 41]	26% [20 - 32]
Severe malaria	32% [14 - 47]	17% [-9 – 38]

RTS'S Lancet 2015

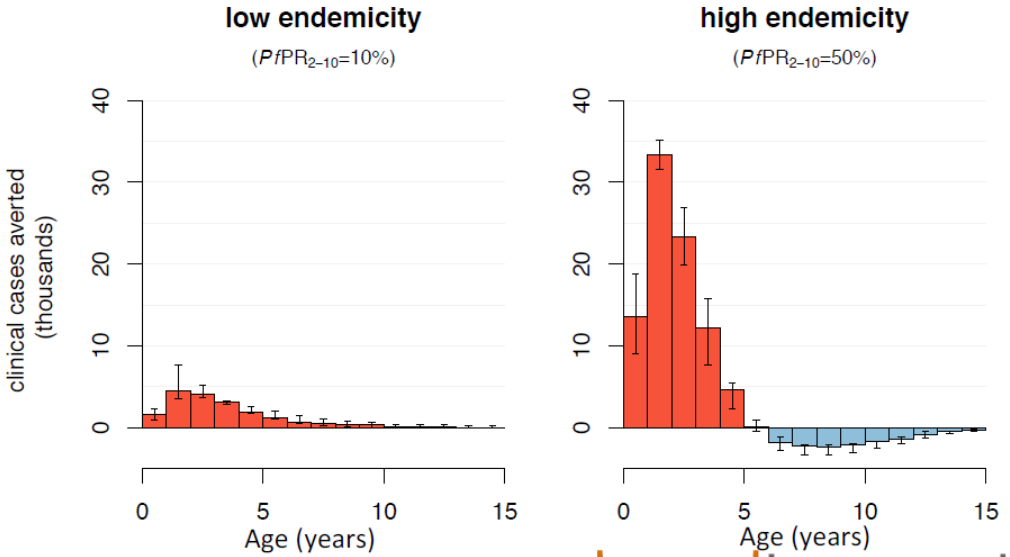
Booster dose needed? How useful could it be ?

http://www.nejm.org/doi/full/10.1056/NEJMoa1515257#t=article



RTS,S/ASO1 Public health impact:

age shift in malaria cases averted /100’000 vac



Vaccinated children not becoming infected

Vaccine protection worn off, left with lower immunity compared to non-vaccinated

Penny et al. Lancet 2016

WHO recommends groundbreaking malaria vaccine for children at risk

Historic RTS,S/AS01 recommendation can reinvigorate the fight against malaria

6 October 2021 | News release | Geneva | Reading time: 3 min (859 words)

WHO recommendation for the RTS,S malaria vaccine

Based on the advice of two WHO global advisory bodies, one for immunization and the other for malaria, the Organization recommends that:

WHO recommends that in the context of comprehensive malaria control the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO. RTS,S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden.

Combined strategies? RTS'S ± Seasonal Malaria Chemoprophylaxis (SMC)

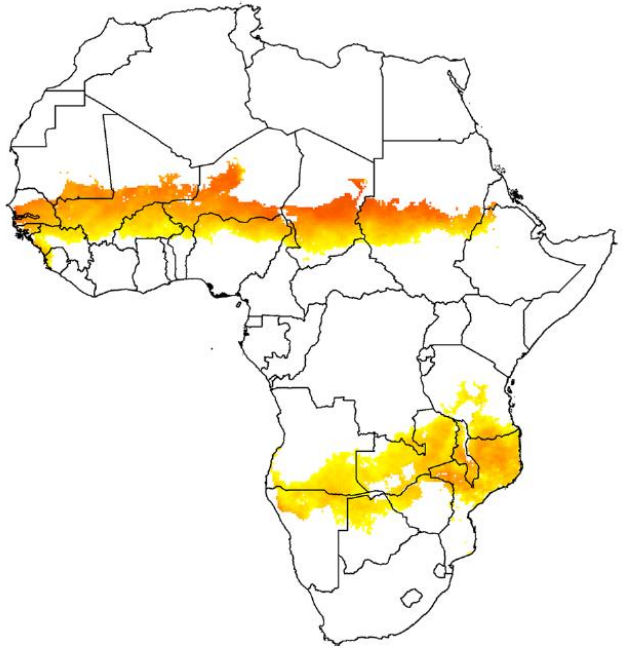
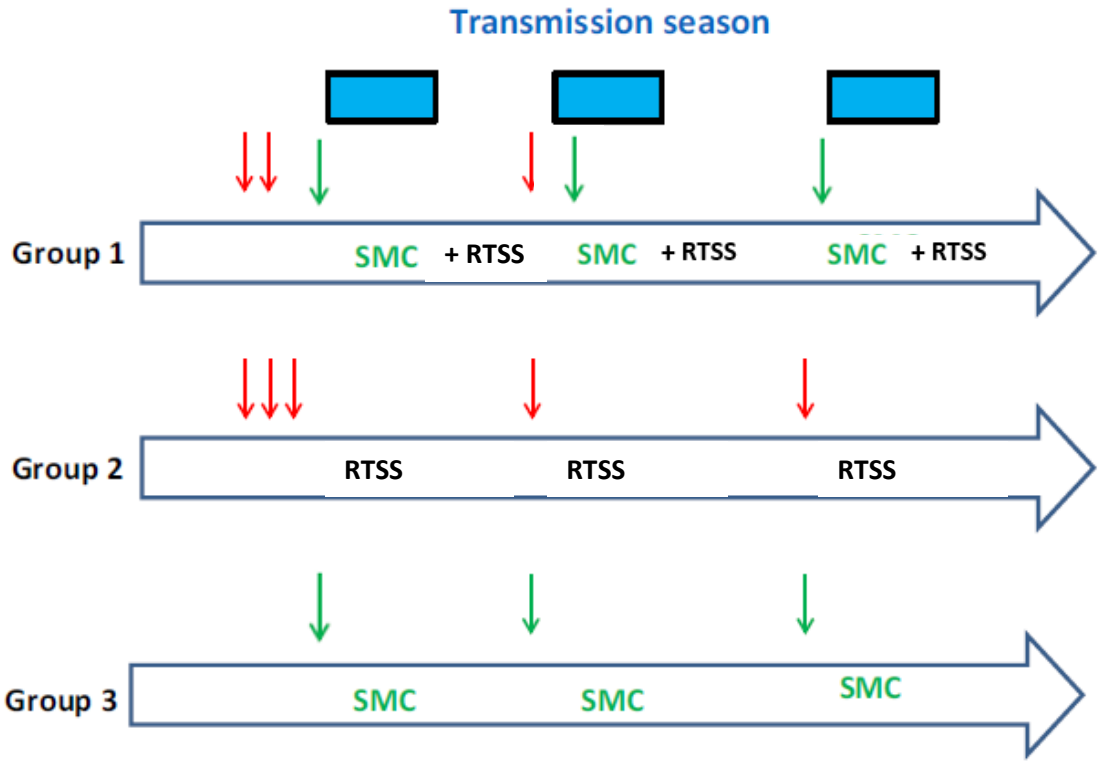
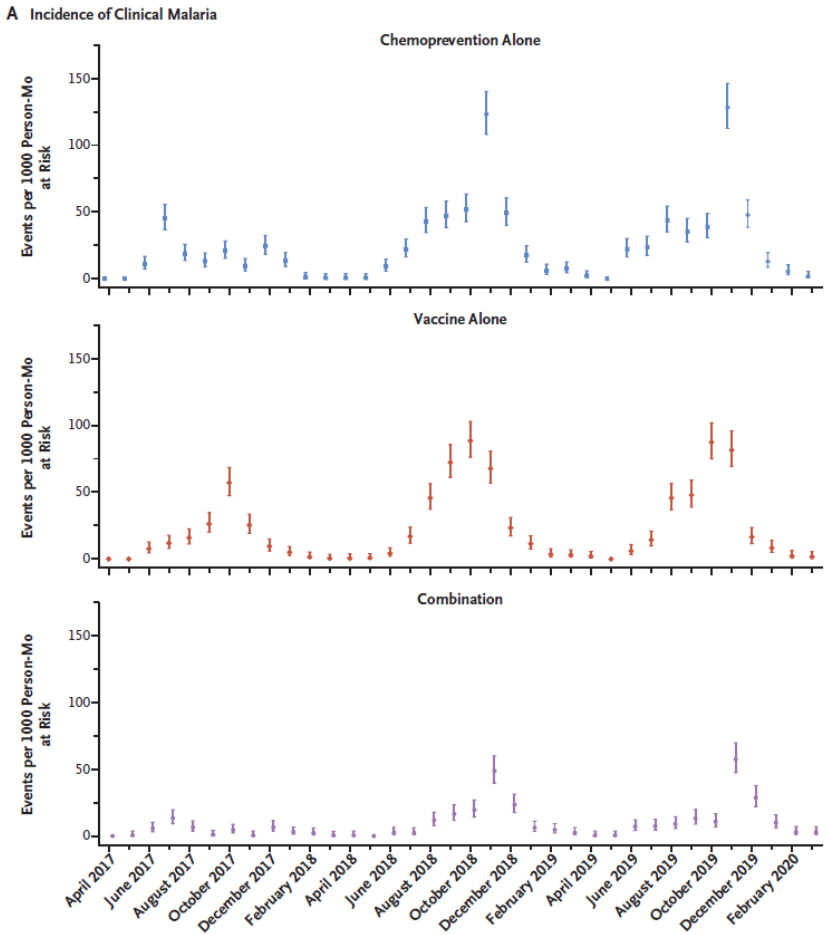


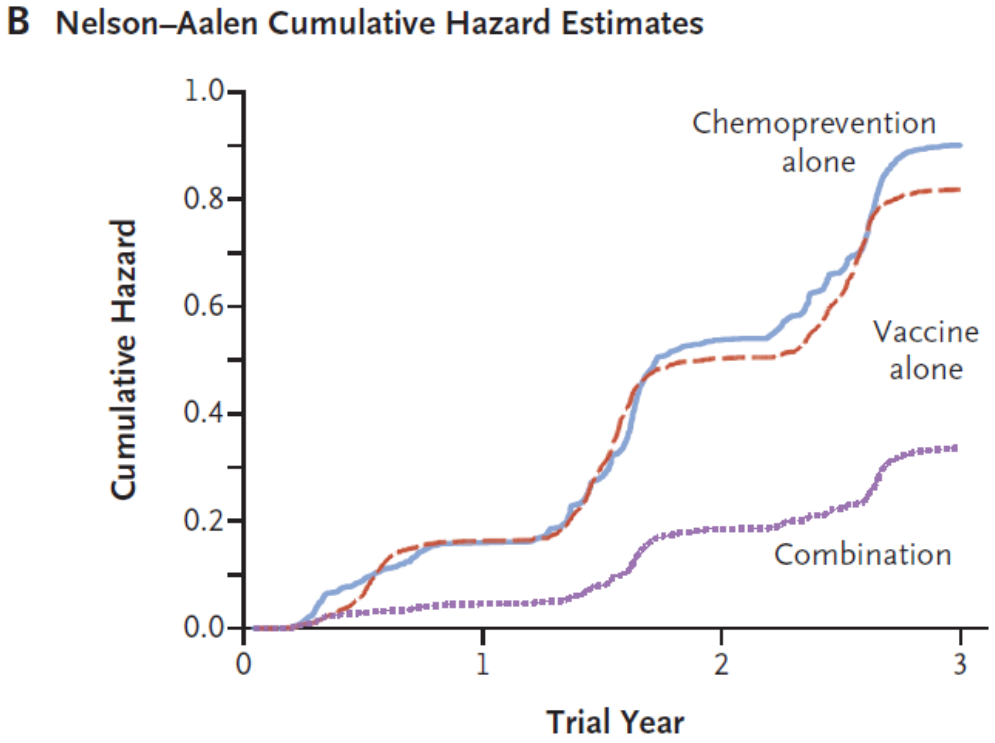
Fig. 1 A map of sub-Saharan Africa showing the areas where malaria transmission is likely to be highly seasonal. *Orange areas* indicate where more than 60% of annual rainfall occurs within 3 months of the year, and where malaria incidence is estimated to exceed 100 cases per 1000 children per year (adapted from Cairns et al. [1])



Greenwood et al, Mal J 2017

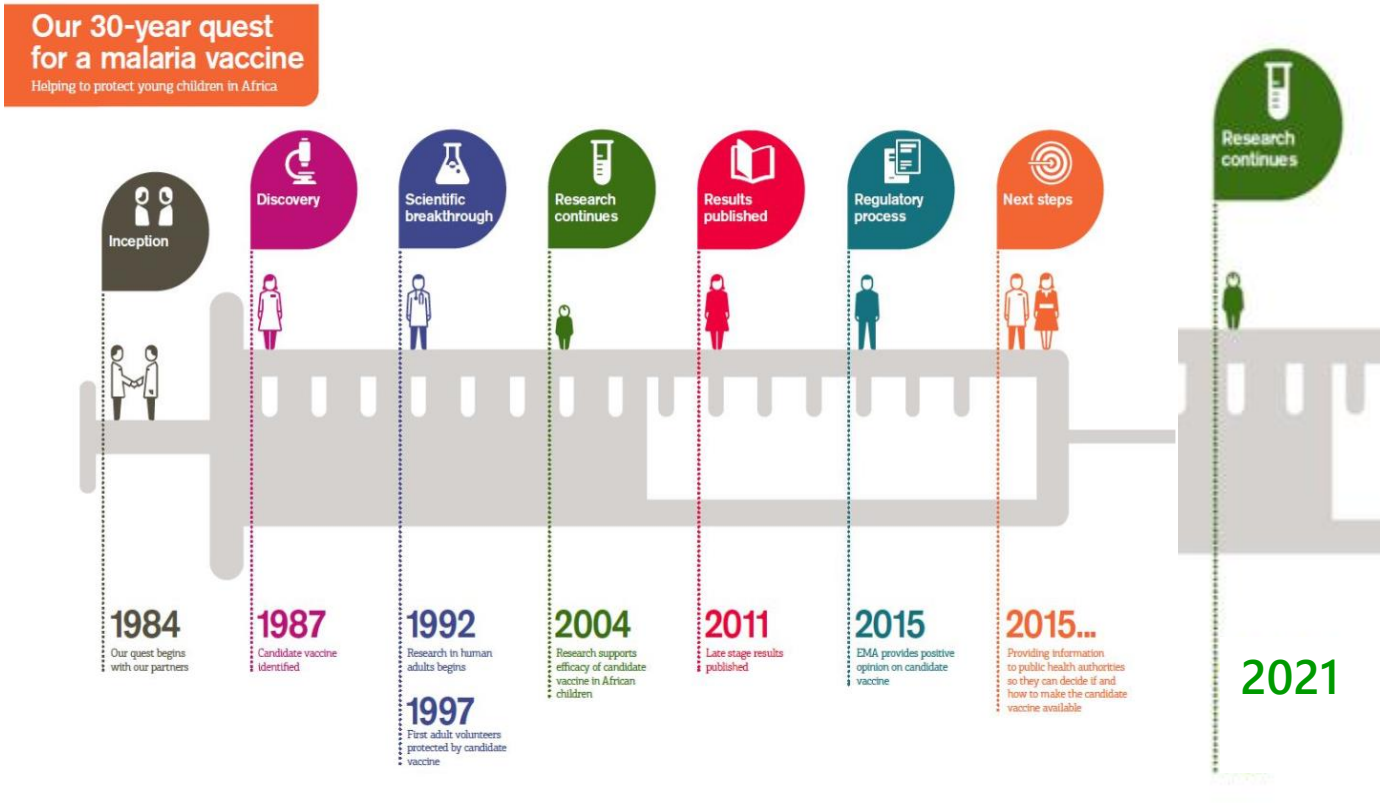
Combined strategies? RTS'S ± Seasonal Malaria Chemoprophylaxis (SMC)





Chandramohan et al, NEJM 2021

RTS'S development time frame



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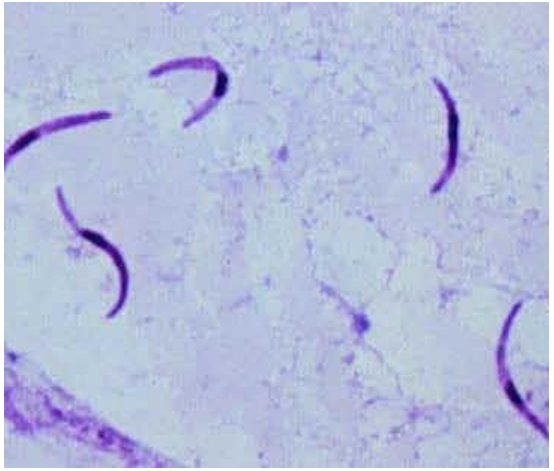
What else?

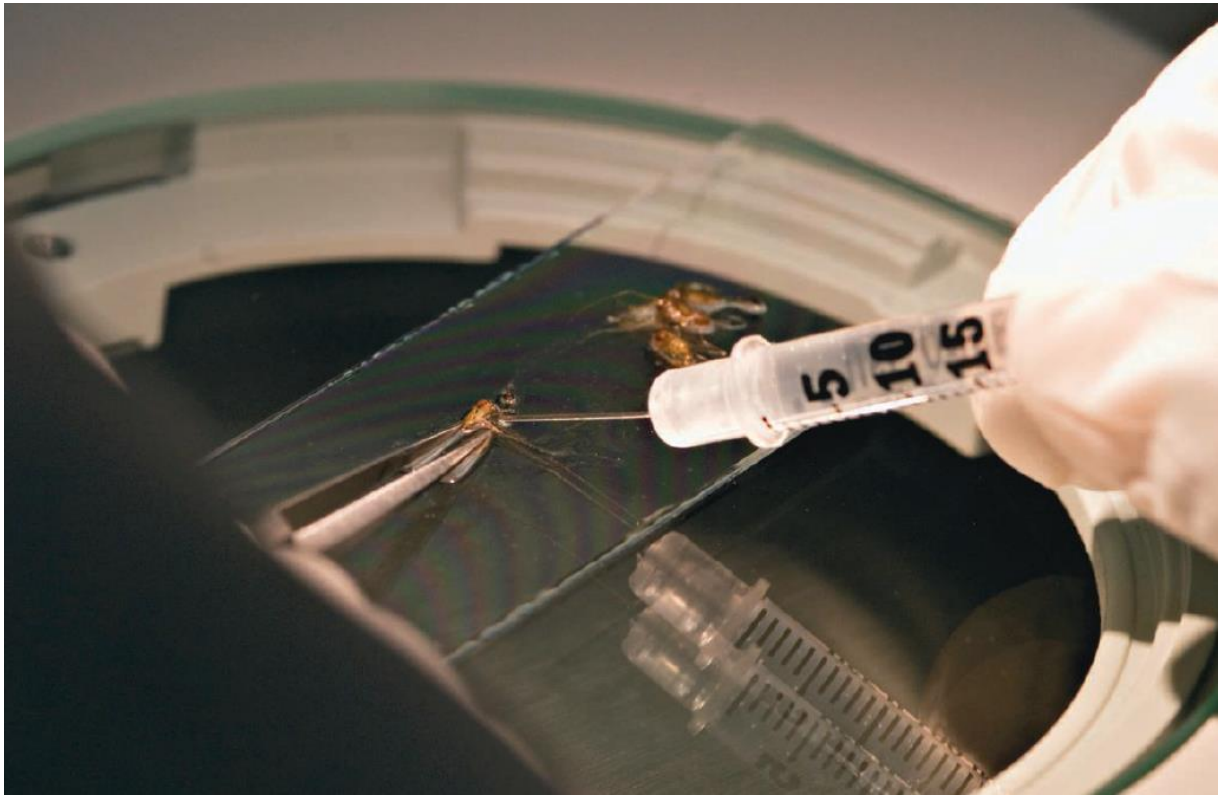


Whole organism vaccine

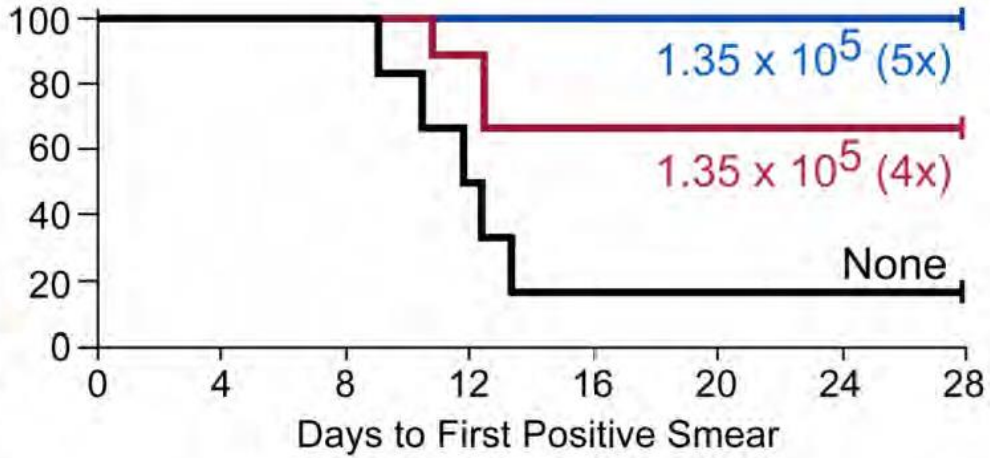
SANARIA

MALARIA ERADICATION THROUGH VACCINATION

Dissecting mosquitoes to get sporozoites, then irradiated



Phase IIa Intravenous immunization with non-replicating sporozoite vaccine (PfSPZ)

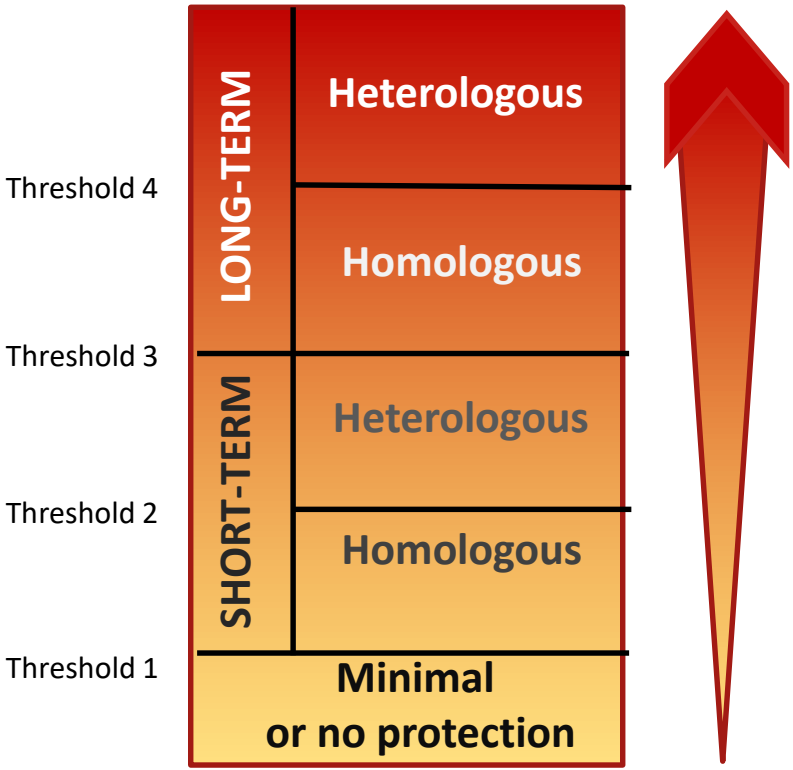


Vaccination Dose	# Inj.	CHMI Parasite*	# of Subjects	Parasite Free	Vaccine Efficacy
None		3D7	6	1	
1.35×10^5	4	3D7	9	6	60%
1.35×10^5	5	3D7	6	6	100%

Seder et al, Science 2013

PfSPZ Efficacy achievments

Need Increased Dosage for Increased Duration and Breadth of Protection



Milestones

54% (9/14) at 33 wks

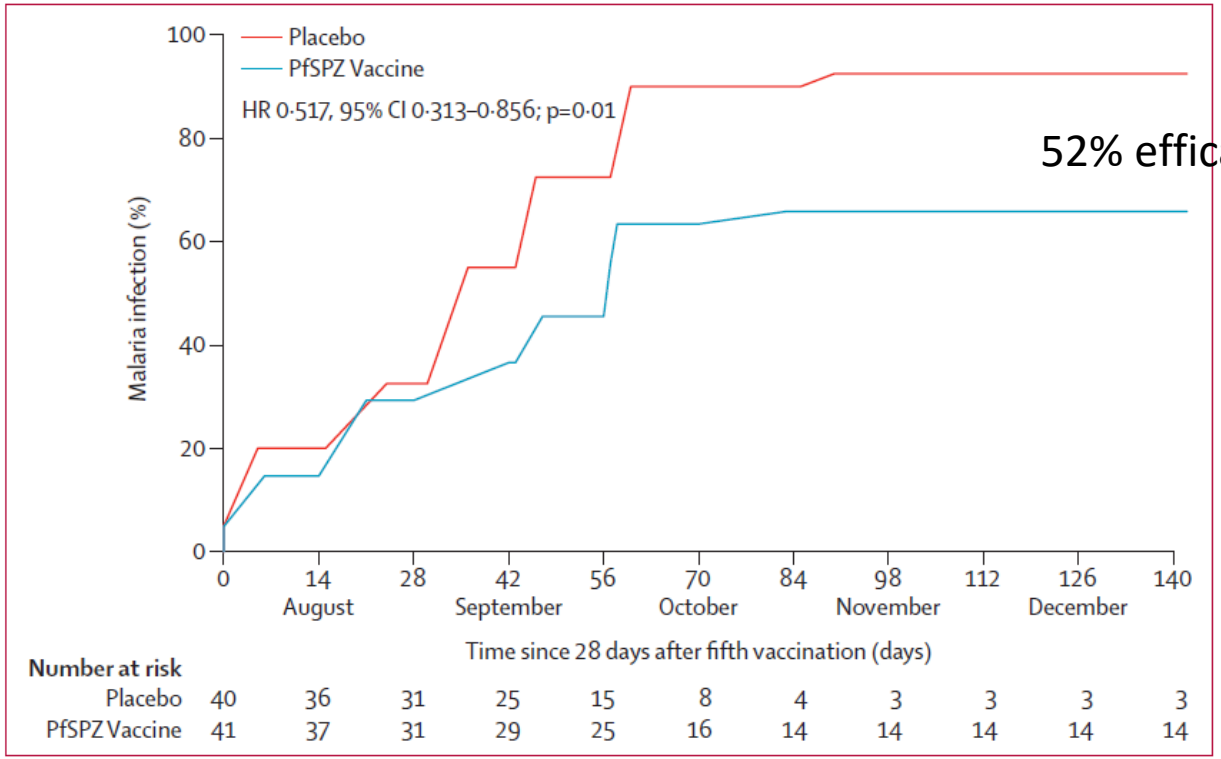
65% (7/10) at 24 wks

80% (4/5) at 3 wks

92% (12/13) at 3 wks

Lyke et al, PNAS 2017; Epstein et al, JCI 2017

PfSPZ IV in semi-immune populations: efficacy after natural infection

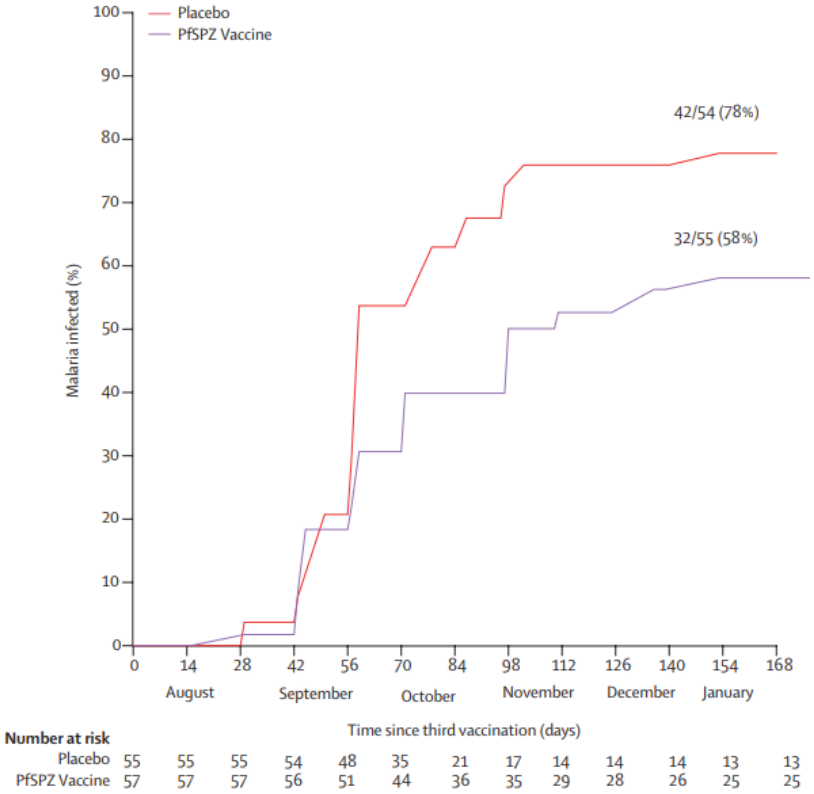


52% efficacy (5 doses)

Figure 2: **Protective efficacy of PfSPZ Vaccine against naturally occurring infection**

Sissiko et al, Lancet Inf Dis 2017

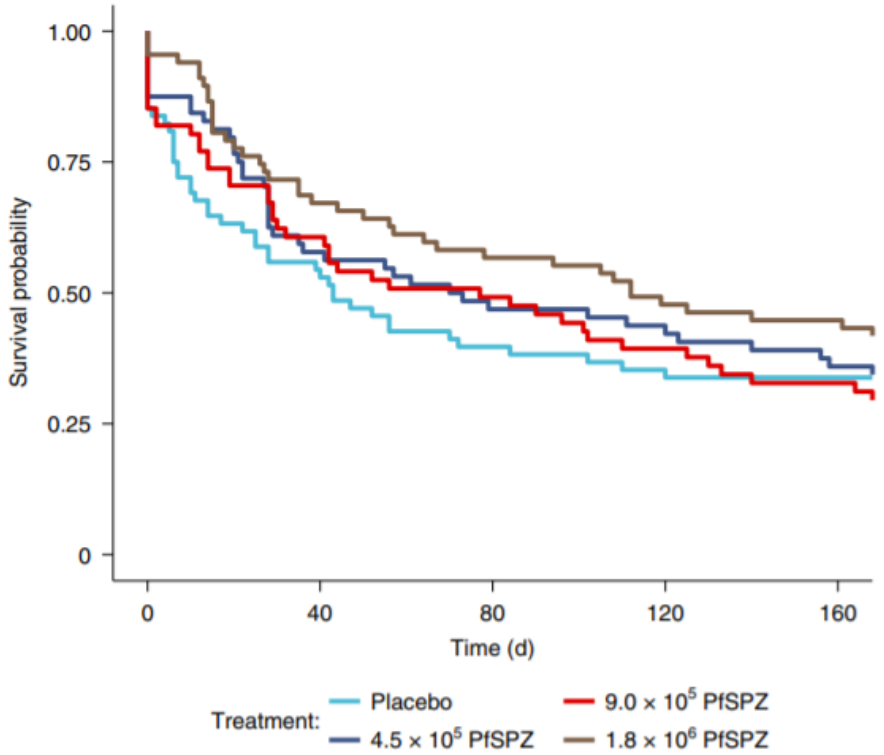
PfSPZ IV in semi-immune populations: efficacy after natural infection



51% efficacy (3 doses)

Sissiko et al, Lancet 2021

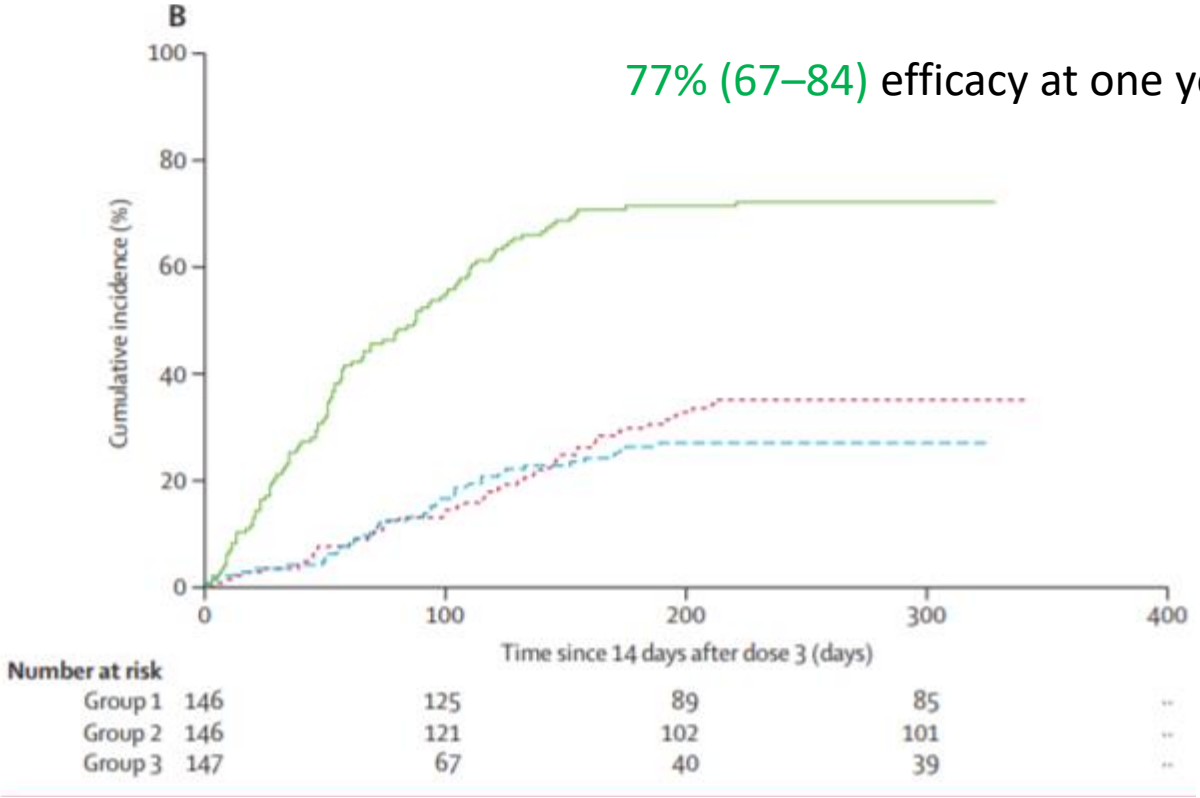
PfSPZ IV in infants: phase 2 in Kenya



46% efficacy (3 doses)

Oneko et al, Nature Medicine 2021

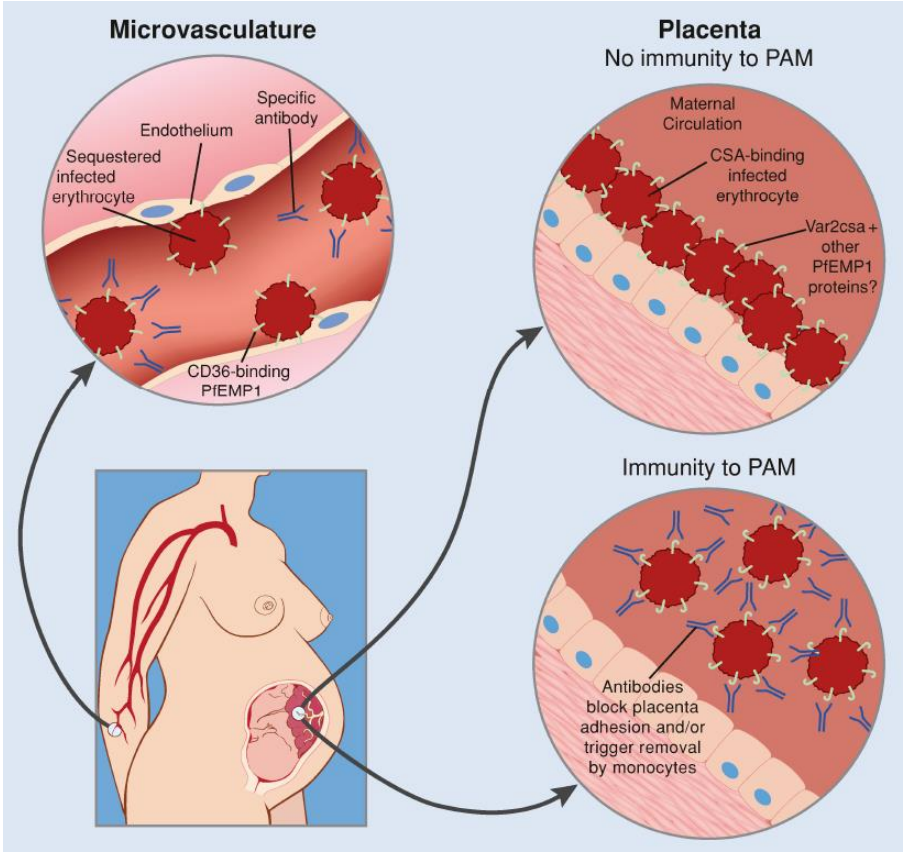
R21 (CSP) in adjuvant Matrix-M: Phase 2 in Burkina Faso



77% (67–84) efficacy at one year

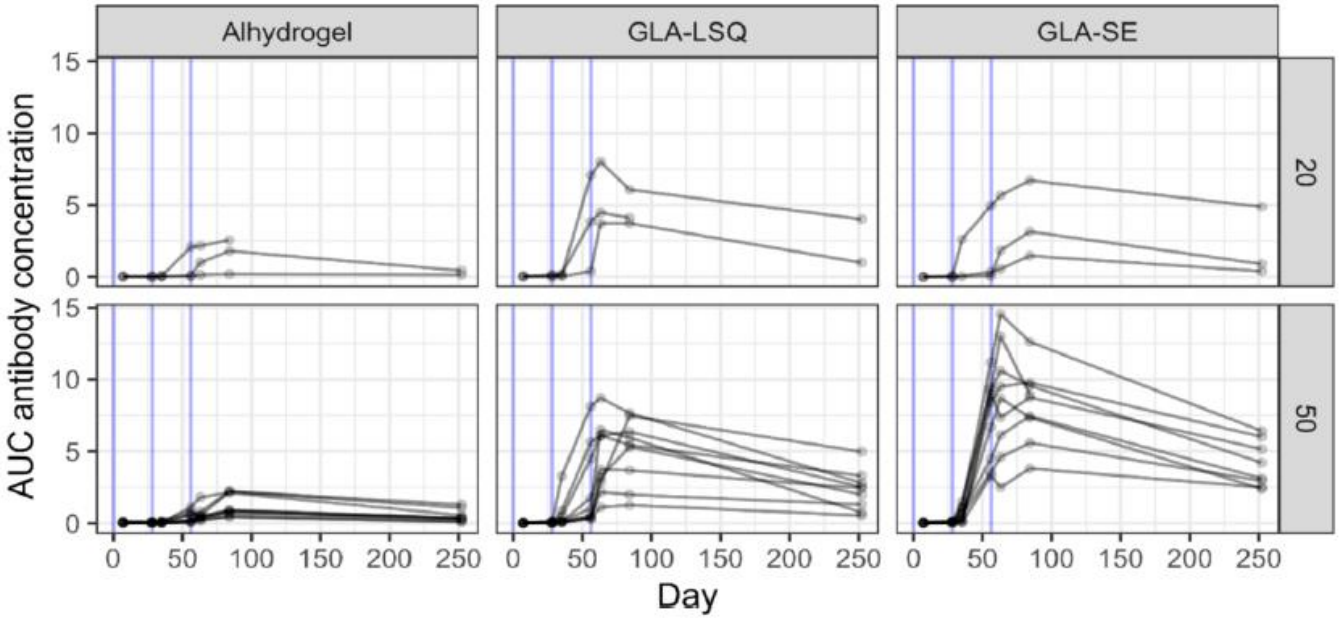
Datoo et al, Lancet 2021

Vaccine against Pregnancy Associated Malaria



Smith & Deitsch, J Exp Med 2004

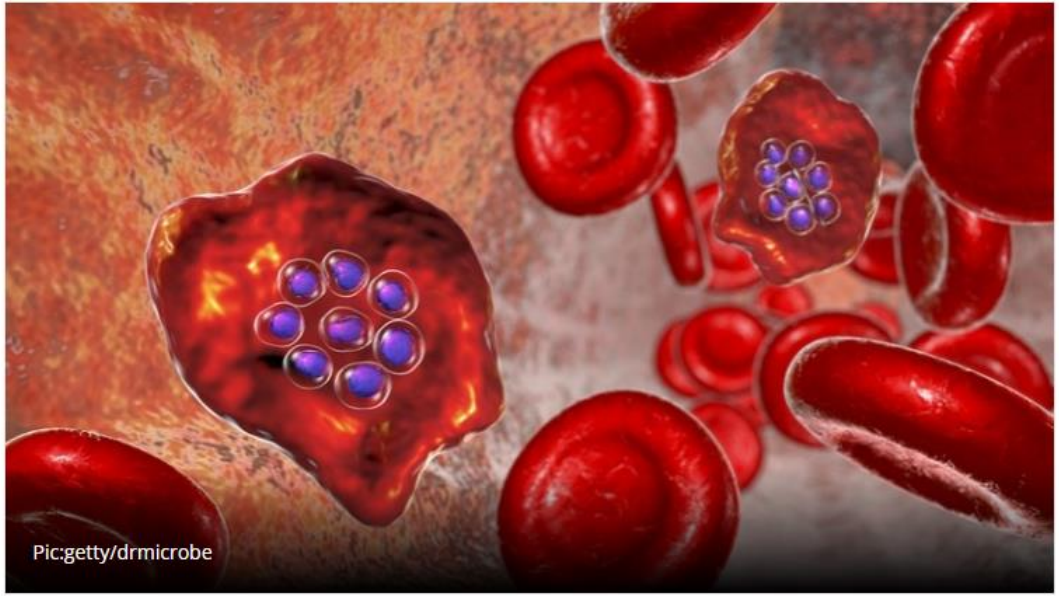
Vaccine for against pregnancy associated malaria
Antibodies against VAR2CSA



Mordmueller, Clin Inf Dis 2019

BioNTech to develop mRNA malaria vaccine; unveils ambitions for Africa vaccine supply

By Rachel Arthur
27-Jul-2021 - Last updated on 26-Nov-2021 at 14:49 GMT



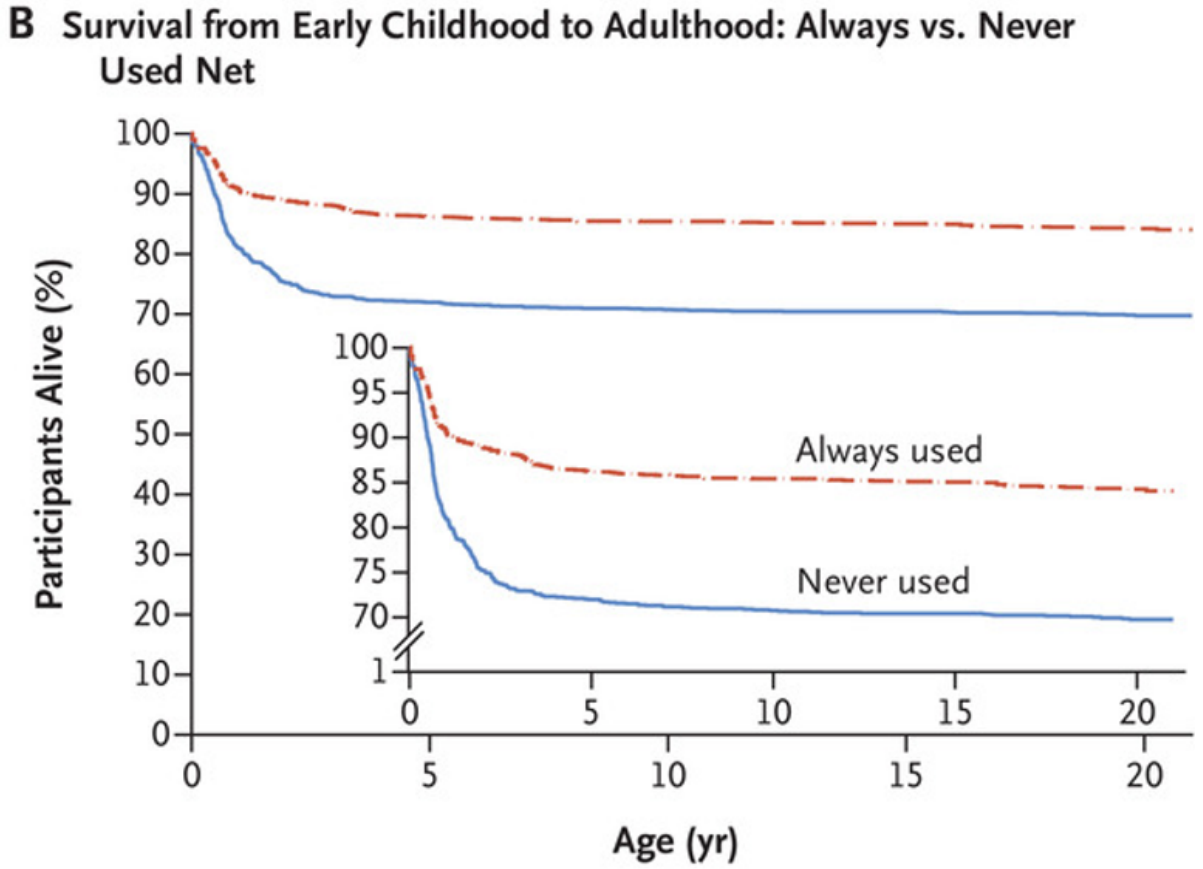
RELATED TAGS: BioNTech, Malaria, Vaccine

BioNTech aims to develop the first mRNA-based malaria vaccine, hoping to reach clinical trials by 2022. Meanwhile, it is also exploring possibilities to set up mRNA manufacturing facilities on the African continent – which could potentially be used for vaccines against a wide range of diseases.

Take home messages

- The concept and feasibility of a malaria vaccine has been proven
- In the absence of good correlate of protection, CHMI can vastly accelerate malaria vaccine development
- The 1st generation malaria vaccine (RTS'S) is partially efficacious and only short-lived but long-term impact is not known, especially for mortality; possible to implement in combination
- 2nd generation malaria vaccines will probably include the whole organism or multiple antigens of different stages and different allelic families
- A malaria vaccine will only be deployed as a complementary strategy to other interventions and its long-term impact should always be assessed

Effect of bednet on adulthood survival



Fink et al, NEJM 2022


Thanks to all