Clinical development of SE36 malaria vaccine

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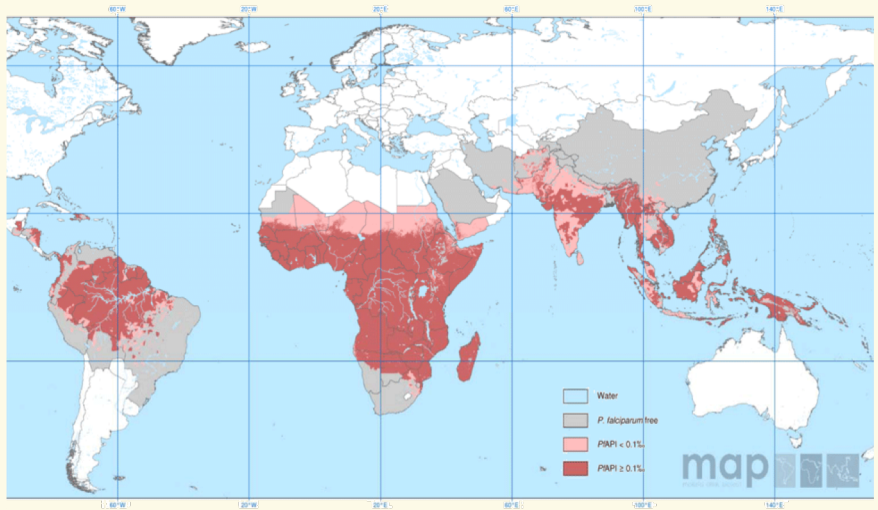
World Epidemic of Malaria tropica

Malaria, transmitted by *Anopheles* mosquito, is endemic in tropical and sub-tropical countries. Annually, 250 million people are infected and 660 thousand are killed mainly in sub-Saharan Africa. Majority of victims are children under 5 years old. In addition, in these regions, when pregnant women became infected with malaria they suffer a serious condition of pregnancy malaria, that may cause death of mothers and/or low birthweights of infants.

Infant patients in a malaria clinic in Uganda

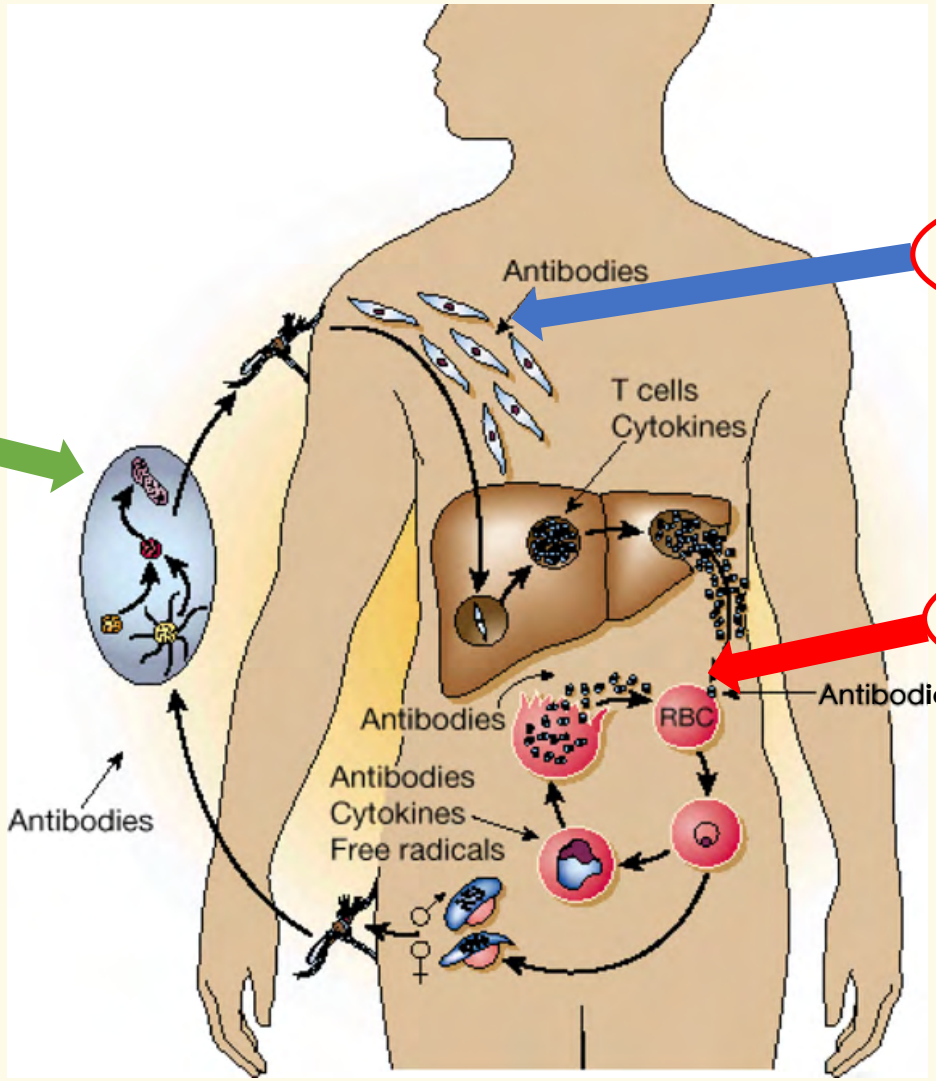
World epidemic regions of Malaria tropica



Target stages of malaria vaccine candidates

Transmission blocking vaccine (Pfs25)

This vaccine provides no merit to vaccinee. Vaccine efficacy can be experimentally measured but not in the field.



Sporozoite vaccine (RTS,S and R21)

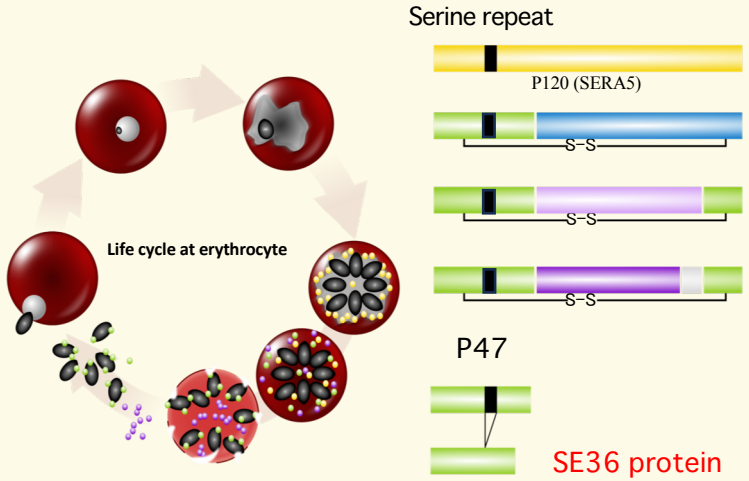
These vaccines protect against infection by intercepting newly invading sporozoite from mosquito but could not protect from symptomatic malaria caused by the escaped sporozoite.

Erythrocytic stage Vaccine (SE36)

Almost all of erythrocytic antigen genes except *SE36* gene show strong genetic polymorphism that disproportionately affects vaccine efficacies. Unlike vaccines based from the other life-cycle stages, SE36 vaccine-induced immunity is boosted by natural malaria infection. Thus, SE36 vaccine reduces the need for frequent vaccinations.

SE36 Malaria Vaccine

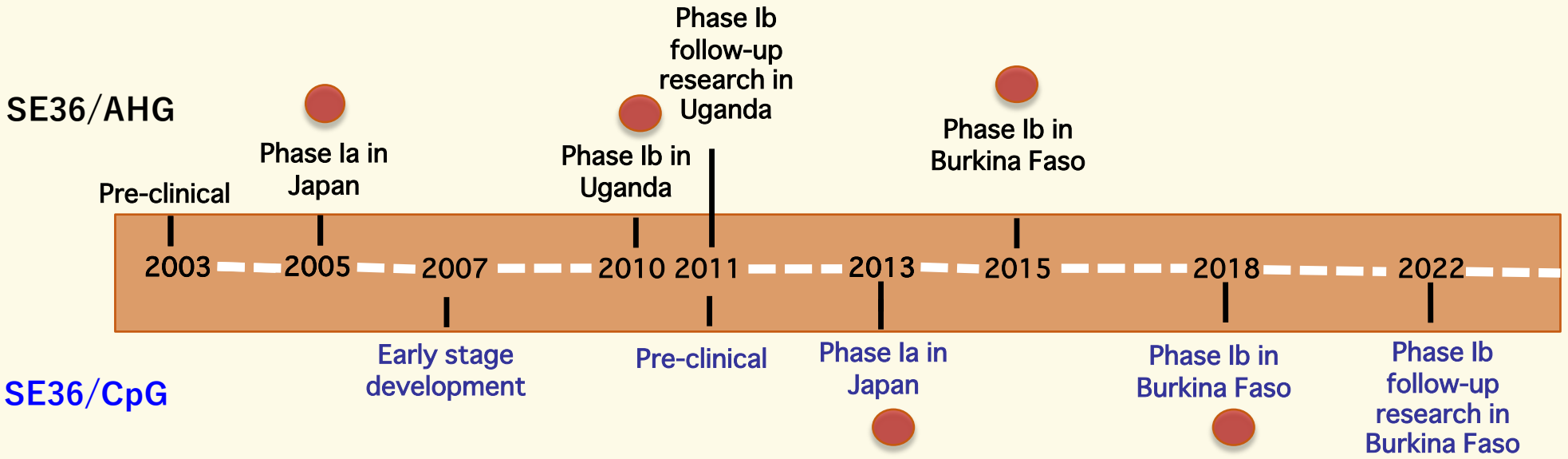
SE36 malaria vaccine is based on the recombinant protein derived from SERA5 (Serine repeat antigen 5) that is expressed by the parasite at the schizont stage. SE36 protein induces antibodies that attack merozoites.



Localization of full length (P120) SERA5 molecule in parasitized red blood cell is shown in color. When the protein is processed the P47 molecule, green ball, surrounds the surface of the merozoite. SE36 is genetically engineered from P47.

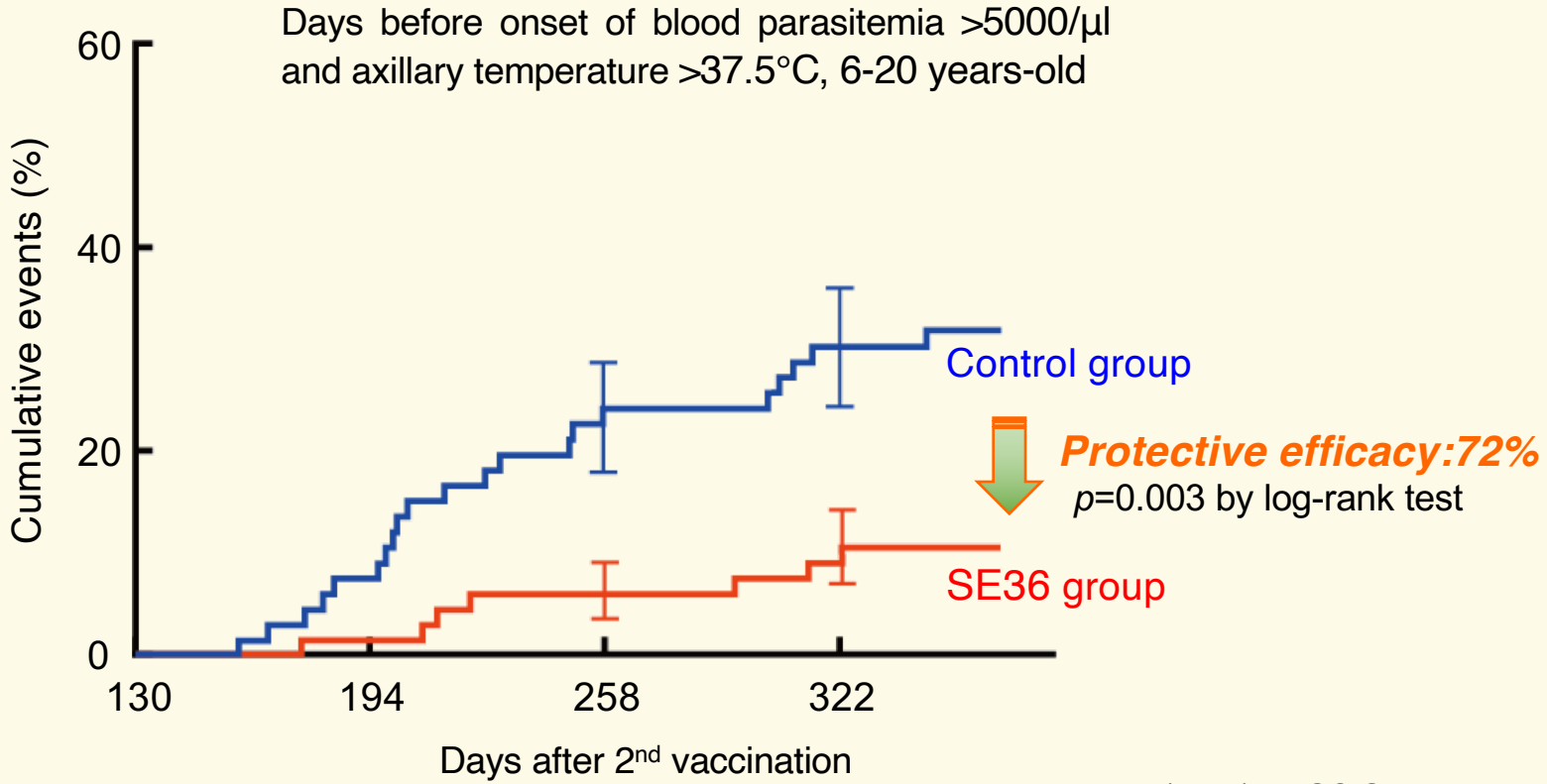
SE36 malaria vaccine investigational product
(SE36 protein adsorbed to Aluminum hydroxide gel and lyophilized)

Clinical trials of SE36 malaria vaccine



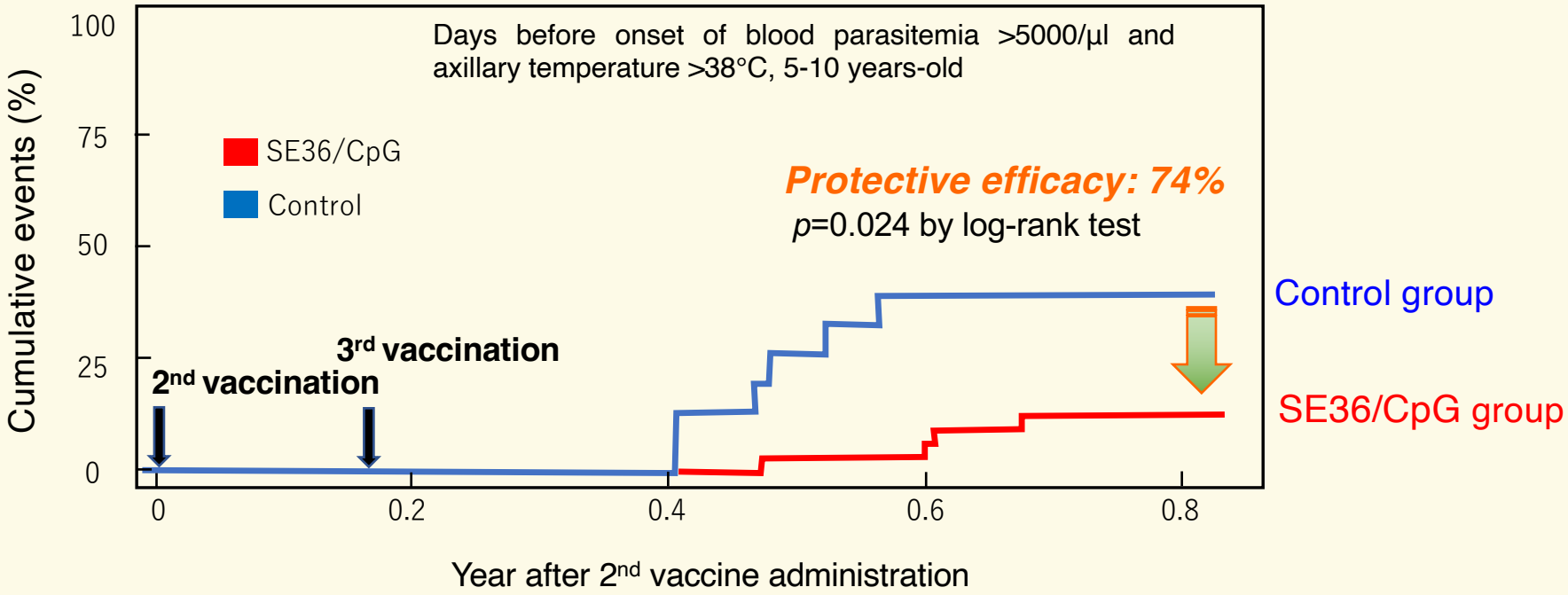
Clinical trials：show that the vaccine is well-tolerated with favorable safety profile and is immunogenic.

Protection against malaria onset by SE36/AHG vaccination (Uganda)



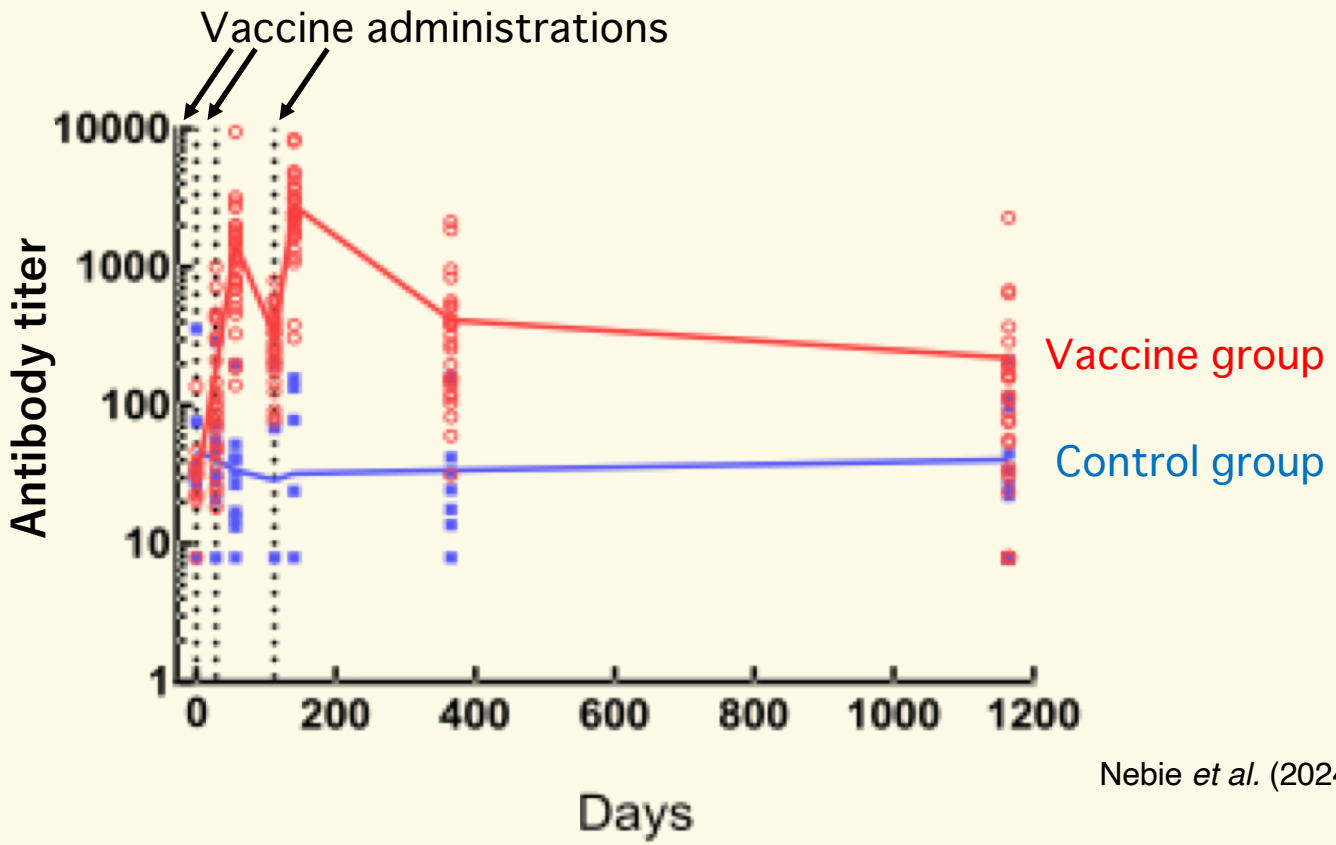
Palacpac *et al.* (2013) *PLOS ONE*

Protection against malaria onset by SE36/CpG vaccination (Burkina Faso)



Ouédraogo et al (2023) *Front. Immunol.*
Nebie *et al.* (2024) *Vaccine*

Persistence of SE36/CpG vaccine induced antibody



Nebie *et al.* (2024) *Vaccine*

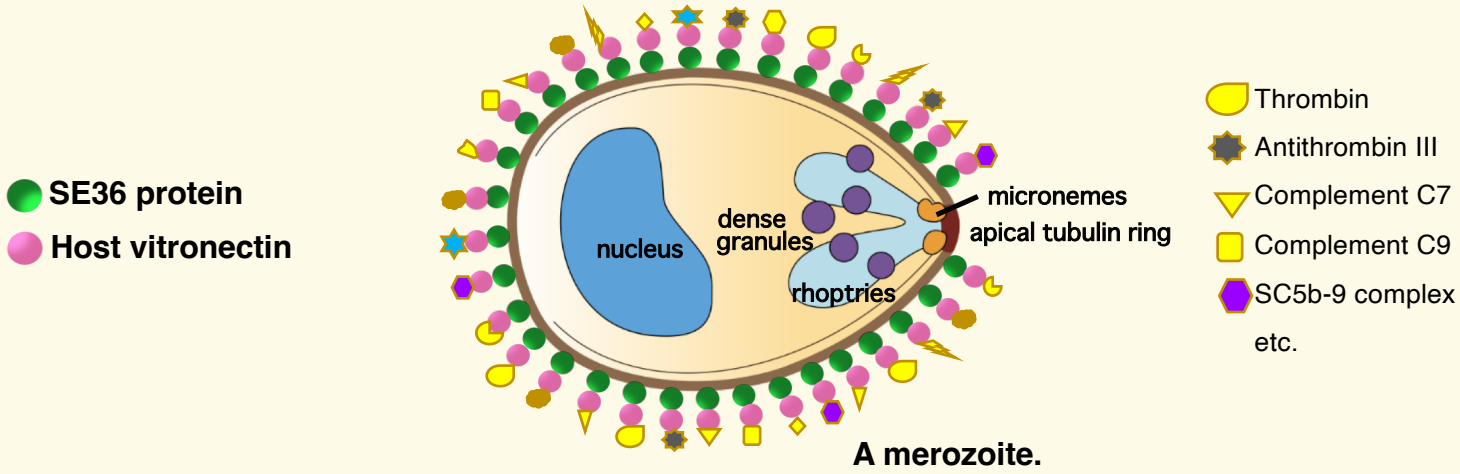
Long persistence of vaccine efficacy and booster effect by natural infection are best options to ensure continuing immunity and support public health policy in endemic areas

Comparison of protective efficacies by major vaccine candidates so far reported

Vaccine	Vaccine target	Stage	Age	No of subject	Study duration	Vaccine Efficacy (First or Only Episode) 0 25 50 75 100%	*Ref*
BK-SE36/AHG	Blood stage	Ph1b	6-20 Y (2dose)	132	15 M		Palacpac et al., 2013
BK-SE36/CpG		Ph1b	5-10 Y	45	10 M		Ouédraogo et al., 2023
GMZ2		Ph2	12-60 M	1849	6M		Sirima et al., 2016
FMP2.1/AS02 (AMA1)		Ph2	1-6 Y	400	6M		Thera et al., 2011
AMA1-C1/Alhydrogel		Ph2	2-3 Y (2dose)	300	4M		Sagara et al., 2009
RTS,S	Liver stage	Ph3	5-17 M	8922	12 M		Vandoolaeghe & Schuerman, 2016
		Ph3	5-17 M (4dose)	8922	48 M		
R21/MM		Ph2	5-17 M	450	12 M		Datoo et al., 2021
ChAd63 MVA ME-TRAP		Ph2	5-17 M (2dose)	700	6 M		Tiono et al., 2018

1. Low efficacy of blood stage vaccines, except for SE36, is caused by genetic polymorphism of the target antigens
2. RTS,S and R21 in blue circles are pre-qualified by WHO.

Function of SE36/P47 protein in the parasite



A merozoite.

1. SE36/P47 protein fully covers the surface of the merozoite and bind to host serum vitronectin. Vitronectin binds to many host serum proteins including complements. This bound complex camouflages merozoite from host immune system. (Tougan *et al.*, 2018 SciRep.)

2. SE36/P47 protein is presented to host immune system with vitronectin. Host immune system develops immune tolerance against SE36/P47 protein through repeated malaria infection in endemic areas. (Bougouma *et al.*, 2022 *Front Immunol.*)

3. Consequently, sero-conversion rate of people in endemic area is low, resulting in lesser genetic polymorphism (Arisue *et al.*, 2022 *Front Cell Infec Microbiol.*)

Perspectives of SE36 Malaria Vaccine

The WHO global strategy for malaria targets children under 5 years old in Africa. SE36 malaria vaccine showed 74% protective efficacy in 5-10 year-old children. Immunogenicity of SE36 in 1.0 year-old infant was much higher than in 5-10 year-old children. Therefore over 90% protective efficacy is expected in younger age groups.

The immunity in SE36 vaccinees was boosted by the natural malaria infection, therefore in terms of vaccine cost, logistics/coordination and sustainability, SE36 is a promising vaccine in terms of public health policy.

Although the immune response of malaria naïve adults was a bit lower than infants, travelers could still be protected by SE36 vaccine with over 80% efficacy.

Public health policy with SE36 malaria vaccine could significantly reduce world malaria burden