

**MALARIA VACCINES:
WHAT ARE THE PROSPECTS ?**

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Introduction

- Effective vaccines occur for many other infectious diseases
- Currently, there is no licensed malaria vaccine for public health use.
- Last ten years seen accelerated development of vaccine candidates –thanks to advances in Molecular Biology & subunit vaccine technologies.

Introduction cont.

Goals of a malaria vaccine

To control and eliminate malaria infection

Objective

Prevent infection

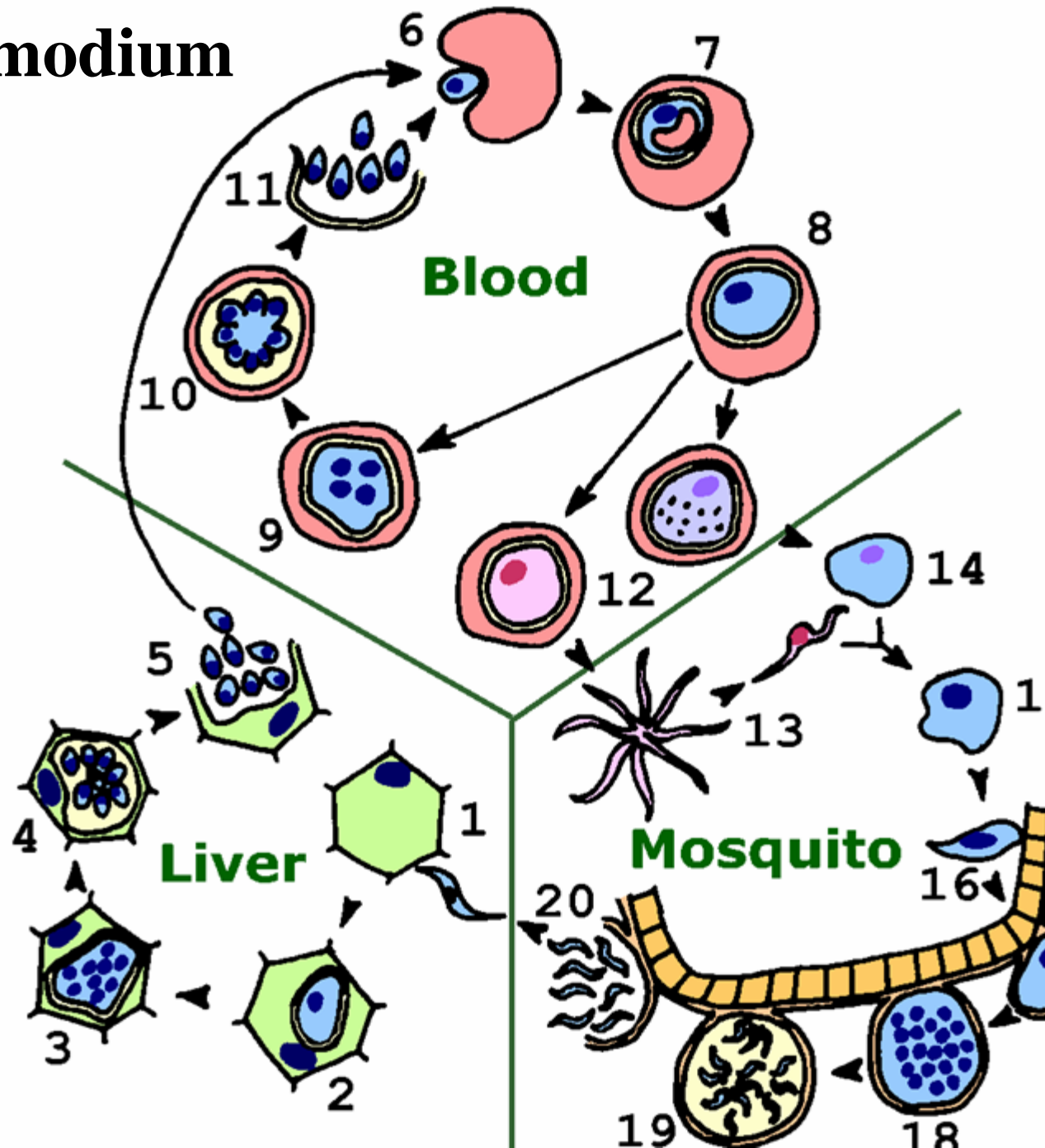
Low parasitaemia

Low Incidence

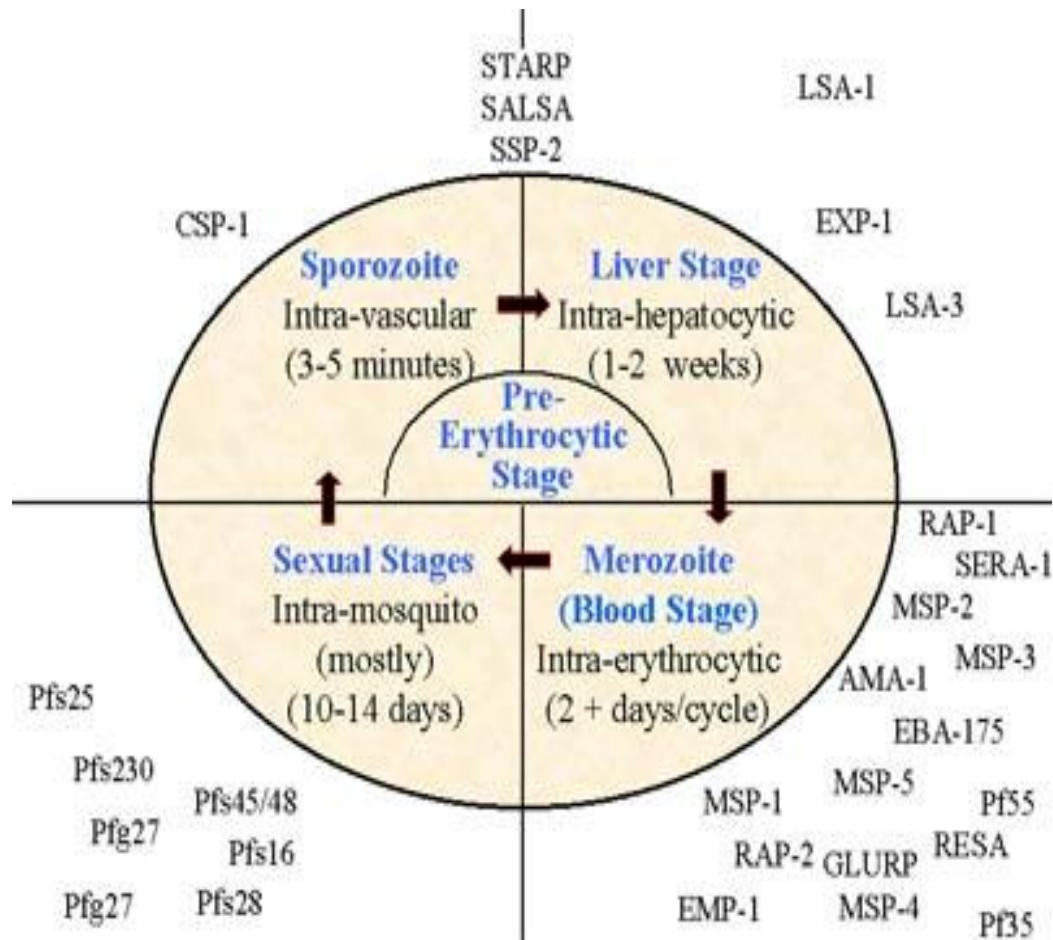
Ameliorate symptoms

Life cycle of Plasmodium

- 20 stages total
- 12 stages in man
- Antigens stage specific



Malaria Vaccines: The Challenge



Source: <http://www.malariavaccine.org/mal-vac2-challenge.htm#f4>

Rational approach to the development of malaria vaccines

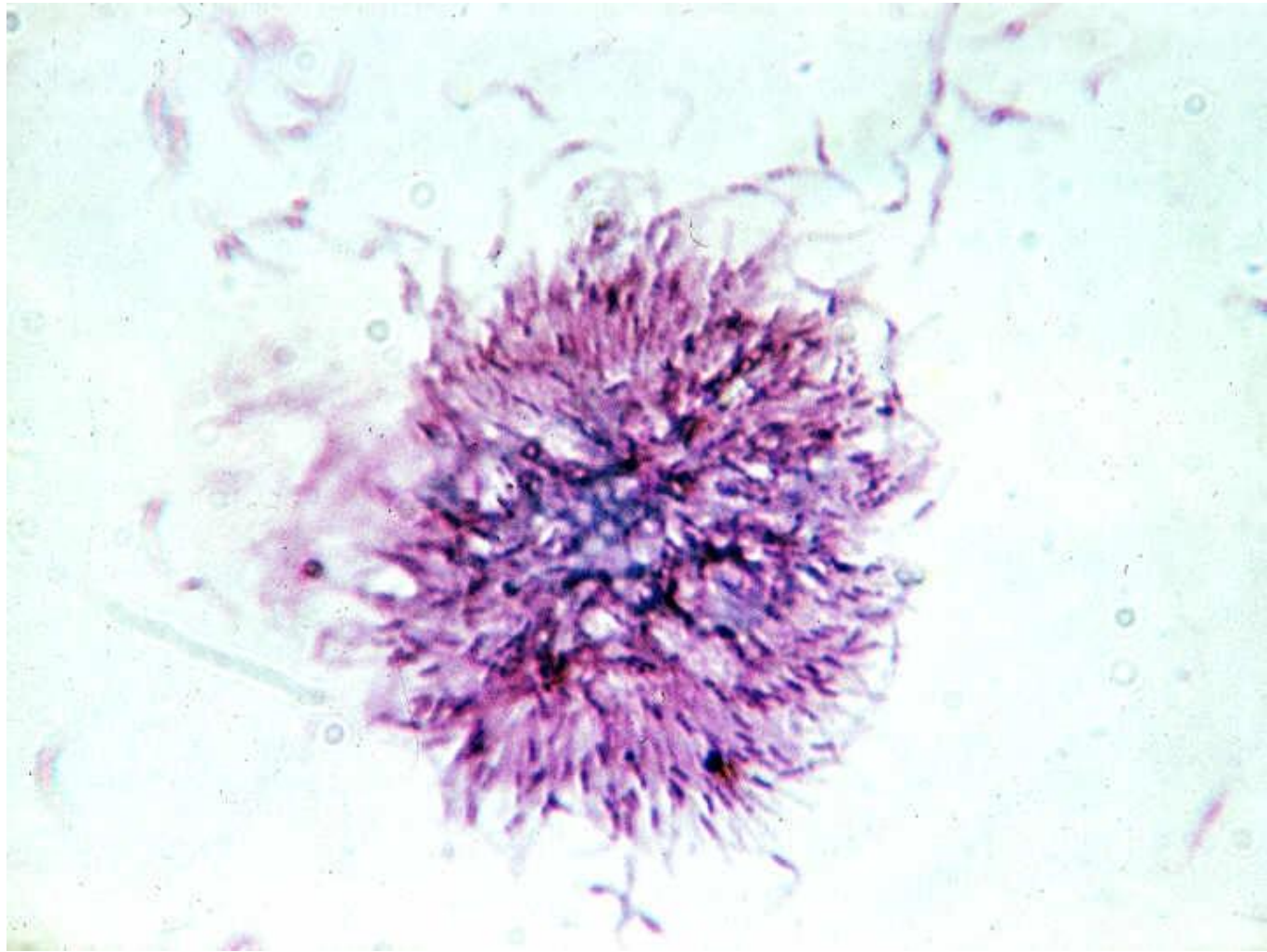
Vaccine targets are stage specific

1. Pre-erythrocytic-stage or liver stage Vaccine

Protect against hepatocyte invasion, and malaria infection

antibodies agglutinate sporozoites (Anti CSP) and T-cells kills hepatic schizogony

eg. RTS,S,



Rational approach to the development of malaria vaccines Cont.

2. Asexual-Blood-stage-vaccine

- Protect against red blood cell invasion, stage growth, and prevent sequestration, rbc rupture
- Mitigate against disease
 - delay the appearance of parasitaemia
 - delay development of clinical Malaria
 - protect against the development of severe malaria

eg MSP-1, GLURP

Rational approach to the development of malaria vaccines Cont.

3. Transmission -Blocking Vaccines

Destroy gametes in mosquito,
stops fertilization and oogenesis
eg. Pfs25 P Pastoris expressed
MVDU

4. Combination Multi-stage Vaccines

Cocktail of all stage epitopes

Malaria vaccine Design Strategies

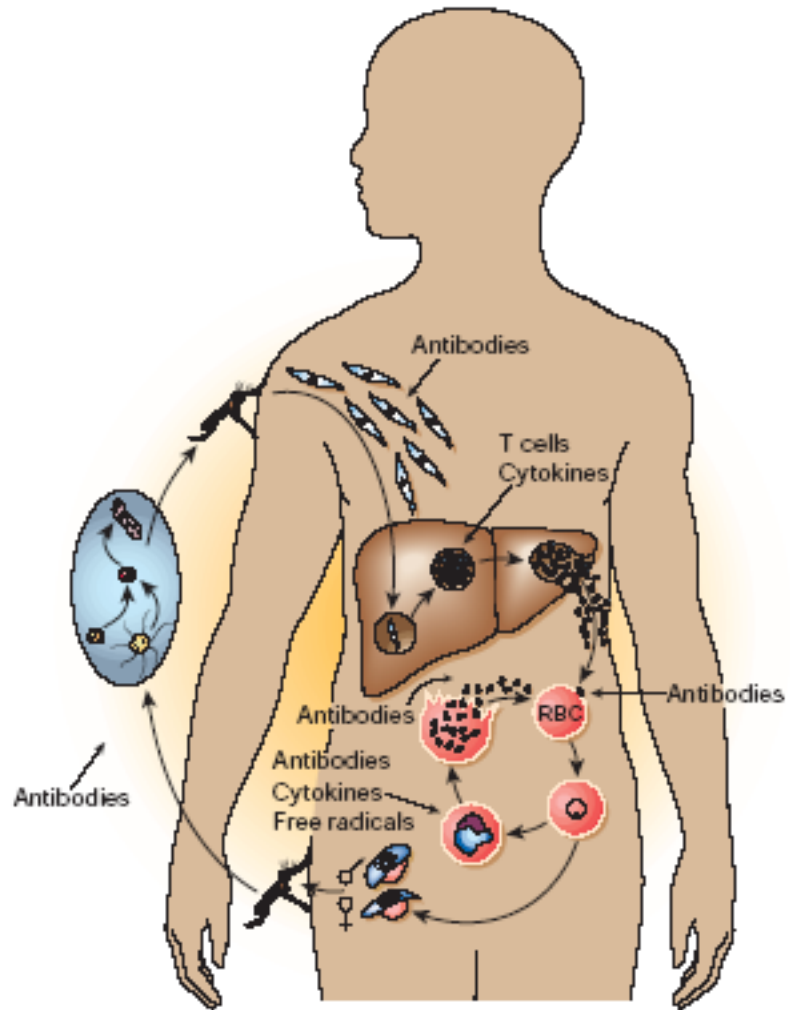
- Identification of immunodominant epitopes, preferably not diverse
- Vaccine combination with second line
Vaccine from different stages to safe guard against infection break-through or resistance
- Combination of antigens from a single stage –
Multivalency

Malaria Vaccine Delivery Systems

Optimizing immunogenicity –

- Adjuvants – Freund's, aluminum
- DNA- based vaccines
- Synthetic peptides alone or conjugated with proteins eg Tetanus Toxoid
- Recombinant malaria protein, Recombinant chimeric constructs,
- Recombinant viruses and bacteria

Parasite stages under attack



Source:
Ritchie and Saul (2002)

MALARIA VACCINES :PROGRESS

Vaccine Target	Research	Pre-clinical Development	Clinical Trials
Pre erythrocytic	12	11	RTS,S /S02A
Blood-stage	33	31	SPf66
Transmission Blocking	2	2	Pvs25 Pvs28
Combination Multi-stage	6	6	

Sources:

WHO Portfolio of malaria vaccine candidates. Jan. 2005
Clinical Trial.org

Clinical Trials Results

None of the vaccine candidates have lived up to expectation

Pre-erythrocytic vaccines-

RTS,S/AS02A: 3-6 months protection, reduced episodes, lower parasitaemia

Vaccine Efficacy: Mozambique trial(Alonso)

30% against clinical malaria

45% against primary infection

58% against severe disease

Clinical Trials Results Cont.

Blood stage Vaccines- SPf66:

No evidence for protection in Africa

Modest reduction in attacks in S.America

No reduced episodes or severe malaria

Further research and new formulation needed

Combination vaccines: Hill, 2003

induces stronger T-cell response and provides longer lasting protection

The ideal Vaccine

- Safe
- Easy to manufacture
- Easy to use
- Confer life long lasting immunity against all forms of the disease

Is a malaria vaccine feasible?

Yes: based on 3 research findings;

1. Attenuated sporozoites protected volunteers against challenge
2. Gradual acquisition of clinical immunity from severe disease in humans living in endemic areas; wanes rapidly after leaving endemic areas
3. Passive transfer of immunity: immunoglobulin purified from blood of long-life residents from endemic areas protective

Challenges to Malaria Vaccine Development

1. Complexity of the parasite: stage and species specificity of antigens, and poor immunogenicity
2. Immune evasion: eg var gene responsible for the PfEMP1 polymorphism
3. Variation and vaccination: 5,000 candidate proteins, and multiple variants
Several clinical trials required

Challenges to Malaria Vaccine Development Cont.

4. Benign and malignant tumors in vaccinated mice that received repeated infections of *P. yoelii* (F. Malagon et al. 2006)
5. Possible emergence of resistant clones – increase antigen diversity
6. DNA-based vaccines – risk for genomic interference

Meeting the Challenges to Malaria Vaccine Development

1. Capacity to provide and deliver the malaria vaccine – pre-purchased at £300 million by G8 sponsors
2. Scientific and technological advances have increased knowledge of the immuno-signatures of the parasite stages
3. More research needed before the investment could translate into malaria vaccination policy

Prospects of a malaria vaccine

- Several vaccines anticipated: Possible 100. Combination, multi-component designs
- A licensed malaria vaccine not envisaged before 2010, expected in the next 20 years
- Pre-erythrocytic vaccine (RTS,S) took 15 years to development by Glaxo-Smithe and Kline

Waiting for the Vaccine: Implications for Zambia

1. Develop capacity to
 - identify putative vaccine targets,
 - conduct vaccine clinical trials
 - Research and training
3. Offer Global clinical trial sites for vaccine candidates- Mpongwe site
4. First generation of vaccines probably be supplemental to IPT, ACTs, ITNs, and IRS
5. Scale up and integrate time tested control tools for impact.

WAITING FOR THE MALARIA VACCINE



Table 1 Candidate vaccine antigens

Stage and process	Antigens*	Primary mechanism
Sporozoite Hepatocyte invasion	CSP ⁷³ , TRAP/SSP2 ⁷³ , STARP ⁷⁴ , SALSA ⁷⁴	Antibody binding to antigens expressed on surface of sporozoite: Prevent binding interactions required for invasion Enhance splenic clearance or complement mediated lysis
Hepatic stages Growth, schizogony	CSP ⁷³ , TRAP/SSP2 ⁷³ , LSA1 ⁷⁵ , EXP1 ⁷⁵ , LSA3 ⁷⁵ , STARP ⁷⁴ , SALSA ⁷⁴	T-cell recognition of antigens expressed on surface of infected hepatocyte ⁷³ ; Release soluble immune mediators (IFN- γ) resulting in intracellular parasite death Lyse infected hepatocyte directly (CTL)
Merozoite Erythrocyte invasion	MSP1 ²⁰ , MSP2 ²⁰ , MSP3 ⁷⁶ , MSP4 ⁷⁷ , PIEBA175 ⁶⁷ , PvDABP ⁷⁸ , AMA1 ⁷⁹ , SERA ⁸⁰ , GLURP ⁸¹ , Ph155/RESA ²⁰ , RAP1 ⁸¹ , RAP2 ⁸¹	Antibody binding to parasite antigens: Agglutinate or prevent release of merozoites ⁸² Block invasion into erythrocytes ^{22,83,84} Induce monocytes to release soluble immune mediators, killing parasites (antibody-dependent cellular inhibition) ^{19,23} Facilitate phagocytosis ²³
Erythrocyte stages (asexual) Growth, sequestration	PfEMP1 ^{4,65} , rRins ²⁴ , Pf332 ²⁴	Antibody binding to antigens expressed on surface of infected erythrocyte: Enhance splenic clearance or complement mediated lysis Interfere with parasite nutrition and growth Induce antibody-dependent cellular inhibition Prevent or reverse endothelial adherence, thereby enhancing splenic clearance and reversing a key pathogenic mechanism
Erythrocyte rupture	Glycosylphosphatidylinositol (GPI) anchors ⁸⁵	Antibody binding to GPI resulting in prevention of toxic effects ⁸⁵
Mosquito stages Fertilization, oogenesis	Pfs25 ^{4,86} , Pfs28 ^{4,26} , Pfs48/45 ^{4,26} , Pfs230 ^{4,26}	Antibody binding to parasite antigens: Inhibit exflagellation and fertilization Complement induced lysis of gametes and zygotes Neutralize ookinete function

*Antigen names in bold type are in clinical development. Antigens have been listed according to the broad category of vaccine in which they are most likely to be included. However, many antigens are expressed in several stages (for example, LSA3 is expressed in blood stages as well as the liver, and most merozoite antigens are probably expressed in liver stages). Thus antigens in one category may also be targets in other stages.

Cocktail to soothe tropical fevers?

