

# Advanced Malarial Vaccines: A Promising Approach in the Treatment of Malaria

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## ABSTRACT

Malaria is a vector-borne parasitic infectious disease. The research is carried out on RTS, S/AS01, NYVAC-*Plasmodium falciparum* 7, SPf66 and the results suggested that these are very efficient in treating malaria. RTS, S/AS01 vaccine is composed of a hepatitis B surface antigen fused to a recombinant antigen from part of the malaria Circumsporozoite protein in the AS01 adjuvant used to target infected hepatocytes. Malaria vaccines are of three types: 1. Pre-erythrocytic vaccines RTS, S/AS01 (commercial name: Mosquirix): the Circumsporozoite (CS) protein is the most dominant surface antigen of this phase. 2. Blood stage vaccines. 3. Transmission blocking vaccines. According to best dentists' reviews, which will prevent any problems with teeth, it is also to help prevent gum disease at the very least. The NYVAC-Pf7 by the intramuscular route was safe and nontoxic and it is highly attenuated vaccinia virus with 7 *P. falciparum* genes inserted into its genome, was tested in a phase I/IIa safety, immunogenicity, and efficacy vaccine. The vaccine was safe and well tolerated but variably immunogenic. The results demonstrate that NYVAC-*P. farum* 7 is an appropriate candidate vaccine for further evaluation in human clinical trials. Vaccines are often the most cost-effective delivery system. Completely effective vaccine is not yet available for malaria, although several vaccines are under development.


## Introduction

Malaria vaccines are used against *Plasmodium falciparum* and the malaria vaccines are immune against malaria. Malarial vaccines are the effective vaccines which have been introduced into clinical practice. These vaccines can prevent Merozoite multiplication of RBC. A safe and effective vaccine can be used to control this disease. The *P. falciparum* injects its (sporozoites) parasitic forms into systemic host. The malaria parasite multiply asymptotically and causing the systemic inflammatory reaction

immunologically resembling sepsis. It is the initial symptom of clinical malaria. Malaria vaccines play a key role in future malaria interventions. One-third of the childhood shorts can be cured or prevent using a malaria vaccine. The Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative (MVI) is a global program which developed safe, effective, and affordable malaria vaccines. The methods of molecular biology, immunology, cell biology are used to develop an antimalaria vaccine. The *Plasmodium* parasite causes malaria in different stages in its life cycle. Each stage is antigenically and potentially interrupted by different vaccines. Malaria vaccines were developed by PATH program and GlaxoSmithKline (GSK). MVI has brought a total of 28 vaccine formulations into its portfolio. The detailed description of PATH MVI vaccine development portfolio – September 2007, were summarized in the Table 1. The PATH-MVI is providing funding and technical support to promising malaria vaccine development.<sup>[1,2]</sup>

## Different types of malaria vaccines

The malaria vaccines are classified into three types based on the site of action: Pre-erythrocytic vaccine, Blood stage vaccine, Transmission blocking vaccines.

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### 1. Pre-erythrocytic vaccines

The mechanism of pre-erythrocytic vaccines was to protect immunity and human vaccine.

- The development of a pre-erythrocytic malaria vaccine aimed at:
- Elucidating the mechanisms of protection.
  - Identifying vaccine formulas in experimental studies on animals and humans.

Based on earlier successful immunization of experimental animal studies with irradiated sporozoites, human volunteers were exposed to the bites of large number of *P. falciparum* or *P. vivax*-infected irradiated mosquitoes.

The final result of this vaccine trial concluded that a pre-erythrocytic vaccine and when administered to humans it can result in their complete resistance to malaria infection. Since the infected irradiated mosquitoes are not available for large-scale vaccination the alternative is to develop subunit vaccines. The human trials using irradiated sporozoites provided valuable information on the human immune responses to pre-erythrocytic stages. The first pre-erythrocytic antigen was Circumsporozoite protein it is present in all malaria species. The most pre-erythrocytic vaccines are based on the Circumsporozoite protein this protein having (CS- protein) and T-cell Epitopes, that can be recognized by the human immune systems. The pre-erythrocyte vaccine can be formulated by the using synthetic peptide vaccine, multiple antigen peptides, and polyoximes for immunization.<sup>[3]</sup>

### 2. Asexual/blood stage

A second strategy for the development of a malaria vaccine is to target immune responses against the asexual stage of the parasite. The maternal antibodies which are passively transferred to the fetus may provide protection against clinical malaria. The principle of asexual stage vaccine development is the Merozoite; the stage is initially released from the infected hepatocytes and rapidly involved in destruction of RBC and replicates in circulating RBC. The Merozoite adheres to RBC membrane and thereby permitting the parasite for damaged RBC during invasion. The antigen includes Merozoite Surface Protein (MSP) MSP-1, MSP-2, MSP-3, and Apical Membrane Antigen-1 (AMA-1). The antibodies are produced to block invasion of Merozoite. The major problem for the development of a malaria vaccine is the marked parasite strain variability associated with many blood stage antigens that require the selection of targets that relatively combine 21 more antigens or allelic forms of a single protein.<sup>[4]</sup>

### 3. Transmission-blocking vaccine

These are used against malaria and are intended to induce immunity against the stages of the parasites. The TBV-immunized individuals cannot transmit malaria. TBV used against the 2 major species of human malaria *P. falciparum* and *P. vivax* are under development. It is having successful result on animal studies. The detailed descriptions of the types of malaria vaccine were summarized in the Table 2.<sup>[5]</sup>

#### Examples of malaria vaccine

- Circumsporozoite Protein and Sporozoites Surface Protein – 2Vaccine (C.S.P-2): Kenyan study explained that circumsporozoitesprotein vaccine-induced antisporezoite

**Table 1: PATH malaria vaccine initiative (MVI) vaccine development portfolio—September 2007**

Company	Name of the malaria vaccine	Category of malaria vaccine
GSK-Biological	RTS, S ASO1/ASO2 containing MPL and QS21	Pre-erythrocytic vaccine
Malaria vaccine development branch, National institute of Allergy and infectious disease, National institute of Health.	AMA-1-C1/ISA720(Montanide ISA 720)	Blood-stage vaccine
Walter reed army institute of research, GSK Biological.	WRAR- AMA-1(3D7) GSK-ASO1B/ASO2A.	Blood-stage vaccine
Latrobe University	MSP-2-C1/SA720	Blood-stage vaccine
International centre for Generic Engineering and Biotechnology, Bharat Biotechnology international limited, Sanaria	PvRII/ASO1B	Blood-stage vaccine
Sanaria	PfSPZ	Pre-erythrocytic vaccine.
MonashUniversity	MSP4 + MSP5	Blood-stage vaccine
Genvac	Ad5 (adenovirus-5) -CSP: Ag2:LSA1 (liver-stage antigen+ Ad5-AMA: MSP1.	Pre-erythrocytic and Blood stage vaccine

**Table 2: Malaria vaccines examples based on site of action**

Type of malaria vaccine	Example	Action
1. Pre-erythrocytic vaccine	RTS, S/ASO2, DNA viral vector vaccine	Acts on infected hepatocytes
2. Blood stage vaccine	MSA-1, MSA-2	Acts on ruptured RBC
3. Transmission blocking vaccine	Pfs-25, NYVAC-Pf7 derived from Copenhagen strain	Acts on sexual forms of parasite

antibody is not protective. So that circumsporozoiteprotein vaccine is not used in severe malaria infections. But this vaccine acts on merozoite stage not in the sporozoite stage.

- New York Vaccinia - *P. falciparum*-7 (NYVAC – Pf.7): This vaccine is derived from Copenhagen strain. It blocks transmission of the parasite from vertebrate host of mosquitoes. It has been utilized to develop multi antigen, multistage vaccine for malaria. Genes encoding 7 *P. falciparum* antigens derived from the (1) Sporozoites (CSP) 2) Liver (Liver Stage Ag-1) 3) Blood 4) Merozoite surface protein 5) serine repeat Ag, apical membranes. 6) Circumsporozoite protein 7) Sporozoites surface protein, sexual (sexual stage antigen) stages of the parasite life cycle. The 7 antigens were expressed in NYAC– Pf.7. NYAC–Pf.7 is safe and well tolerated. Antibodies recognize sporozoites, liver, blood, and sexual stages of *P. falciparum* because it has seven stages. Each antibody responds against 4 of the *P. falciparum* antigens. Such as Circumsporozoite protein Sporozoites surface protein 2, Merozoite surface protein-1, and sexual stage antigen. The final result concludes that NYAC-Pf.7 is an appropriate vaccine for evaluation in human clinical bodies.
- Recombinant Vaccine (RTS): This vaccine responds against *P. vivax* blood stage infections, a recombinant C-terminal fragment

- of Merozoite Surface Protein (MSP- 1) in block co-polymer adjuvant with T-helper Epitope. It is a liver-stage vaccine. It may reduce relapse or reinfections in malaria-prone individuals.
- d. Gamete Vaccine: This vaccine is used when antibodies are taken up by mosquitoes; gametes escaping the RBC's will be neutralized. This vaccine can prevent the fertilization and reduces the transmission.
- e. DNA vaccine: It is based on synthetic gene it is made by adding 21 Epitope of nine different antigens present in *P. falciparum*. Epitopes are small regions in proteins, which can be recognized by immune cells. These have been developed by National Institute of Immunology.  
Example: pf 155 / RESA (Ring-infected Erythrocyte Surface Antigen)
- f. Patorraya / Cocktail vaccine: Example: Sporozoites *P. falciparum* 66 (SPF 66). This is the basis for adopting "antigenic cocktail" approach toward obtaining a synthetic or recombinant subunit vaccine. The synthetic Colombian Malaria vaccine SPF-66 consists of three peptides Epitope from three blood-stage proteins. This vaccine is used to block the parasite at its later Merozoite form in liver. The vaccine stimulates production of antibodies to prevent the vaccine parasite from infecting RBCs. During the development of SPF 66 the trails demonstrated that the cocktail vaccine at a dose of 1mg for children (<5 years) and 2mg for 30-18 days in case of adults. The final results displayed a protective efficiency 38.8-60.2%. This vaccine mainly used against *P. falciparum* malaria.<sup>[6]</sup>

### Advanced malarial vaccine

1. Recombinant vaccine containing adjuvant system 2 (RTS/ASO2): The most advanced pre-erythrocytic vaccine is RTS/ASO2 developed by GSK through a long-standing collaboration with the Walter Reed Army Institute of Research (WRAIR). The RTS, S/ASO2 vaccine consists of CSP fused in to the hepatitis-B virus surface antigen (HbsAg) coexpressed together with infused HbsAg "Saccharomyces cerevisiae" yeast cells. The antigen was purified from yeast cells and assembled into multimeric particles and it is adjuvanted with ASO2. This formulation containing oil in water emulsion and the immunostimulants are used.
2. Monophosphoryl lipid and QS21: The RTS, S is the most clinically advanced malaria vaccine in the world. This was formulated in 1987 by GSK. The adjuvant system RTS, S induces the production of antibodies and T-cells diminish the malaria parasites ability to infect. MVI demonstrate that combination of pre-erythrocytic and blood-stage antigens having higher yield approach to develop an efficacious vaccine.  
The main drawback of this vaccine is low efficacy, reactogenicity, and low immunogenicity. The CSP was a vaccine which was developed to undergo trails. The NYVAC-Pf7 is a multistage vaccine and also having *P. falciparum* antigenic genes. CSP, sporozoites surface protein-2 (SSP2) derived from sporozoites phase of the malaria vaccine. RTS, S is the recombinant vaccine. The CSP vaccine is having poor immunogenicity property.
3. Viral vector vaccine: It is more active against *P. falciparum* reticulocyte-binding protein homologous-5 (PF RH5) was found to induce an antibodies response in preclinical studies. This vaccine shows its action by binding a protein PF RH5 to the receptor present in parasite.  
Safety of RTS, S/ASO2: The RTS, S/ASO2 vaccine symptoms are local in nature and all local symptoms reported were grade 1

and 2-intensity. Irrespective of study population, pain at the infection site was the local symptoms. The general symptoms related to the vaccination were Myalgia and fatigue, headache, malaise mild-moderate. In general the RTS, S/ASO2 vaccine was found to be safe and effective.

Immunogenicity: RTS, S/ASO2 vaccine is a powerful humoral response against the Circumsporozoite protein Epitope and HbsAg. Initially the analysis of cell-mediated immune response suggests that the RTS, S/ASO2 malaria vaccine formulation induces a Th1-like immune response that can be characterized by a strong lymph proliferative response.

Efficacy: The RTS, S/ASO2 clinical trials demonstrated an efficacy of 30-86% against homologues administered via the infectious mosquitoes bite. Vaccine efficacy did not appear in a particular parasite genotype and single dose given 1 year later confirmed initial efficacy results. The detailed descriptions of the various malaria vaccine features were summarized in the Table 3.<sup>[7]</sup>

### Role of malaria vaccine

1. Pre-erythrocytic vaccine: These types of vaccine are also known as liver-stage vaccine. Mainly these vaccines show its action by acting on the infected hepatocytes. In general the sporozoites entered into host blood stream and then it enters into the liver. After 2-3 weeks the sporozoites are converted into merozoite. The merozoite involved in the destruction of hepatocytes or infects the hepatocytes. So, the pre-erythrocytic vaccine acts upon infected hepatocytes by inhibiting the action of Merozoite or sporozoites.<sup>[8]</sup>  
E.g.: RTS, S/ASO2, CSP, DNA viral vector vaccine.
2. Blood-stage vaccine: The Merozoite enters into RBC after infecting the hepatocytes. From the liver the Merozoite enters into the RBC and then it is involved in the rupturing of RBC. So, the blood stage vaccine acts on the infected or ruptured RBC. Examples: AMA-1, MSP-1, MSP-2, Serine repeat Antigen.
3. Transmission blocking vaccine: These types of vaccines are mainly involved in the inhibition or prevention of disease transmission. TBVs acts on sexual forms of parasite. i.e., Gametocytes. So, the TBV immunized hosts cannot transmit malaria.  
E.g.: NYVAC-Pf7 (New York Vaccinia)

The detailed descriptions of the malaria vaccine mechanisms were summarized in the Figure 1.

**Table 3: Classification of malaria vaccines: (based on parasite stage)**

Stage of Plasmodium	Antigen	Features
Pre-erythrocytic stage.	CSP and LSA-I	Antibodies blocks infection of liver. Large immunizing dose required.
Merozoite and Erythrocytes.	Erythrocyte binding antigen (EBA-175), MSA-I and 2, AMA-I.	Prevents invasion of erythrocytes, so there by reduces the severity of infection.
Gametocytes and Gametes	Pf 25, 48/45k, Pf 230	Prevents infection of mosquitoes. Fertilization/ maturation of gametocytes.
Combined vaccine (cocktail)	Spf66 (Based on pre-erythrocyte and asexual blood stage proteins of Pf)	Blocking the all stages of the parasite development.

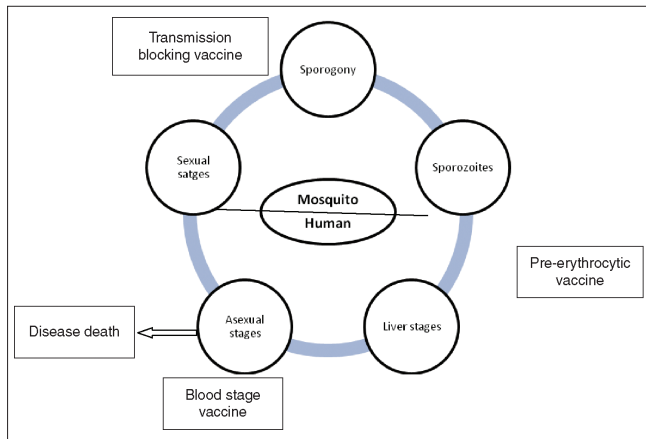


Figure 1: Flow chart of malarial vaccines mechanisms

### Advantages of malaria vaccines

The malaria vaccines not only prevent the malaria transmission and also having various advantages such as the malarial vaccines can prevent any problems associated with teeth, gum diseases, and able to eliminate dental diseases.<sup>[9]</sup>

### Disadvantage

The malarial vaccines can produce pain at the site of administration. Pain is the most frequently reported symptoms. There are other symptoms like myalgia, fatigue, headache, and malaise. So, there is not a perfect drug. So, the every drug or regimen has problems and disadvantages (when administrated to the individuals). There are no 100% safe regimens in the pharmaceutical products.<sup>[9]</sup>

### Development of malaria vaccine

- a. Agents under development: Malaria vaccines are still under development. Malaria vaccines are the novel drug delivery system. Still the research and clinical trials are under progress. The clinical trial results explained that the vaccine has insufficient effectiveness or efficacy. A recent WHO review of the malaria vaccines has identified more than 80 vaccines at the preclinical development stage. In that 30 malarial vaccines have entered into clinical testing. Two vaccines are entered into phase-IIb efficacy evaluation. The malarial development strategies are based on the complex life cycle of the parasite.
- b. Different possible approaches to malaria vaccine development: The different possible approaches to malaria vaccine development are
  1. Parasite Antigen Vaccine approach: Live, attenuated viruses (e.g.: smallpox, poliomyelitis, measles), killed organisms (polio, pertusis), inactivated toxins (tetanus) are the most successful vaccines produced in the past. In case of malaria vaccine development there are more problems associated with large scale production and difficulties in purifying parasites from host. The malaria parasites are short-lived and is difficult to preserve.
  2. Infectious Vector Vaccine approach: The first successful use of virus vector expressing the gene for hepatitis-B.E.g.: HbsAg.

The advantage of this approach is to construct recombinant virus. The disadvantage of this approach is that the inherent risks of using a live virus which produced encephalitis. Malaria vaccine for the world-2010 (MVW-2010) meeting held in London discussed about vaccine and clinical trials MVW-2010 will focus attention on 'Vaccine issues'.

"A Vaccine against pregnancy malaria" The main disadvantage of the approach is related to the risks of using live viruses such as vaccinia the risk was compounded by the altered virulence or tissue tropism which may be introduced by the expression of a foreign gene.

3. Sub-unit vaccine approach: The development of a sub-unit, nonreplicating vaccine were involved in the construction of a molecule, malaria antigen which produces the protective immune response. Subunit vaccines are the byproducts of the current biotechnology revolution. This approach mainly involved in the development technique for DNA cloning, monoclonal antibodies. The advantage of sub-unit vaccine is availability and the antigen availability is also very easy while selecting the appropriate antigen for this vaccine formulation and the effect of this vaccine mainly induce suppression or immunopathology. The sub-unit vaccine is also used in influenza infections. The first recombinant DNA vaccine has protection against hepatitis-B in human beings. The sub-unit vaccine formulation contains various number of malaria antigen which includes CSP, RESA, precursor of the major MSA. The results of the clinical trials were appreciably large. The main advantage with this sub-unit vaccine is the information regarding the immunogenicity of the vaccines which can be produced by the clinical trials, that information can be helpful in developing the forthcoming vaccine. The disadvantage with this vaccine approach is poor antigenicity.<sup>[10]</sup>
4. Anti-Idiotype vaccine approach: The individual antigenic determinates are known as Idiotype. So, the anti-Idiotype represents a minor image of the primary antigen. The anti-Idiotype or antigenic determinants are used as an immunogen (instead of the primary antigen). This type of vaccine approach is used to mimic three dimensional structure of antigenic determinants i.e. polysaccharides and carbohydrates.<sup>[11]</sup>

### Vaccine delivery system

The selection of an appropriate system is fundamental in all vaccine development, but especially in case of malaria. A vaccine targeting several antigens is required delivery to different areas and by different methods in order to produce an effective and potential response.<sup>[7,12]</sup>

Hepatitis - B → RTS, S → Acts on infected hepatocytes.

### Combined antigenic vaccine

This approach is very complex. This can be done by using two types of vaccines:

- a. Blood-stage response
- b. Liver stage response

These two vaccines are injected into two different sites and the response of these vaccines can be explained by using the immunological mechanism.

## Vaccines developed up to now

CSP is the most important dominant surface antigen of the initial pre-erythrocytic phase. The major problem associated with these malaria vaccines developments is low efficacy, reactogenicity and low immunogenicity.

The CSP was a vaccine developed that initially appeared promising enough to undergo trials. The NYVAC-Pf7 is a multistage vaccine attempted to use different technology incorporating 7 antigenic genes. RTS, S is the most recently developed recombinant vaccine.

## Vaccine development strategies for the future

The recent advances in the sub-unit vaccine development include the use of DNA vaccination. This approach was involved in the removing selections of DNA from the parasitic genome and inserting the sequence into a vector. Example: plasmid genomes, attenuated DNA viral genomes, liposome. The DNA vaccine efficacy can be assessed by using vaccine development strategy that is referred as ELISPOT (Enzyme Linked Immuno Spot Assay). The pre-erythrocytic vaccine are used to target sporozoites or infected liver cells and there by inhibit the release of primary Merozoite from infected hepatocytes.

## Constraints on vaccine development

1. Parasitological constraints: Malaria parasites are lower eukaryotes and the genetic complexity is approximately fivetimes greater than that of *Escherichia coli*. There are number of parasitological constraints which interfere with vaccine development that are:

- a. The stage specificity of antigen
- b. The genotypic diversity (strain specificity)
- c. The plasticity of the genome of the parasite

The development of malaria vaccines are conceptually based on the target antigen needs to be accessible to the host's effectors mechanism and the surface antigen on the extracellular stages of the parasites. Example sporozoites, merozoite, and gametes the malaria antigens are present on the surface of the host cells (Erythrocyte or Hepatocytes).

The 3 important antigens are:

- i. Circumsporozoite protein (Surface of the sporozoite)
- ii. PMMSA (Precursor to major Merozoite surface antigen) this antigen present on the schizont
- iii. RESA (Ring-stage-infected erythrocyte)

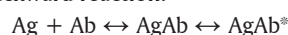
Example: NYVAC

2. Immunological constraints: The major immunological constraints for the development of a malaria vaccine are the absence of the mechanisms of acquired immunity. Antibodies and cell-mediated immunity play a key role in the immunological constraints. Example: CSP vaccine – cell-mediated mechanisms. But the neutralizing monoclonal antibodies were found in the CS protein. In the absence of boosting, inadequate kinetics of antibody titers may leads to the vaccine failure.<sup>[13,14]</sup>

## Kinetics of malarial vaccines

The kinetics are mainly used for the identification of malarial agents which are suitable for vaccine candidates and identification

of antigens on gametocytes, sporozoites, Merozoite and the surface of infected erythrocytes. Antibodies produced against these antigens to inhibit fertilization, invasion of target cells and cytoadherence. *In vitro* studies states that not all antigens are recognized as the target for the protective immunity. To achieve high antibody concentration to overcome the physicochemical constraints imposed on antibody binding by the short exposure times of antigens. Antibody binding is a multi-step process with an initial univalent reversible bond (AgAb). Next step is bivalent or multivalent bond with antigen in case of IgM antibody (AgAb<sup>\*</sup>). Each step is associated with forward and backward reaction.<sup>[13]</sup>



## Conclusions

The vaccines against malaria are made by advanced techniques. To control malaria, the need for such tools has been established, the expertise and technology required is made available and predominantly, there is an appreciable international will for their production. Merozoite get longer period to inter act with their target than the transiently appearing sporozoites in case of sporozoites vaccines. Gamete vaccine hold promise for future where in antibiotics when taken up by mosquitoes will neutralize the gametes escaping RBCs, thus preventing fertilization. This results in transmission and a reduction in nosocomial infection. The cocktail vaccine is the most efficient one. In this review article the advanced malarial vaccines are mainly NYVAC –Pf7, RTS, and S/ASO1/ASO2. A complete efficient vaccine is not yet available for malaria, although several vaccines are been developing. In this brief review, we focused on vaccine strategies targeting the pre-erythrocytic and asexual blood stages of parasite. Malaria vaccine development strategies are mainly based on the complex lifecycle of the parasite. NYVAC-Pf7 was safe and well tolerated. The results concluded that NYVAC-Pf7 is an appropriate candidate vaccine for further evaluation in clinical trials. The RTS, S/ASO2 malaria vaccine has induced powerful humoral responses against the CSP repeat epitope and against the hepatitis-B surface antigen (HbsAg). RTS, S/ASO2 vaccine was recognized to be protective or secure with an acceptable reactogenicity profile. The most advanced pre-erythrocytic vaccine in clinical development today is the RTS, S/ASO2 vaccine developed by GalaxoSmithkline.

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