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Investigation of the Immune Response to Malaria Vaccines

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Abstract

Objective: This review article synthesizes the molecular, cellular, and structural mechanisms governing host immune responses to modern malaria vaccines. It critically evaluates current correlates of protection, adjuvant modulation pathways, and the biological bottlenecks driving individual variations in vaccine immunogenicity.

Methodology: Following a structured scoping methodology adapted from the PRISMA guidelines, a systematic evaluation of literature published between January 2015 and April 2026 was conducted across PubMed, Scopus, and Cochrane databases. Analysis was restricted to human clinical trial datasets (Phases I–III) and cohort studies examining licensed VLP platforms and advanced whole-sporozoite candidates.

Results: Humoral protection hinges on inducing high-avidity IgG antibodies against the central circumsporozoite protein (CSP) NANP repeat region. Next-generation high-density VLPs (R21) maximize B-cell receptor cross-linking compared to carrier-diluted arrays (RTS, S), yielding enhanced antibody avidity. Sustaining these protective thresholds requires helper responses driven by circulating T follicular helper (cTfh) cells and polyfunctional CD4+ T-cells, which are selectively expanded by advanced liposome-based (AS01) and saponin-nanoparticle (Matrix-M) adjuvants. Current platforms fail to trigger intrahepatic cytotoxic CD8+ T-cell responses to clear escaped parasites. Host-specific factors induces T-cell exhaustion, maternal antibody masking in young infants, and nutritional status to introduce substantial immunogenic variability across endemic populations.

Conclusion: Resolving rapid decay of vaccine-induced immunity is critical for absolute malaria eradication. Future strategies must optimize alternative delivery mechanisms, such as fractional dosing schedules, to enhance antibody durability. Concurrently, transitioning toward multi-stage polyvalent vaccine formulations and lipid-nanoparticle (LNP)-formulated mRNA platforms will be vital to trigger necessary cytotoxic CD8+ responses and overcome regional parasite polymorphisms.

Keywords: Malaria Vaccines; RTS, S/AS01; R21/Matrix-M; Circumsporozoite Protein; Immunity; Protection

1. Introduction

Malaria remains one of the most devastating public health crises in human history, imposing an unyielding burden of morbidity and mortality across tropical and subtropical regions. In 2024, the World Health Organization (WHO) reported an estimated 249 million cases and over 608,000 deaths globally, with a disproportionate 95% of this burden borne by children under five years of age in sub-Saharan Africa [1]. For decades, global elimination strategies relied heavily on vector control via insecticide-treated nets, indoor residual spraying, and chemoprevention regimens [2]. While these interventions successfully curtailed transmission intensities in the early 21st century, progress has

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dangerously plateaued due to the rapid spread of pyrethroid resistance in *Anopheles* vectors and emerging antimalarial drug resistance in *Plasmodium* parasites [1, 2]. Consequently, the development of a highly effective, long-lasting vaccine is widely recognized as the single most critical tool required to achieve absolute malaria eradication [3].

The biological complexity of *Plasmodium falciparum*, the primary agent of severe human malaria, presents unprecedented challenges to conventional vaccinology. Unlike simple viral or bacterial pathogens that present stable, uniform surface antigens, *Plasmodium* possesses a complex, multi-stage lifecycle split between a female *Anopheles* mosquito vector and a human host. Each phase, from the initial motile sporozoite injected into the skin, to the intracellular replication phase within hepatocytes, and finally the destructive lytic cycle inside erythrocytes, which presents an entirely distinct profile of surface proteins [4]. Furthermore, the parasite has evolved sophisticated mechanisms of antigenic variation and immune evasion, most notably driven by highly polymorphic gene families such as *var*, which encodes *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) [5]. This phenotypic plasticity allows the parasite to continuously alter its immunogenic profile, effectively distracting host B- and T-cell responses and preventing the acquisition of sterile natural immunity [4, 5].

Despite these evolutionary hurdles, the landscape of malaria vaccinology has transitioned into a historic milestone era. Decades of candidate screening culminated in the regulatory WHO prequalification of RTS,S/AS01 (Mosquirix) in 2021 [6], followed by the subsequent endorsement of R21/Matrix-M in 2023 [7, 8]. Both formulations are pre-erythrocytic, virus-like particle (VLP) vaccines designed to target the highly conserved circumsporozoite protein (CSP) [9]. By intercepting the sporozoite immediately upon inoculation, these vaccines aim to eliminate the parasite before it can establish a foothold in the liver, effectively preventing downstream blood-stage clinical disease [4, 9]. While the deployment of RTS,S and R21 represents a monumental triumph for public health, real-world data and phase III clinical trials have exposed substantial gaps. Notably, the sterile protection elicited by these platforms is incomplete and exhibits a rapid, pronounced decay in efficacy within 6 to 12 months post-vaccination, requiring complex, multi-dose booster regimens to maintain protective thresholds [9, 10].

This review article provides a comprehensive synthesis of the molecular and cellular mechanisms governing the host immune response to modern malaria vaccines. By dissecting the precise interactions between target antigens, novel adjuvant technologies, and host immune compartments, this paper critiques the current correlates of protection. Specifically, we evaluate the kinetics of humoral anti-NANP IgG responses, the role of helper and cytotoxic T-cell populations, and the biological factors such as pre-existing natural immunity and age-dependent immunosenescence that induce variability in vaccine performance. Finally, we outline how these immunological insights are actively shaping next-generation vaccinomics, including the transition toward multi-stage polyvalent designs and lipid nanoparticle-formulated mRNA platforms [11]. Understanding these intricate immunological parameters is essential not only to optimize current deployment strategies but to engineer a vaccine capable of delivering sustained, sterile protection against malaria.

2. Methodology

To ensure a rigorous, transparent, and reproducible synthesis of literature evaluating the immunology of modern malaria vaccines, this review followed a structured scoping methodology adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

2.1. Search Strategy and Information Sources

A comprehensive, systematic literature search was executed across three primary electronic databases: PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search architecture was restricted to peer-reviewed articles, clinical trial registries, and official regulatory documents published between January 1, 2015, and April 2026. This decade-long window was intentionally selected to capture the critical transition from experimental phase I/II formulations to the real-world phase III efficacy profiles and deployment data of licensed platforms.

The search string combined Medical Subject Headings (MeSH) terms with specific Boolean operators and keyword variations to target relevant immunological data. The exact search matrix utilized is detailed below:

("Malaria Vaccines"[Mesh] or "RTS,S" OR "Mosquirix" or "R21" OR "Matrix-M" or "AS01" OR "PfSPZ") and ("Immune Response" or "Antibody Kinetics" or "Immunity, Cellular"[Mesh] or "T-Lymphocytes"[Mesh] or "Immunogenicity" or "Correlates of Protection") and ("Clinical Trial, Phase III"[Mesh] or "Randomized Controlled Trial"[Mesh] or "Efficacy" or "Waning Immunity")

To complement electronic database screening, manual reference harvesting ("backward citation tracking") was performed on all retrieved systematic reviews, meta-analyses, and consensus statements issued by the World Health Organization (WHO) and the Strategic Advisory Group of Experts (SAGE) on Immunization [13].

2.2. Inclusion and Exclusion Criteria

Articles were screened and selected based on strict predefined parameters to isolate high-quality immunological datasets:

Inclusion Criteria: (1) Human clinical trials (Phases I, II, or III) or prospective longitudinal cohort studies evaluating malaria vaccine candidates; (2) Quantitative assessment of humoral markers (e.g., anti-NANP IgG concentrations, antibody avidity) or cell-mediated parameters (e.g., CD4+, CD8+, or circulating T follicular helper cell kinetics); (3) Studies evaluating licensed pre-erythrocytic formulations (RTS,S/AS01, R21/Matrix-M) or advanced whole-sporozoite platforms (PfSPZ); (4) Publications written in the English language.

Exclusion Criteria: (1) Studies strictly assessing vector control, chemoprevention, or antimalarial drug efficacy without a vaccine component; (2) In vitro or animal-model studies lacking direct translation or correlation to human clinical trial data; (3) Editorial letters, conference abstracts lacking peer-reviewed datasets, and preliminary non-peer-reviewed preprints.

2.3. Data Extraction and Synthesis

A standardized data extraction template was deployed to compile relevant parameters from each qualifying study. Extracted data fields included: publication year, clinical trial phase, host demographics (age cohorts, geographical location, and local malaria transmission intensity), specific adjuvant formulations utilized, primary immunogenicity endpoints (peak antibody titers, cellular cytokine profiles), rate of immune waning over 6–24 months, and calculated correlates of clinical protection. Given the heterogeneity of trial designs, assay protocols, and reporting units, a qualitative narrative synthesis was conducted, supplemented by a comparative analytical framework of structural vaccine attributes.

3. Scope and Background of the Structural Review

Understanding the interaction between malaria vaccines and the host immune system requires a foundational overview of the biological boundaries and historical bottlenecks that define this scientific field. This section establishes the scope of this review by delineating the structural parameters of the parasite lifecycle, the evolution of vaccine design philosophy, and the fundamental differences between natural and vaccine-induced immunity.

3.1. The Parasite Lifecycle as an Immunological Moving Target

The absolute core bottleneck in malaria vaccinomics is the multi-stage lifecycle of *Plasmodium falciparum* within the human host, which operates across three distinct compartments, each requiring a fundamentally unique arm of the host immune system [4]:

- **Pre-Erythrocytic Stage**: Initiated when an infected female *Anopheles* mosquito inoculates motile sporozoites into the skin. These sporozoites quickly travel through the bloodstream to invade hepatocytes. Because this phase lasts only minutes to hours and is completely asymptomatic, a vaccine targeting this stage must induce exceptionally high, ultra-rapid neutralizing antibody titers to clear sporozoites before liver entry. Alternatively, it must trigger robust cellular responses to destroy infected hepatocytes [14].
- **Erythrocytic (Blood) Stage**: Occurs when infected hepatocytes rupture, releasing thousands of merozoites that invade red blood cells. The subsequent cyclic replication and lysis of erythrocytes drive all clinical symptoms, severe pathologies (such as cerebral malaria and severe anemia), and mortality [4]. Immunologically, blood-stage candidates must generate massive antibody concentrations capable of blocking highly diverse merozoite surface proteins to limit parasite replication and clinical severity.
- **Transmission-Blocking (Sexual) Stage**: A small subset of blood-stage parasites differentiate into male and female gametocytes. When a mosquito bites an infected individual, it ingests these gametocytes, which undergo fertilization inside the mosquito midgut. Vaccines targeting this stage do not protect the vaccinated individual from clinical disease; instead, they induce antibodies that disrupt parasite development inside the mosquito, effectively breaking the community transmission cycle.

3.2. The Milestone Paradigm: RTS, S vs. R21

For over thirty years, the circumsporozoite protein (CSP), which is the dominant surface protein covering the sporozoite has served as the premier candidate for pre-erythrocytic vaccine designs [15]. The structural architecture of modern malaria vaccines centres entirely on virus-like particles (VLPs) that display key immunogenic segments of CSP, specifically its central NANP amino acid repeat region (the primary B-cell target) fused to the Hepatitis B surface antigen (HBsAg) [9].

This review focuses heavily on comparing the two globally licensed VLP platforms, highlighting a major evolution in structural design:

RTS, S/AS01 (Mosquirix): Formulated as a hybrid VLP where only about 25% of the total surface proteins carry the CSP antigen fragment; the remaining 75% consist of free, unfused HBsAg helper proteins [15]. This structural dilution means the host immune system is heavily exposed to the viral carrier, which can distract from the targeted malaria antigens [3].

R21/Matrix-M: Engineered as a next-generation, high-density VLP where approximately 100% of the surface-expressed proteins are fused directly to the CSP antigen fragment [16]. By removing excess, unfused carrier proteins, R21 presents a much higher density of malaria epitopes to host B-cells, allowing for highly efficient antigen presentation and triggering strong immune responses using lower total antigen doses [8, 16].

3.3. Natural Immunity vs. Vaccine-Induced Sterile Protection

A critical distinction must be made between naturally acquired immunity and vaccine-induced sterile protection. In endemic areas, individuals exposed to repeat parasite bites over many years slowly develop clinical immunity. This natural response does not prevent infection; rather, it keeps blood-stage parasite levels low enough to prevent severe, life-threatening symptoms [4, 5].

In contrast, pre-erythrocytic vaccines like RTS, S and R21 aim to achieve **sterile protection and** complete prevention of infection by blocking 100% of sporozoites from invading the liver [9]. Because a single sporozoite escaping immune surveillance can multiply into tens of thousands of blood-stage merozoites, vaccine-induced immunity must maintain exceptionally high, continuous antibody thresholds [10]. This requirement makes these vaccines highly vulnerable to the rapid antibody decay typically seen post-vaccination [14, 16].

4. Vaccine Platforms & Targeting Life Cycle Stages

To successfully disrupt the lifecycle of *Plasmodium falciparum*, vaccine platforms must hit specific physiological targets before the intracellular stage begins [13, 18]. The major vaccine strategies are categorized by the specific life cycle stages they target.

4.1. Pre-Erythrocytic Virus-Like Particles (VLPs)

Pre-erythrocytic VLP platforms represent the most clinically successful malaria vaccine strategy to date, as demonstrated by the licensed RTS, S/AS01 and R21/Matrix-M vaccines [9]. These platforms target the motile sporozoite stage immediately following mosquito inoculation. Their design uses recombinant technology to display the circumsporozoite protein (CSP) on the surface of a virus-like particle derived from the Hepatitis B surface antigen (HBsAg). By introducing high densities of the central NANP repeat region to host immune cells, these vaccines induce massive numbers of neutralizing antibodies [21]. These antibodies bind to sporozoites in the skin and blood, immobilizing them and blocking their ability to invade hepatocytes. Because this platform intercepts the parasite before it enters the liver, it acts as a gatekeeper, preventing downstream clinical disease and bloodstream replication. [1, 2, 3]

4.2. Whole Sporozoite Vaccines

Whole sporozoite platforms, such as the PfSPZ vaccine, take a comprehensive approach by using the entire parasite rather than a single isolated antigen [24]. These vaccines use live-attenuated, metabolically active *P. falciparum* sporozoites that have been weakened by radiation or combined with antimalarial drugs [24]. When administered intravenously, these sporozoites successfully invade host liver cells but are genetically or chemically blocked from replicating or breaking out into the bloodstream. This approach exposes the host immune system to a wide array of liver-stage antigens, triggering broad cellular immune responses, particularly intrahepatic cytotoxic CD8+ T-cells, which recognize and destroy infected liver cells.

4.3. Blood-Stage Candidates

Blood-stage vaccine candidates target the merozoite, the form of the parasite responsible for invading red blood cells and driving all clinical symptoms of malaria [4]. These vaccines focus on key surface proteins required for erythrocyte entry, such as Reticulocyte-binding protein Homolog 5 (RH5), Merozoite Surface Protein 1 (MSP1), and Apical Membrane Antigen 1 (AMA1). The goal of a blood-stage vaccine is to induce high concentrations of antibodies that block these entry proteins, leaving merozoites exposed in the plasma where they can be cleared by host immune cells. While blood-stage vaccines do not prevent initial infection, they control replication rates within the blood. This control reduces parasite loads and prevents severe clinical complications like cerebral malaria or severe anemia [4, 1]

4.4. Transmission-Blocking Vaccines (TBVs)

Transmission-blocking vaccines operate on a community-wide level rather than providing direct clinical protection to the vaccinated individual [20]. These platforms target the sexual stages of the parasite lifecycle, focusing on surface antigens expressed by gametocytes, such as Pfs25 and Pfs230. When a person receives a TBV, their immune system generates targeted antibodies against these sexual-stage proteins. When a mosquito bites the vaccinated individual and ingests a blood meal containing parasites, it also takes in these vaccine-induced antibodies. Inside the mosquito's midgut, the antibodies bind to the gametocytes, disrupting fertilization and halting parasite development. This disruption prevents the mosquito from transmitting the disease to the next host, making TBVs a vital tool for breaking regional transmission cycles. [1].

5. Humoral Immune Responses & Correlates of Protection

The clinical efficacy of licensed pre-erythrocytic malaria vaccines depends on the induction and maintenance of a strong humoral immune response [10]. Antibodies serve as the primary line of defence, neutralizing sporozoites before they can establish infection in the liver. [1].

5.1. Antibody Specificity and Avidity

Humoral protection driven by RTS, S and R21 centres on generating IgG antibodies specific to the circumsporozoite protein (CSP) [19]. The primary target for these neutralizing antibodies is the central region of CSP, which contains repeating blocks of the amino acid sequence **NANP**. Antibodies binding to these NANP repeats create a physical barrier around the sporozoite, preventing it from binding to heparin sulfate proteoglycans on liver cells. [1].

Beyond total antibody numbers, **antibody avidity** which is the overall binding strength between antibodies and the target antigen is a critical factor in successful protection [16]. Next-generation structural designs, like the high-density R21 platform, present a tightly packed, uniform arrangement of CSP fragments without unfused HBsAg to host B-cells. This arrangement triggers strong B-cell receptor cross-linking, driving somatic hypermutation in germinal centres and yielding antibodies with significantly higher binding avidity than those produced by older, less dense vaccine designs. [1]

5.2. Quantitative Thresholds of Protection

A central challenge in malaria vaccinology is defining a reliable, universal surrogate endpoint which is a specific antibody concentration that guarantees clinical protection [22]. Data from R21 trials show that achieving a high anti-NANP IgG concentration at peak response correlates strongly with high short-term protection against clinical disease [22].

However, setting a single, universal threshold across different populations remains difficult due to variations in local transmission levels [10]. In areas with high, year-round malaria transmission, individuals often require higher baseline antibody levels to withstand constant parasite exposure [10]. Conversely, in seasonal transmission zones, lower antibody thresholds can still provide effective protection if peak vaccine immunity is timed to coincide with the start of the rainy season. [1].

5.3. Antibody Kinetics and Waning Immunity

While current VLP vaccines induce exceptionally high initial antibody levels following the primary three-dose series, these titers follow a distinct biphasic decay curve [10, 1].

- **Rapid Decay Phase**: In the first 6 months post-vaccination, antibody concentrations drop sharply by approximately 70% to 80% as short-lived plasma cells die off.

- **Sustained Waning Phase**: Following this initial drop, antibody levels decline at a slower, steadier rate driven by long-lived plasma cells in the bone marrow. This rapid early decline poses a major challenge for long-term vaccine efficacy, often causing sterile protection to drop significantly within a year [10]. To counteract this waning immunity, modern vaccination schedules require a fourth-dose booster 12 months after the primary series. This booster reactivates memory B-cell populations, restoring protective antibody thresholds and extending clinical protection through subsequent transmission seasons [22, 1]

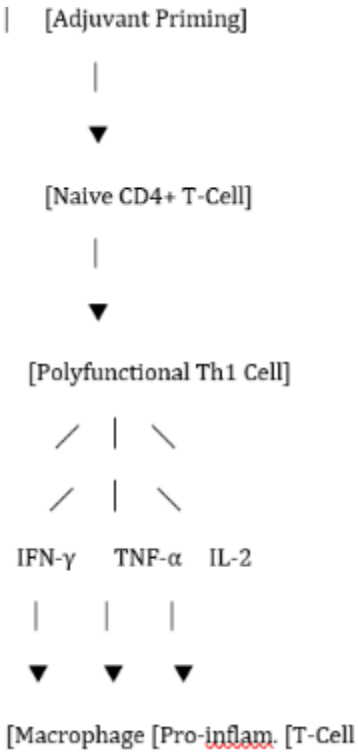
6. Cell-Mediated Immunity (CMI)

While neutralizing antibodies are the primary drivers of sterile protection in licensed malaria vaccines, their generation, maturation, and maintenance depend fundamentally on cellular immune networks [4]. Cell-mediated immunity plays a double role: it coordinates the helper responses needed for long-term B-cell memory and acts as a direct cytotoxic weapon against intracellular liver stages [25].

6.1. CD4+ T-cell Profiles and B-cell Help

The induction of high-affinity anti-NANP IgG antibodies by virus-like particles (VLPs) is highly dependent on antigen-specific CD4+ T helper (\(T{h}\)) cells [9]. Upon vaccination, dendritic cells process the circumsporozoite protein (CSP) and present its T-cell epitopes to naive CD4+ T-cells, priming them into active helper phenotypes. Within this network, **circulating T follicular helper (cTfh) cells** are critical regulators [26]. These cTfh cells migrate to the borders of B-cell follicles, where they interact directly with antigen-specific B-cells through surface markers like CD40L and the secretion of Interleukin-21 (IL-21). This interaction drives B-cell proliferation, isotype switching to highly functional IgG1 and IgG3 subclasses, and somatic hypermutation within germinal centers. Clinical assessments of both RTS,S/AS01 and R21/Matrix-M show that individuals who develop strong, early cTfh cell responses maintain higher antibody levels and experience slower rates of immunity waning [9, 22].

6.2. Cytokine Profiles Co-Expression Matrix



6.3. The Missing CD8+ Cytotoxic Response in VLP Platforms

A structural limitation of current VLP vaccines like RTS, S and R21 is their inability to induce strong intrahepatic memory CD8+ cytotoxic T-cell responses [3]. Clear cells infected with *Plasmodium* require CD8+ T-cells to scan the surface of hepatocytes, recognize parasite fragments presented on Major Histocompatibility Complex class I (MHC-I) molecules, and release perforin and granzymes to destroy the infected cell. Because RTS, S and R21 use non-replicating,

exogenous protein subunits, the target antigens are processed primarily through the endocytic pathway and presented on MHC-II molecules, which selectively activates CD4+ helper networks. Consequently, if a sporozoite escapes antibody neutralization and infects a liver cell, these vaccines provide minimal backup cellular protection to destroy the parasite before it multiplies. This structural gap highlights the need for advanced platforms, such as whole-sporozoite vaccines (PfSPZ) or viral vectors, designed to deliver antigens directly into the host cytoplasm and trigger robust CD8+ T-cell expansion [4, 24].

7. Adjuvants: Modulating the Host Response

Because recombinant proteins like CSP are inherently weak immunogens when administered alone, the success of modern malaria vaccines depends heavily on advanced adjuvant systems. Adjuvants act as danger signals that mimic natural pathogens, triggering the innate immune pathways required to shape adaptive B- and T-cell responses [27].

7.1. AS01 Adjuvant System: Liposome-Based Synergy

The RTS, S vaccine uses the AS01 adjuvant system, a liposome-based formulation containing two distinct immunostimulants: 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and QS-21 (a natural saponin extracted from the *Quillaja saponaria* tree) [28]. AS01 operates through a synergistic dual mechanism:

- **MPL Signaling**: MPL acts as a non-toxic agonist for Toll-Like Receptor 4 (TLR4**)** on the surface of antigen-presenting cells (APCs). This binding triggers the MyD88 and TRIF signaling pathways, inducing the rapid production of pro-inflammatory cytokines like Interleukin-12 (IL-12).
- **QS-21 Integration**: QS-21 enters the cell via endocytosis and disrupts lysosomal membranes, activating the **NLRP3 inflammasome** pathway. This activation leads to the release of Interleukin-1-beta ({IL-1} beta)) and Interleukin-18 (IL-18).

Together, these two pathways create a local immune environment in the draining lymph nodes that promotes rapid antigen uptake by dendritic cells, increases the expression of co-stimulatory molecules (CD80/CD86), and drives the expansion of polyfunctional CD4+ T-cells [27, 28].

7.2. Matrix-M Adjuvant: Saponin Nanoparticle Kinetics

The R21 vaccine utilizes the **Matrix-M adjuvant**, a newer, saponin-based nanoparticle formulation composed of 40-nanometer structured particles made from *Quillaja saponaria* Molina fractions, cholesterol, and phospholipids [29]. Matrix-M achieves high immunogenicity through precise physical kinetics at the injection site:

Cellular Recruitment: Upon injection, Matrix-M triggers a rapid, local influx of innate immune cells, including neutrophils, monocytes, and natural killer (NK) cells, into the draining lymph nodes. Enhanced Antigen Presentation: The nanoparticle structure acts as a slow-release delivery platform, protecting the CSP antigen from early degradation and extending the window of time that dendritic cells can process and present it. By driving high-density antigen presentation without causing systemic inflammation, Matrix-M promotes strong germinal center reactions. This leads to high concentrations of neutralizing anti-NANP IgG antibodies and strong CD4+ T-cell activation, even when using lower total antigen doses [8, 29].

8. Factors Influencing Vaccine Immunogenicity

The deployment of licensed malaria vaccines has revealed that immunogenicity is not uniform across all populations [2]. Vaccine performance is shaped by a complex interplay of environmental exposure, age at vaccination, and host-specific biological variables that can alter both the strength and durability of protective immunity.

8.1. Pre-existing Immunity and Environmental Exposure

In regions with high, perennial malaria transmission, the host immune system is under constant exposure to blood-stage and pre-erythrocytic *Plasmodium* antigens [1]. This relentless parasite pressure can lead to chronic immune activation and **T-cell exhaustion**, marked by the upregulation of inhibitory receptors like PD-1 and CTLA-4 on antigen-specific lymphocytes [31]. When individuals with high levels of pre-existing, naturally acquired non-sterile immunity receive a CSP-based vaccine, their immune systems can undergo **antigenic distraction** [30]. This causes the immune response to prioritize highly variable, non-protective epitopes over the conserved, neutralizing NANP repeat region [19].

Clinical trials evaluating R21/Matrix-M have addressed this issue by using a seasonal deployment strategy [8]. By administering primary doses or boosters just before the peak rainy season, clinicians can time peak vaccine-induced antibody levels to coincide with high vector transmission, minimizing the impact of chronic parasite exposure on long-term immune memory [10].

8.2. Age-Dependent Immune Responsiveness

Age at vaccination is an important factor determining the quality of the adaptive immune response to pre-erythrocytic vaccines [32]. Infants (5–17 months): Children in this age group generally develop highly robust, durable antibody responses when given adjuvanted formulations like RTS, S/AS01 or R21/Matrix-M [22]. Their immune systems are highly receptive to adjuvant-driven germinal center reactions, resulting in high numbers of long-lived plasma cells [9].

Younger Infants (6–12 weeks): When vaccines are integrated into standard expanded programs on immunization (EPI) schedules alongside routine infant vaccines, immunogenicity levels often drop [6]. This lower response is driven by two main factors: the immaturity of the neonatal B-cell compartment and interference from maternal anti-CSP antibodies [33]. These maternal antibodies can bind to and mask the vaccine antigens, preventing efficient B-cell receptor activation [16].

8.3. Nutritional and Genetic Host Variations

Host-specific biological variables introduce further differences in vaccine performance across endemic populations. Nutritional deficiencies, such as severe acute malnutrition and vitamin A or D deficiencies, impair the protein synthesis pathways required for high-volume antibody production and limit T-cell proliferation [34]. Additionally, common genetic variations in human leukocyte antigen (HLA Class II) alleles directly affect how efficiently helper T-cells process and present CSP epitopes [35]. This genetic variation explains why some individuals develop lower antibody levels despite receiving identical vaccine doses and adjuvants [3].

9. Current Challenges & Future Directions

While the rollout of RTS, S/AS01 and R21/Matrix-M marks a major milestone in public health [6, 7], long-term eradication strategies must address current performance limitations and leverage next-generation technology to achieve durable, high-level protection.

9.1. The Waning Paradox and Fractional Dosing Solutions

The rapid decay of protective anti-NANP IgG antibodies within 6 to 12 months post-vaccination creates a significant vulnerability, leaving children exposed once seasonal transmission peaks end [14]. To resolve this waning paradox, researchers are evaluating alternative delivery schedules, including fractional-dose regimens [36].

In a fractional-dose strategy, the third or fourth dose is reduced to one-fifth of the standard antigen content [36]. Clinical data show that this lower dose delays the maturation of the immune response, encouraging higher antibody avidity and promoting a more efficient shift from short-lived to long-lived plasma cells in the bone marrow [22]. This approach extends the durability of protection without requiring continuous annual booster campaigns [10].

9.2. Next-Generation Multi-Stage and Polyvalent Vaccines

No single-antigen vaccine targeting a single lifecycle stage has achieved sustained, high-level sterile protection [4]. Future vaccine strategies are shifting toward multi-stage polyvalent designs that combine antigens from different phases of the *Plasmodium* lifecycle into a single formulation [11].

By fusing pre-erythrocytic antigens (e.g., CSP) [21] with blood-stage invasion proteins (e.g., RH5) [20] and transmission-blocking components (e.g., Pfs230), these multi-stage designs create multiple lines of defence. If a sporozoite escapes the initial antibody barrier and establishes a liver infection, the blood-stage antibodies work to suppress merozoite replication, while the transmission-blocking antibodies prevent the parasite from spreading further within the community [2].

9.3. mRNA Vaccine Platforms and Intracellular Targeting

The successful deployment of lipid nanoparticle (LNP)-formulated mRNA platforms has opened new possibilities for malaria vaccinology [11]. mRNA technology offers distinct advantages over traditional protein-subunit VLP structures:

Cytoplasmic Translation: mRNA vaccines deliver genetic sequences directly into the host cell cytoplasm, allowing antigens to be processed via the endogenous pathway and presented on MHC Class I molecules [11]. This presentation pathway triggers the expansion of intrahepatic cytotoxic CD8+ T-cells, filling a major gap in current VLP vaccines [24].

Rapid Multi-Antigen Customization: mRNA platforms allow multiple distinct antigen sequences to be combined within a single LNP formulation [11]. This simplifies the manufacturing of complex, multi-stage vaccines, making it easier to update formulations in response to emerging regional mutations in *Plasmodium* target genes [5].

10. Conclusion

Deciphering the immune response to malaria vaccines has advanced from early antigen discovery to the real-world deployment of highly engineered VLP platforms. While RTS, S/AS01 and R21/Matrix-M provide vital protection for children across sub-Saharan Africa, addressing the challenge of rapid antibody decay remains a priority. Resolving this issue will require a deeper understanding of the relationships between adjuvant kinetics, cTfh cell activation, and long-term plasma cell maintenance. By combining current VLP deployment data with advanced fractional dosing, multi-stage formulations, and flexible mRNA platforms, global health programs can work toward the ultimate goal of absolute malaria eradication.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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