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Efficacy of mRNA-Based Sporozoite Vaccines Versus RTS in Preventing Malaria Infection Among Children: A Review

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ABSTRACT

Malaria remains a leading cause of childhood morbidity and mortality in endemic regions, with current vaccine options like RTS providing only modest and short-lived protection. This review aimed to compare the efficacy of mRNA-based sporozoite vaccines versus RTS in preventing malaria infection among children, highlighting mechanistic differences, immunogenicity, clinical prospects, and implementation challenges. A narrative review methodology was employed, synthesising recent preclinical and emerging clinical studies on mRNA-based sporozoite vaccines and RTS efficacy. mRNA-based sporozoite vaccines demonstrated superior mechanistic potential by inducing robust humoral and CD8+ T cell responses essential for pre-erythrocytic immunity. Preclinical studies reported sterilising immunity rates up to 90% in animal models, while early-phase clinical trials showed promising immunogenicity and safety profiles. In contrast, RTS showed approximately 36% efficacy over four years, with protection waning rapidly and minimal CD8+ T cell induction. mRNA-based sporozoite vaccines represented a promising novel intervention with potential to surpass RTS in preventing malaria infection among children. However, large-scale efficacy trials, formulation optimisation for thermostability, and health system integration strategies remain critical before widespread implementation.

Keywords: mRNA-based sporozoite vaccine**,** RTS malaria vaccine**,** Malaria prevention**,** Paediatric malaria immunization**,** Vaccine efficacy comparison.

INTRODUCTION

Malaria remains a leading cause of morbidity and mortality among children under five years in sub-Saharan Africa [1, 2]. The World Health Organization (WHO) estimates that over 247 million malaria cases occurred globally in 2021, resulting in approximately 619,000 deaths, with children accounting for the vast majority [3, 4]. The causative agent, *Plasmodium falciparum*, has developed complex immune evasion strategies, complicating efforts to develop highly effective vaccines. For decades, vaccine research has focused on pre-erythrocytic antigens, particularly the circumsporozoite protein (CSP), leading to the development of RTS/AS01 (Mosquirix), the first malaria vaccine approved for pilot implementation.

RTS induce modest protection, with efficacy ranging from 30–50% against clinical malaria and rapidly waning within 3–4 years [5, 6]. This limited efficacy underscores the need for next-generation vaccines with improved immunogenicity, durability, and scalability. Recent advances in mRNA vaccine technology, as evidenced by the success of COVID-19 mRNA vaccines, have inspired exploration of mRNA-based malaria vaccines. mRNA vaccines offer rapid production, potent antigen expression, and induction of balanced humoral and cellular immune responses, positioning them as promising alternatives to protein-based vaccines like RTS [7, 8].

This review critically examines the comparative efficacy of mRNA-based sporozoite vaccines versus RTS in preventing malaria infection among children. It explores mechanistic differences, immunogenicity profiles, preclinical and emerging clinical evidence, potential implementation challenges, and future directions. By synthesising current knowledge, this review provides insights into whether mRNA-based sporozoite vaccines represent a viable strategy to overcome the limitations of RTS and substantially reduce malaria burden among children in endemic regions.

Mechanistic Basis of RTS and mRNA-Based Sporozoite Vaccines

RTS is a recombinant protein vaccine comprising the central repeat and C-terminal regions of *P. falciparum* CSP fused to the hepatitis B surface antigen (HBsAg), formulated with the AS01 adjuvant [9, 10]. It induces CSP-specific antibodies that inhibit sporozoite invasion of hepatocytes, alongside CD4+ T cell responses that support antibody production. However, RTS elicits minimal CD8+ T cell responses, limiting its ability to target infected hepatocytes directly.

In contrast, mRNA-based sporozoite vaccines deliver lipid nanoparticle-encapsulated mRNA encoding the full-length or immunogenic domains of CSP or other sporozoite antigens. Once internalised by host cells, the mRNA is translated into protein antigens, which are processed via endogenous pathways to stimulate robust CD4+ and CD8+ T cell responses in addition to high-titre antibodies. This dual activation is critical for pre-erythrocytic immunity, as CD8+ T cells can directly eliminate infected hepatocytes before merozoite release.

Moreover, mRNA vaccines avoid anti-vector immunity seen with viral-vectored vaccines and can incorporate multiple antigens to broaden immune protection [11]. The manufacturing process is cell-free, rapid, and adaptable to new *Plasmodium* strains or antigenic variants. Collectively, these mechanistic advantages suggest that mRNA-based sporozoite vaccines could surpass RTS in inducing potent, durable, and functional immune responses against malaria.

Immunogenicity and Preclinical Efficacy of mRNA-Based Sporozoite Vaccines

Preclinical studies have demonstrated the potential of mRNA vaccines encoding CSP to elicit strong humoral and cellular immunity [12]. In murine models, mRNA vaccines induced high levels of CSP-specific IgG antibodies with inhibitory activity against sporozoite invasion and robust IFN-γ-producing CD8+ T cell responses targeting infected hepatocytes. Studies employing modified nucleoside mRNA and optimised lipid nanoparticles showed improved stability, translational efficiency, and tolerability.

For instance, a recent study by Pardi et al. utilised nucleoside-modified mRNA encoding full-length CSP encapsulated in lipid nanoparticles, demonstrating sterilising immunity in 90% of immunised mice following sporozoite challenge [13]. Similarly, experimental mRNA vaccines targeting multiple sporozoite antigens, including thrombospondin-related anonymous protein (TRAP), yielded synergistic antibody and T cell responses superior to single-antigen vaccines.

In non-human primate models, preliminary data indicate that mRNA vaccines generate CSP-specific IgG titres comparable to or exceeding those of RTS, with potent effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and opsonophagocytosis. Importantly, mRNA vaccines induced higher frequencies of multifunctional CD8+ T cells producing IFN-γ, TNF-α, and IL-2, which are critical for clearing infected hepatocytes [14].

Clinical Development of mRNA-Based Malaria Vaccines

While clinical data for mRNA-based malaria vaccines remain in early stages, promising advancements have been reported. BioNTech, in collaboration with the University of Oxford and the WHO, initiated a first-in-human trial in 2022 evaluating an mRNA vaccine encoding CSP and other pre-erythrocytic antigens [15]. Interim data revealed that the vaccine was safe, well-tolerated, and elicited high-titre CSP-specific antibodies with neutralising activity alongside polyfunctional CD4+ and CD8+ T cell responses.

Furthermore, Moderna has announced preclinical success of its mRNA malaria vaccine candidate, demonstrating immunogenicity profiles surpassing RTS in animal models, and plans to advance to Phase I trials in endemic regions [16]. These trials will evaluate dose optimisation, safety, immunogenicity, and preliminary efficacy among children aged 6 months to 5 years, the target group for malaria vaccination.

If clinical trials validate the superior immunogenicity and safety of mRNA-based sporozoite vaccines, they could address key shortcomings of RTS, including limited durability and lack of CD8+ T cell induction. However, long-term efficacy, protection against diverse parasite strains, and feasibility in low-resource settings remain critical considerations.

Comparative Efficacy: mRNA-Based Sporozoite Vaccines Versus RTS

Comparing mRNA-based sporozoite vaccines to RTS requires analysis across immunological, clinical, and operational dimensions. RTS demonstrated approximately 36% efficacy against clinical malaria over four years in Phase III trials, with efficacy highest during the first-year post-vaccination and waning rapidly thereafter [17]. Booster doses partially restore protection but pose logistical challenges in endemic settings.

In contrast, mRNA vaccines' ability to induce strong CD8+ T cell responses alongside antibodies may confer sterilising immunity or longer-lasting protection by eliminating infected hepatocytes before blood-stage infection

ensues [18]. Moreover, the flexibility of mRNA platforms allows incorporation of conserved epitopes across multiple parasite strains, potentially enhancing cross-strain efficacy compared to strain-specific RTSs.

However, the comparative efficacy of mRNA vaccines versus RTS in children remains theoretical until Phase II/III trial data are available. Factors such as immunosenescence in young children, pre-existing immunity, and environmental co-factors may modulate vaccine effectiveness. Nonetheless, based on mechanistic superiority and preclinical data, mRNA vaccines hold promise of achieving >50% efficacy, surpassing the WHO's minimum efficacy target for next-generation malaria vaccines.

Implementation Challenges and Considerations

Despite their potential, mRNA-based malaria vaccines face several implementation challenges. First, the cold chain requirements for current mRNA vaccines (-20°C to -80°C) may be prohibitive in rural endemic regions. However, ongoing formulation research aims to develop thermostable mRNA vaccines that can be stored at 2–8°C or even at ambient temperatures.

Second, the manufacturing costs of mRNA vaccines, while declining, remain higher than traditional protein subunit vaccines [19, 20]. Equitable access will require technology transfer, local manufacturing, and funding mechanisms to subsidise costs for low-income countries.

Third, public perception and vaccine hesitancy must be addressed through community engagement, especially given misinformation surrounding novel mRNA technology. Clear communication of safety, efficacy, and benefits will be critical to achieving high coverage rates.

Finally, integration into existing Expanded Programme on Immunization (EPI) schedules, ensuring compatibility with other vaccines, and aligning booster schedules with seasonal transmission patterns will influence real-world impact.

Future Directions

These advances will be pivotal in determining whether mRNA-based sporozoite vaccines can complement or replace RTS as the cornerstone of malaria vaccination strategies in children. Future research should focus on:

i. **Antigen optimisation:** Identifying conserved epitopes across *P. falciparum* strains to enhance cross-protection.
ii. **Multivalent mRNA vaccines:** Encoding multiple life-cycle antigens (e.g., sporozoite and blood-stage) to broaden protection.
iii. **Thermostable formulations:** Developing lyophilised or thermostable mRNA vaccines for deployment in tropical climates.
iv. **Adjuvant incorporation:** Combining mRNA vaccines with immunomodulators to enhance immunogenicity and durability [21].
v. **Longitudinal efficacy trials:** Evaluating long-term protection, safety, and immunogenicity profiles in diverse endemic settings.

CONCLUSION

Malaria remains a formidable threat to child health globally, and current vaccination strategies such as RTS provide only modest and transient protection. The emergence of mRNA vaccine technology offers a transformative opportunity to overcome these limitations. mRNA-based sporozoite vaccines exhibit superior mechanistic properties, inducing robust antibody and CD8+ T cell responses crucial for pre-erythrocytic immunity. Preclinical studies have demonstrated sterilising protection and durable immunity, while early clinical trials indicate promising safety and immunogenicity profiles. However, challenges including cold chain requirements, manufacturing costs, and integration into endemic healthcare systems must be addressed to realise their full potential. Comparative efficacy data in children remain pending, but mRNA vaccines hold promise of exceeding the WHO efficacy targets and substantially reducing malaria morbidity and mortality among vulnerable paediatric populations. In conclusion, mRNA-based sporozoite vaccines represent a novel, potentially paradigm-shifting intervention in malaria control, offering prospects of durable and high-level protection where RTS falls short. Rigorous clinical evaluation, implementation research, and global investment will be essential to translate this technological innovation into meaningful public health impact in the fight against malaria.

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