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RTS,S/AS01 mRNA Booster Platforms for Sustaining Protective Immunity Against *Plasmodium Falciparum* in African Children

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ABSTRACT

Malaria caused by *Plasmodium falciparum* remained a leading cause of morbidity and mortality among African children, with hundreds of thousands of paediatric deaths annually despite expanded control measures. The RTS,S/AS01 pre-erythrocytic vaccine had demonstrated moderate efficacy, reducing clinical malaria episodes by approximately 45–50% in children aged 5–17 months, but protection wanes over time and is substantially lower in young infants, underscoring the need for strategies that sustain and amplify vaccine-induced immunity. This narrative review exploreed emerging concepts around RTS,S/AS01 mRNA booster platforms as a means to prolong protective immunity against *P. falciparum* in African children, integrating current evidence on RTS,S/AS01 performance, mRNA vaccine immunobiology, and booster strategies in high-transmission settings. A narrative review methodology was employed, drawing from randomized trials, implementation studies, and mRNA vaccine literature indexed in major databases up to mid-2026. Findings from phase 3 trials revealed that RTS,S/AS01 efficacy is enhanced by a fourth booster dose and by seasonal schedules combined with chemoprevention, but long-term protection remains incomplete. Parallel advances in mRNA technology suggested that mRNA-encoded circumsporozoite antigen boosters could re-engage B and T cell memory more flexibly and repeatedly, potentially overcoming waning immunity while enabling rapid adaptation to parasite antigenic variation. RTS,S/AS01 mRNA booster platforms represented a promising, though still theoretical, avenue for sustaining protective immunity against *P. falciparum* in African children, contingent on solving challenges of cost, cold-chain logistics, and equitable access.

Keywords: RTS,S/AS01, Malaria vaccine, mRNA booster, *Plasmodium falciparum*, African children.

INTRODUCTION

Severe malaria due to *Plasmodium falciparum* remains one of the most devastating infectious diseases affecting African children, with the highest burden concentrated in sub-Saharan Africa [1, 2]. Large-scale epidemiological data indicate that African children under five years of age account for most global malaria deaths, with many countries recording tens of thousands of paediatric fatalities annually despite progress in vector control and chemoprevention. This ongoing toll reflects persistent transmission, insecticide resistance, health system constraints, and the absence of a highly efficacious, durable vaccine [3]. RTS,S/AS01, the first malaria vaccine to reach large phase 3 evaluation and WHO pilot implementation, targets the circumsporozoite protein of *P. falciparum* and has demonstrated moderate protection against clinical malaria in African children. In phase 3 trials, efficacy against clinical malaria in children aged 5–17 months was approximately 45–50% in the 18 months after the primary three-dose series, with vaccine efficacy against severe malaria and malaria hospitalization around 34–41%. However, efficacy is lower in infants 6–12 weeks of age, and in both age groups vaccine-induced protection wanes over time, with seven-year follow-up studies showing declining effectiveness and continued need for complementary control measures. Booster doses at 20 months have improved protection, and seasonal schedules

combined with seasonal malaria chemoprevention have sustained substantial protection over five years, but long-term, high-level immunity remains elusive [4]. This pattern of moderate initial efficacy followed by progressive waning raises a critical problem: how can the immunologic imprint of RTS,S/AS01 be reinforced repeatedly and efficiently in African children living in high-transmission settings, without overwhelming health systems or families with complex, multi-dose schedules? The success of mRNA vaccine platforms in other infectious diseases has catalyzed interest in mRNA-based boosters, which can be rapidly manufactured, antigenically updated, and deployed to restimulate memory immune responses. Conceptually, mRNA boosters encoding circumsporozoite antigens or optimized epitopes might serve as immunologic "refreshers" layered upon RTS,S/AS01 priming, sustaining antibody titres and T cell responses that protect against infection and severe disease [5].

This narrative review examines RTS,S/AS01 mRNA booster platforms as a theoretical but increasingly plausible strategy to sustain protective immunity against *P. falciparum* in African children. The first section summarizes the performance characteristics of RTS,S/AS01 in African paediatric populations, emphasizing efficacy, waning protection, and current booster approaches. The second section outlines core principles of mRNA vaccine immunobiology relevant to booster design in malaria-endemic settings. The third section considers how mRNA boosters could be integrated with RTS,S/AS01 schedules to extend protection, drawing analogies from other vaccine-preventable diseases. The fourth section explores implementation, safety, and operational challenges for deploying mRNA boosters in African health systems. The fifth section identifies research priorities and future directions needed to translate these concepts into evidence-based policies [5].

The purpose of this review is to provide a structured, biochemically informed perspective on the potential of RTS,S/AS01 mRNA booster platforms to sustain protective immunity in African children, while realistically appraising current data gaps and system-level constraints that must be overcome to realize their promise.

RTS,S/AS01 Performance and the Problem of Waning Protection

RTS,S/AS01 has undergone extensive evaluation in African children and infants, providing a robust evidence base for its efficacy and safety profile [6]. In the pivotal phase 3 trial conducted at multiple African sites, three doses of RTS,S/AS01 given to children aged 5–17 months reduced clinical malaria episodes by roughly 45–50% over 18 months compared with control vaccines, with even greater numbers of cases averted in high-transmission areas. Protection against severe malaria and malaria hospitalization, while more modest, was still clinically meaningful, and vaccine impact was highest where baseline malaria incidence was greatest [7]. However, efficacy in infants 6–12 weeks of age was notably lower, around 27%, and there was limited evidence of protection against severe malaria in this younger group, reflecting age-related immunologic differences and potential interference from routine infant vaccines. Longitudinal follow-up of vaccinated children over seven years has shown that RTS,S/AS01 efficacy declines over time, with cumulative protection remaining beneficial but reduced compared with the early post-vaccination period. Importantly, analyses of vaccine efficacy trajectories demonstrate significant waning in both clinical and severe malaria endpoints, emphasizing the need to reinforce immunity beyond the initial three-dose series [8]. Booster strategies have been evaluated to address this problem. A fourth dose administered around 20 months after the primary series improved overall protection, enhancing vaccine efficacy and prolonging the period during which clinical episodes were averted. More recently, seasonal RTS,S/AS01 vaccination combined with seasonal malaria chemoprevention in Burkina Faso and Mali sustained substantial protection over five years, suggesting that strategic timing of boosters can match seasonal transmission patterns and optimize impact [9, 10]. Nonetheless, these approaches involve complex schedules and logistical demands, and immunity still wanes between booster campaigns, leaving children vulnerable during gaps or in areas with perennial transmission [3].

In sum, RTS,S/AS01 has proven capable of reducing clinical and severe malaria burden in African children, but its moderate efficacy and waning protection necessitate innovative booster strategies that are biologically sound and operationally feasible [5].

mRNA Vaccine Immunobiology and Relevance to Malaria Boosters

mRNA vaccines deliver synthetic messenger RNA encoding selected antigens into host cells, where the transcript is translated into protein, presented to the immune system, and subsequently degraded [11]. This platform elicits both humoral and cellular responses and has demonstrated strong immunogenicity, rapid scalability, and the ability to incorporate multiple antigenic variants. From a biochemical standpoint, engineered mRNA constructs incorporate modified nucleosides, optimized untranslated regions, and codon usage tailored to enhance stability, translation efficiency, and innate immune tolerability [12]. For booster applications, mRNA vaccines offer several advantages. They can be rapidly redesigned to encode updated antigens, respond to emerging pathogen variants, and tailor epitopes to improve breadth and durability of the immune response. mRNA-based boosters have been successfully deployed to restimulate memory B and T cells primed by earlier vaccination or infection, yielding increased antibody titres, improved neutralization breadth, and reinforced T cell functional capacity. Additionally, mRNA vaccines are non-integrating and transient in expression, which may reduce certain long-term safety concerns compared with integrating vectors [12]. In the context of malaria, mRNA boosters encoding

circumsporozoite protein or optimized fragments could theoretically capitalize on RTS,S/AS01-induced memory pools, rekindling high-level antibody responses and CD4 T cell help while potentially enhancing CD8 T cell involvement [13-17]. The flexibility of mRNA design might allow incorporation of multiple epitopes from distinct parasite stages or allelic variants, aiming to counteract antigenic diversity and maintain protection across different *P. falciparum* populations. Moreover, the capacity for repeated boosting with mRNA constructs, given appropriate safety and tolerability, aligns with the chronic, recurrent nature of malaria exposure in African children [3].

Thus, fundamental features of mRNA vaccine immunobiology provide a compelling rationale for considering mRNA-based boosters layered upon RTS,S/AS01 priming as a strategy to sustain and broaden protective immunity against *P. falciparum* [12,18-20].

Conceptual Integration of RTS,S/AS01 and mRNA Booster Platforms

Integrating RTS,S/AS01 with mRNA-based booster platforms requires thoughtful alignment of antigenic design, immunologic timing, and field realities. RTS,S/AS01 primes the immune system with circumsporozoite antigen in a protein-based formulation linked to a potent adjuvant system, generating initial antibody and T cell responses that wane over several years. mRNA boosters could be deployed at intervals timed to precede high transmission seasons or to coincide with routine childhood visits, delivering renewed circumsporozoite antigen expression that reactivates memory responses and elevates protective antibody titres [4].

One conceptual model involves administering RTS,S/AS01 as a primary series in early childhood, followed by periodic mRNA booster doses encoding circumsporozoite protein variants, potentially combined with antigens from other parasite stages to broaden coverage. These boosters could be given annually or seasonally, depending on local transmission patterns, in tandem with existing interventions such as insecticide-treated nets and chemoprevention. Another model envisions hybrid schedules in which some boosters remain protein–adjuvant based while others employ mRNA, seeking to balance established safety profiles with the flexibility of mRNA platforms [14]. Analogies can be drawn from other vaccine-preventable diseases where mRNA boosters have been layered onto prior priming with conventional vaccines, yielding enhanced and broader protection [15]. In malaria-endemic African settings, such integrated approaches would need to account for co-administration with routine childhood immunizations, nutritional and comorbidity burdens, and health system capacity. The potential benefits include greater durability of protection, improved matching to parasite diversity, and more responsive adaptation to changing transmission patterns [5]. While empirical trials of RTS,S/AS01 mRNA booster sequences in African children have not yet been reported, the conceptual framework is consistent with current immunologic and platform science, providing a fertile agenda for translational research [14,21-24].

Implementation, Safety, and Operational Challenges in African Settings

Deploying RTS,S/AS01 mRNA booster platforms in African children would face significant implementation and safety challenges that must be addressed early in development. Cold-chain requirements for current mRNA formulations are stringent [16], often necessitating ultra-cold storage that is difficult to maintain in rural and resource-limited settings where malaria burden is highest. Efforts to develop more thermostable mRNA products are ongoing but not yet widely realized, making logistical feasibility a central concern [3]. Cost and supply are additional barriers. mRNA technologies remain relatively expensive compared with conventional vaccines, and global manufacturing capacity is unevenly distributed [17]. Equitable access would demand substantial investment, technology transfer, and international coordination, particularly given the large birth cohorts and high malaria incidence in many African countries. Safety and tolerability must also be rigorously evaluated; while mRNA vaccines have shown acceptable profiles in other populations, African children with high background rates of infection, malnutrition, and comorbidities may present different risk contexts [7]. Health system readiness will influence deployment success. Integrating mRNA boosters into routine immunization schedules, seasonal malaria campaigns, or school-based programmes will require clear communication, training, and monitoring frameworks. Surveillance systems must be capable of detecting rare adverse events and tracking vaccine effectiveness over time, building on experience from RTS,S/AS01 pilot implementation. Community acceptance is another critical factor; perceptions of novel gene-based technologies may vary, and engagement with caregivers, local leaders, and clinicians will be crucial to maintain trust [7,18,23-26]. Thus, while mRNA booster platforms offer promising immunologic advantages, their translation to African malaria contexts will depend on solving interconnected logistical, economic, safety, and sociocultural challenges [8].

Future Directions and Research Priorities

Several research priorities emerge from consideration of RTS,S/AS01 mRNA booster platforms for African children. First, detailed immunologic studies of RTS,S/AS01-induced memory B and T cell populations in diverse African settings are needed to inform optimal booster timing and antigen design [19]. Second, preclinical and early-phase clinical studies of circumsporozoite-targeted mRNA constructs, alone and in combination with RTS,S/AS01 priming, should assess immunogenicity, safety, and durability of responses in paediatric cohorts. Third, modelling work that integrates epidemiologic data, vaccine efficacy trajectories, and health system capacities can help predict the impact and cost-effectiveness of different booster schedules under real-world

conditions [4]. Fourth, technological innovation aimed at improving mRNA thermostability, reducing dose requirements, and simplifying delivery devices will be essential to make booster platforms operationally viable in rural African settings [20]. Fifth, implementation science research should explore strategies for integrating mRNA boosters with existing malaria and child health interventions, focusing on acceptability, equity, and resilience of service delivery. Importantly, ethical and governance frameworks must be strengthened to ensure transparent decision-making and fair distribution of advanced vaccine technologies [8]. Collectively, these priorities underscore that RTS,S/AS01 mRNA booster platforms represent a long-term, multidisciplinary endeavour requiring collaboration between molecular vaccinologists, epidemiologists, health system researchers, and policy makers to translate theoretical promise into tangible reductions in malaria burden among African children [5].

CONCLUSION

RTS,S/AS01 has opened a new chapter in malaria control by demonstrating that vaccination can meaningfully reduce the clinical and severe burden of *P. falciparum* infection among African children, yet its moderate efficacy and waning protection highlight the need for more durable immunologic solutions. mRNA vaccine platforms provide a versatile, rapidly adaptable technology that could, in principle, serve as booster layers on RTS,S/AS01 priming, re-engaging memory responses and potentially broadening coverage against parasite diversity. Conceptual integration of these modalities aligns with immunologic principles and experience from other infectious diseases, but empirical evaluation in malaria-endemic African settings is still lacking.

Implementation challenges related to cold-chain logistics, cost, manufacturing capacity, and health system readiness, combined with safety and acceptability considerations, mean that RTS,S/AS01 mRNA booster platforms will require careful phased development and robust evidence before routine deployment can be justified. Nonetheless, the potential to sustain and amplify protective immunity against *P. falciparum* in high-risk children warrants serious exploration of this strategy as part of a broader, integrated malaria control agenda. Rigorous, multi-country translational research programmes should be initiated to evaluate RTS,S/AS01-primed, circumsporozoite-targeted mRNA booster strategies in African children, with explicit attention to immunologic durability, safety, operational feasibility, and equitable access in high-transmission settings.

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