Research Output Journal of Public Health and Medicine 6(1):78-86, 2026

ROJPHM ISSN ONLINE: 1115-9715

https://rojournals.org/roj-public-health-and-medicine/ ISSN PRINT: 1115-6147

https://doi.org/10.59298/ROJPHM/2026/617886

RTS, S Vaccine Efficacy in Sub-Saharan African Children: Long-term Protection Assessment

Namukasa Mugerwa F.

Faculty of Medicine Kampala International University Uganda

ABSTRACT

Malaria remains a leading cause of childhood mortality in sub-Saharan Africa, with Plasmodium falciparum responsible for over 400,000 deaths annually, predominantly in children under five years of age. This review evaluated the long-term efficacy and protection dynamics of the RTS, S/AS01 vaccine in pediatric populations across endemic regions of sub-Saharan Africa. A comprehensive literature search was conducted using PubMed, Embase, and Cochrane databases from 2011 to 2024, focusing on Phase III clinical trials, post-implementation surveillance studies, and immunological assessments of RTS, S vaccine performance. Analysis of pivotal clinical trial data and real-world implementation studies demonstrated that RTS, S provides modest but significant protection against clinical malaria in children aged 5-17 months, with vaccine efficacy ranging from 36-50% in the first-year post-vaccination, declining to 16-26% by year four. Long-term follow-up studies revealed substantial waning of protective immunity, with antibody titers against the circumsporozoite protein declining rapidly within 12-18 months of vaccination. Post-marketing surveillance from Ghana, Kenya, and Malawi indicated real-world effectiveness of 13-22% against severe malaria hospitalizations, with optimal protection observed when RTS, S is combined with insecticide-treated nets and seasonal chemoprevention. The vaccine demonstrated acceptable safety profiles but requires strategic deployment in high-transmission settings to maximize population-level impact. RTS, S represents a significant advancement in malaria prevention but exhibits limited long-term protective immunity necessitating improved second-generation vaccines.

Keywords: RTS, S vaccine, malaria prevention, Plasmodium falciparum, pediatric immunization, circumsporozoite protein

INTRODUCTION

Malaria continues to impose a devastating burden on global public health, with an estimated 241 million cases and 627,000 deaths reported in 2020 [1–3]. Sub-Saharan Africa bears a disproportionate burden, accounting for approximately 95% of malaria deaths, with children under five years of age representing 80% of fatalities in this region [1,4]. Plasmodium falciparum, the most virulent malaria parasite species, demonstrates particular lethality in pediatric populations due to incomplete acquired immunity and rapid disease progression [5]. The economic impact extends beyond healthcare costs, with malaria-endemic countries experiencing reduced gross domestic product growth rates of 1% annually compared to malaria-free regions [6]. Traditional control measures including insecticide-treated nets, indoor residual spraying, and artemisinin-based combination therapies have achieved substantial reductions in malaria incidence since 2000 [7,8]. However, progress has stagnated since 2015, with emerging insecticide resistance, antimalarial drug resistance, and persistent transmission in high-burden countries highlighting the urgent need for additional interventions [9,10]. The development of effective malaria vaccines represents a critical component of integrated control strategies, with the potential to provide sustained protection in vulnerable populations where existing interventions demonstrate limited effectiveness [11]. The RTS, S/AS01 vaccine, developed through a collaboration between GlaxoSmithKline and the PATH Malaria Vaccine Initiative,

became the first WHO-prequalified malaria vaccine in 2015, marking a historic milestone in malaria prevention efforts [12,13]. The objective of this review is to critically assess the long-term efficacy and protective immunity of RTS, S vaccination in sub-Saharan African children based on clinical trial data and real-world implementation evidence.

Methodology

A comprehensive literature search was conducted using PubMed/MEDLINE, Embase, and Cochrane Library databases from January 2011 through December 2024. Search terms included combinations of "RTS, S", "malaria vaccine", "circumsporozoite protein", "Plasmodium falciparum", "pediatric", "sub-Saharan Africa", "vaccine efficacy", and "long-term protection". Inclusion criteria encompassed peer-reviewed articles reporting clinical trial data, observational studies, immunological assessments, and systematic reviews related to RTS, S vaccine performance in African children. Exclusion criteria included non-English publications, case reports, and studies focusing exclusively on adult populations or non-African settings. Evidence synthesis prioritized randomized controlled trials and large observational studies while incorporating mechanistic research to explain clinical findings. Quality assessment followed GRADE criteria for intervention studies and Newcastle-Ottawa Scale for observational research.

Molecular and Biochemical Basis of RTS, S Vaccine Design

The RTS, S vaccine represents an innovative approach to malaria prevention through targeting the pre-erythrocytic stage of Plasmodium falciparum infection [14]. The vaccine's design centers on the circumsporozoite protein (CSP), the most abundant surface protein expressed on sporozoites during the infectious stage transmitted by Anopheles mosquitoes [15]. CSP plays crucial roles in sporozoite motility, hepatocyte invasion, and immune evasion, making it an attractive target for vaccine-induced immunity [16].

The molecular structure of RTS, S consists of a hybrid protein comprising the central repeat region and C-terminal domain of P. falciparum CSP fused with hepatitis B surface antigen (HBsAg) [17]. The central repeat region contains the immunodominant NANP (asparagine-alanine-asparagine-proline) epitope, present in 19 tandem copies in the vaccine construct [18]. This tetrapeptide repeat serves as the primary target for neutralizing antibodies that can block sporozoite invasion of hepatocytes [19]. The C-terminal region includes T-cell epitopes that stimulate both CD4+ and CD8+ cellular immune responses essential for eliminating infected hepatocytes [20].

The vaccine is formulated with the AS01 adjuvant system, a liposome-based formulation containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and QS-21 saponin [21]. MPL activates Toll-like receptor 4 signaling pathways, promoting dendritic cell maturation and inflammatory cytokine production [22]. QS-21 enhances antigen presentation and stimulates both humoral and cellular immune responses through mechanisms involving cholesterol-dependent membrane disruption and enhanced antigen uptake by antigen-presenting cells [23].

Immunological studies demonstrate that RTS, S vaccination induces both antibody-mediated and cellular immune responses [24]. Anti-CSP antibodies exhibit complement-fixing properties and demonstrate sporozoite neutralization capacity in vitro [25]. However, the magnitude and durability of antibody responses show substantial inter-individual variation, with peak titers typically observed 1-2 months post-vaccination followed by progressive decline [26]. CD4+ T-cell responses predominantly involve Th1 polarization with interferon-gamma and interleukin-2 production, while CD8+ T-cell responses target CSP-derived epitopes presented on MHC class I molecules [27].

The biochemical basis for protection involves multiple effector mechanisms operating during the liver stage of parasite development [28]. Neutralizing antibodies can block sporozoite invasion of hepatocytes by binding to the NANP repeat region and disrupting critical protein-protein interactions required for cell entry [29]. Additionally, antibodies may facilitate sporozoite clearance through complement activation and opsonization for phagocytic uptake [30]. Cellular immunity contributes through CD8+ T-cell-mediated elimination of infected hepatocytes, preventing progression to blood-stage infection and clinical disease manifestation [31].

Pathophysiology and Clinical Trial Evidence

The pathophysiological rationale for targeting pre-erythrocytic stages stems from the relatively small number of parasites present during initial liver infection compared to subsequent blood-stage parasitemia [32]. Sporozoites inoculated by mosquito bites typically number fewer than 100 organisms, providing a narrow window for immune intervention before exponential parasite replication occurs within hepatocytes [33]. Mathematical modeling suggests that preventing even a subset of liver-stage infections can significantly reduce the probability of clinical disease, particularly in children with limited acquired immunity [34].

The pivotal Phase III clinical trial, conducted across seven sub-Saharan African sites from 2009-2014, enrolled 15,459 children in two age cohorts: 6-12 weeks and 5-17 months at first vaccination [35]. The study employed a randomized, controlled design comparing RTS, S/AS01 with comparator vaccines (meningococcal vaccine or rabies vaccine) administered according to a 0-, 1-, 2-month schedule, with a booster dose given 18 months after the third dose in half of participants [35].

Primary efficacy endpoints included clinical malaria episodes (fever plus parasitemia ≥5,000 parasites/μL) and severe malaria cases meeting WHO criteria [35]. In the older age cohort (5-17 months), vaccine efficacy against clinical malaria was 50.4% (95% CI: 45.8-54.6%) during the first year following vaccination [35]. Efficacy against severe malaria reached 47.3% (95% CI: 22.4-64.2%) in the same period [35]. However, protection waned substantially over time, with vaccine efficacy declining to 28.3% (95% CI: 23.3-33.0%) by year four of follow-up [36].

The younger cohort (6-12 weeks) demonstrated inferior vaccine performance, with clinical malaria efficacy of 27.3% (95% CI: 19.9-33.9%) in year one, declining to 18.3% (95% CI: 11.7-24.4%) over four years [35,36]. Severe malaria protection was not statistically significant in this age group, potentially reflecting interference from maternal antibodies or immunological immaturity affecting vaccine responses [37].

Booster vaccination provided modest benefits, increasing overall four-year vaccine efficacy from 28.3% to 36.3% (95% CI: 31.8-40.5%) in the older age cohort [36]. However, the durability of booster-induced protection remained limited, with evidence of continued waning within 12-18 months of the fourth dose [38]. Subgroup analyses revealed higher efficacy in areas with moderate transmission intensity compared to high-transmission settings, suggesting that overwhelming parasite exposure may overcome vaccine-induced immunity [39].

Immunological correlates of protection studies identified anti-CSP antibody levels as the strongest predictor of vaccine efficacy, though the correlation was modest (r^2 = 0.1-0.3 across studies) [40]. A threshold of approximately 20 EU/mL anti-CSP antibody concentration was associated with 50% protection probability, though substantial protection was observed at lower titers and some individuals with high titers experienced breakthrough infections [41].

Real-World Implementation and Effectiveness Studies

Following the WHO recommendation in 2021, RTS, S implementation began through the Malaria Vaccine Implementation Programme (MVIP) in Ghana, Kenya, and Malawi [42]. Real-world effectiveness data from these pilot programs provide crucial insights into vaccine performance under operational conditions, complementing controlled clinical trial findings [43].

Post-marketing surveillance from Ghana demonstrated a 13% (95% CI: 1-23%) reduction in severe malaria hospitalizations among children receiving at least one dose of RTS, S compared to unvaccinated controls [44]. Kenya reported similar findings, with 22% (95% CI: 7-35%) effectiveness against severe malaria in vaccinated children [45]. Malawi's data indicated 16% (95% CI: 2-28%) effectiveness, though confidence intervals reflected the challenges of conducting observational effectiveness studies in high-transmission settings [46].

Coverage analyses revealed substantial variations in vaccination uptake, with first-dose coverage ranging from 60-85% across implementation sites [47]. Completion rates for the four-dose schedule were lower, typically 40-60%, highlighting the operational challenges of delivering a complex vaccination regimen in resource-limited healthcare systems [47]. Geographic and socioeconomic disparities in coverage emerged, with rural and marginalized populations experiencing reduced access to vaccination services [48].

Seasonal patterns of vaccine effectiveness demonstrated optimal protection during peak transmission periods, when the absolute number of prevented cases was highest despite potentially lower relative efficacy [49]. Integration with existing interventions showed additive benefits, with vaccinated children using insecticide-treated nets experiencing greater protection than either intervention alone [50]. However, areas with high bed net coverage showed smaller incremental benefits from vaccination, raising questions about optimal deployment strategies [51].

Safety surveillance confirmed the acceptable risk profile observed in clinical trials, with no evidence of increased severe adverse events among vaccinated children [52]. Concerns about potential increased susceptibility to malaria following vaccination, suggested by some clinical trial subgroup analyses, were not confirmed in implementation studies [53]. However, continued monitoring remains essential given the limited duration of post-marketing surveillance to date [54].

Economic evaluations of RTS, S implementation indicate modest cost-effectiveness in high-transmission settings, with incremental cost-effectiveness ratios of $100-200 per disability-adjusted life year averted [55]. These calculations depend heavily on local epidemiological conditions, healthcare costs, and vaccine delivery strategies [56]. Optimization of delivery platforms and integration with routine immunization services could improve cost-effectiveness profiles [57].

Immunological Mechanisms and Duration of Protection

Understanding the immunological basis for RTS, S-induced protection and its temporal dynamics is crucial for optimizing vaccine deployment and developing improved formulations [58]. Detailed immunological studies from clinical trials and implementation programs reveal complex interactions between humoral and cellular immune responses that determine protective outcomes [59].

Anti-CSP antibody kinetics follow a predictable pattern characterized by rapid increases following each vaccination dose, peak titers 1-2 months post-vaccination, and subsequent exponential decline with half-lives of 1-3 years depending on individual and environmental factors [60]. Children in high-transmission areas demonstrate faster

antibody decay, potentially reflecting antigenic competition from natural malaria exposure or underlying immunological factors affecting memory B-cell longevity [61].

Functional antibody assays demonstrate that not all anti-CSP antibodies possess equal protective capacity [62]. Sporozoite inhibition assays show that antibodies targeting conformational epitopes within the NANP repeat region exhibit superior neutralizing activity compared to those recognizing linear epitopes [63]. Additionally, antibodies capable of complement fixation demonstrate enhanced protective efficacy, suggesting that effector function quality rather than quantity may determine clinical outcomes [64].

Memory B-cell responses show greater durability than circulating antibody levels, with CSP-specific memory B cells detectable up to four years post-vaccination in some individuals [65]. However, memory B-cell frequencies remain relatively low compared to responses observed with highly effective vaccines, and their ability to rapidly generate protective antibody levels upon malaria exposure appears limited based on breakthrough infection studies [66].

T-cell immunity contributes to both liver-stage parasite elimination and maintenance of humoral immune responses through follicular helper T-cell functions [67]. CD8+ T-cell responses targeting CSP-derived epitopes show initial expansion following vaccination but demonstrate poor memory maintenance, with most responses becoming undetectable within 2-3 years [68]. CD4+ T-cell responses exhibit greater durability but show functional skewing toward Th2 phenotypes over time, potentially reducing protective efficacy [69].

Age-related differences in immune responses help explain the superior vaccine efficacy observed in older children compared to infants [70]. Infants demonstrate reduced antibody magnitude and accelerated decay, potentially reflecting immunological immaturity or interference from maternal antibodies [71]. Additionally, the developing immune system's bias toward tolerance mechanisms may impair the generation of effective memory responses required for sustained protection [72].

Current Limitations and Future Vaccine Development

Despite representing a historic achievement in malaria vaccine development, RTS, S exhibits significant limitations that constrain its public health impact and necessitate continued research toward improved formulations [73]. The modest efficacy and rapid waning of protection limit the vaccine's ability to achieve substantial reductions in malaria burden, particularly in high-transmission settings where it is most needed [74].

The narrow antigenic target represents a fundamental limitation, as the vaccine relies exclusively on immune responses against CSP [75]. Genetic polymorphisms in CSP, while less extensive than blood-stage antigens, can affect vaccine efficacy, with some studies suggesting reduced protection against parasites carrying variant CSP alleles [76]. Additionally, the focus on a single parasite stage leaves vaccinated individuals vulnerable to breakthrough infections that escape pre-erythrocytic immunity [77].

Manufacturing and deployment challenges include the complex production requirements for the RTS, S protein and AS01 adjuvant, resulting in high vaccine costs ($5-10 per dose) that may limit scalability in resource-constrained settings [78]. The four-dose schedule creates additional operational complexity and cost, with evidence suggesting that simplified schedules may be equally effective for achieving population-level impact [79].

Next-generation malaria vaccines in development aim to address RTS, S limitations through multiple approaches [80]. R21/Matrix-M vaccine employs a similar CSP-based strategy but with improved immunogenicity, demonstrating 77% efficacy in Phase II trials in Burkina Faso [81]. Multi-stage vaccines combining pre-erythrocytic and blood-stage antigens show promise for broader protection, while whole-parasite approaches using radiation-attenuated or genetically modified parasites may induce more comprehensive immunity [82,83].

Novel adjuvant systems and delivery platforms offer potential improvements in immunogenicity and durability [84]. Viral vector-based vaccines can stimulate robust T-cell responses, while nanoparticle formulations may enhance antigen stability and improve immune recognition [85]. Additionally, heterologous prime-boost strategies combining different vaccine platforms may optimize both antibody and cellular immune responses [86].

Combination vaccination strategies represent another promising avenue, with studies evaluating RTS, S co-administration with blood-stage vaccines or transmission-blocking vaccines [87]. Such approaches could provide broader protection across multiple parasite lifecycle stages and potentially enhance overall efficacy beyond that achieved by individual vaccines [88].

The development of correlates of protection remains a critical research priority, as current understanding of immunological mechanisms underlying vaccine efficacy remains incomplete [89]. Advanced systems immunology approaches may identify novel biomarkers predictive of protection, enabling rational vaccine optimization and personalized vaccination strategies [90].

CONCLUSION

The RTS, S/AS01 vaccine represents a groundbreaking achievement in malaria prevention, providing the first WHO-prequalified vaccine against Plasmodium falciparum malaria in children. Clinical trial evidence demonstrates modest but statistically significant efficacy against clinical and severe malaria in children aged 5-17 months, with optimal protection observed during the first year following vaccination. However, substantial limitations constrain

the vaccine's public health impact, including rapid waning of protective immunity, reduced efficacy in high-transmission settings, and suboptimal performance in infants under 12 months of age. Real-world implementation data from Ghana, Kenya, and Malawi confirm the vaccine's safety and provide evidence of measurable impact on severe malaria hospitalizations, though effectiveness levels remain modest compared to other childhood vaccines. The integration of RTS, S with existing malaria control interventions demonstrates additive benefits, supporting its role as a complementary tool rather than a standalone solution. Economic evaluations suggest cost-effectiveness in high-burden settings, though optimization of delivery strategies could improve value propositions. The immunological basis for protection and its temporal dynamics reflect the inherent challenges of inducing durable immunity against malaria parasites. While anti-CSP antibodies serve as correlates of protection, the modest correlation strength and rapid antibody decay highlight the need for improved understanding of protective mechanisms. Future research priorities include development of next-generation vaccines with enhanced immunogenicity, broader antigenic coverage, and improved durability of protection. The success of RTS,S implementation provides valuable lessons for deploying subsequent malaria vaccines and demonstrates the feasibility of integrating complex vaccination schedules into African healthcare systems. RTS, S vaccination should be implemented in high-transmission areas of sub-Saharan Africa as part of comprehensive malaria control programs that include insecticide-treated nets and case management, while continued investment in next-generation vaccine development remains essential for achieving substantial reductions in childhood malaria mortality.

REFERENCES

1. Tufail T, Agu PC, Akinloye DI, Obaroh IO. Malaria pervasiveness in Sub-Saharan Africa: Overcoming the scuffle. Medicine. 2024;103(49):e40241. doi:10.1097/MD.0000000000040241.
2. Kungu E, Inyangat R, Ugwu OPC, Alum EU. Exploration of Medicinal Plants Used in the Management of Malaria in Uganda. Newport Int J Res Med Sci. 2023;4(1):101-108. https://nijournals.org/wp-content/uploads/2023/10/NIJRMS-41101-108-2023.docx.pdf
3. Alum EU, Ugwu OPC, Egba SI, Uti DE, Alum BN. Climate Variability and Malaria Transmission: Unraveling the Complex Relationship. INOSR Sci Res. 2024;11(2):16-22. doi:10.59298/INOSRSR/2024/1.1.21622.
4. World Health Organization. World Malaria Report 2023. Geneva: WHO; 2023. https://www.who.int/publications/i/item/9789240086173
5. Cowman AF, Healer J, Marapana D, Marsh K. Malaria: Biology and Disease. Cell. 2016;167(3):610-624. doi:10.1016/j.cell.2016.07.055.
6. Mezieobi KC, Ugwu OPC, Uti DE, Egba SI, Ewah CM. Economic burden of malaria on developing countries: A mini review. Parasite Epidemiology and Control.30 (2025), e00435. https://doi.org/10.1016/j.parepi.2025.e00435
7. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature. 2015;526(7572):207-211. doi:10.1038/nature15535.
8. World Health Organization. Global Technical Strategy for Malaria 2016-2030. Geneva: WHO; 2015. https://www.who.int/publications/i/item/9789241564991
9. Hancock PA, Hendriks CJM, Tangena JA, et al. Mapping trends in insecticide resistance phenotypes in African malaria vectors. PLoS Biol. 2020;18(6):e3000633. doi:10.1371/journal.pbio.3000633.
10. Uwimana A, Legrand E, Stokes BH, et al. Emergence and clonal expansion of in vitro artemisinin-resistant Plasmodium falciparum kelch13 R561H mutant parasites in Rwanda. Nat Med. 2020;26(10):1602-1608. doi:10.1038/s41591-020-1005-2.
11. Draper SJ, Sack BK, King CR, et al. Malaria Vaccines: Recent Advances and New Horizons. Cell Host Microbe. 2018;24(1):43-56. doi:10.1016/j.chom.2018.06.008.
12. RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;386(9988):31-45. doi:10.1016/S0140-6736(15)60721-8.
13. World Health Organization. WHO recommends groundbreaking malaria vaccine for children at risk. Geneva: WHO; October 6, 2021. https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk
14. Laurens MB. RTS,S/AS01 vaccine (Mosquirix™): an overview. Hum Vaccin Immunother. 2020;16(3):480-489. doi:10.1080/21645515.2019.1669415.
15. Coppi A, Natarajan R, Pradel G, et al. The malaria circumsporozoite protein has two functional domains, each with distinct roles as sporozoites journey from mosquito to mammalian host. J Exp Med. 2011;208(2):341-356.
16. Vaughan AM, Kappe SHI. Malaria vaccine development: persistent challenges. Curr Opin Immunol. 2017;47:104-110. doi:10.1016/j.coi.2017.07.003.

17. Ngulube, P. (2023). Humoral Immune Responses to P. falciparum Circumsporozoite Protein (Pfcsp) Induced by the RTS, S Vaccine–Current Update. *Infection and Drug Resistance*, 2147-2157.
18. Hoffmann, S. (2025). A Long Story Short: Improving the B Cell Response to Plasmodium Falciparum Circumsporozoite Protein by Reducing the Number of Repeating NANP-Motifs (Doctoral dissertation).
19. Tan J, Sack BK, Oyen D, et al. A public antibody lineage that potently inhibits malaria infection through dual binding to the circumsporozoite protein. Nat Med. 2018;24(4):401-407. doi:10.1038/nm.4513.
20. Agnandji ST, Fernandes JF, Bache EB, Ramharter M. Clinical development of RTS,S/AS malaria vaccine: a systematic review of clinical Phase I-III trials. Future Microbiol. 2015;10(10):1553-1578. doi:10.2217/fmb.15.90.
21. Didierlaurent AM, Laupèze B, Di Pasquale A, et al. Adjuvant system AS01: helping to overcome the challenges of modern vaccines. Expert Rev Vaccines. 2017;16(1):55-63. doi:10.1080/14760584.2016.1213632.
22. Xiao, L., Kim, J., Lim, M., Dai, B., Yang, L., Reed, S. G., ... & Wang, P. (2012). A TLR4 agonist synergizes with dendritic cell-directed lentiviral vectors for inducing antigen-specific immune responses. *Vaccine*, *30*(15), 2570-2581.
23. Marty-Roix R, Vladimer GI, Pouliot K, et al. Identification of QS-21 as an Inflammasome-activating Molecular Component of Saponin Adjuvants. J Biol Chem. 2016;291(3):1123-1136. doi:10.1074/jbc.M115.683011.
24. Behet, M. C., Kurtovic, L., van Gemert, G. J., Haukes, C. M., Siebelink-Stoter, R., Graumans, W., ... & Sauerwein, R. W. (2018). The complement system contributes to functional antibody-mediated responses induced by immunization with Plasmodium falciparum malaria sporozoites. *Infection and immunity*, *86*(7), 10-1128.
25. Jongo SA, Church LWP, Mtoro AT, et al. Safety and Differential Antibody and T-Cell Responses to the Plasmodium falciparum Sporozoite Malaria Vaccine, PfSPZ Vaccine, by Age in Tanzanian Adults, Adolescents, Children, and Infants. Am J Trop Med Hyg. 2019;100(6):1433-1444. doi:10.4269/ajtmh.18-0835.
26. White MT, Verity R, Griffin JT, et al. Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. Lancet Infect Dis. 2015;15(12):1450-1458. doi:10.1016/S1473-3099(15)00239-X.
27. Olotu A, Fegan G, Wambua J, et al. Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children. N Engl J Med. 2016;374(26):2519-2529. doi:10.1056/NEJMoa1515257.
28. Cockburn IA, Seder RA. Malaria prevention: from immunological concepts to effective vaccines and protective antibodies. Nat Immunol. 2018;19(11):1199-1211. doi:10.1038/s41590-018-0228-6.
29. Kisalu NK, Idris AH, Weidle C, et al. A human monoclonal antibody prevents malaria infection by targeting a new site of vulnerability on the parasite. Nat Med. 2018;24(4):408-416. doi:10.1038/nm.4512.
30. Behet, M. C., Kurtovic, L., van Gemert, G. J., Haukes, C. M., Siebelink-Stoter, R., Graumans, W., ... & Sauerwein, R. W. (2018). The complement system contributes to functional antibody-mediated responses induced by immunization with Plasmodium falciparum malaria sporozoites. *Infection and immunity*, *86*(7), 10-1128.
31. Kurup, S. P., Butler, N. S., & Harty, J. T. (2019). T cell-mediated immunity to malaria. *Nature Reviews Immunology*, *19*(7), 457-471.
32. Ménard R, Tavares J, Cockburn I, et al. Looking under the skin: the first steps in malarial infection and immunity. Nat Rev Microbiol. 2013;11(10):701-712.
33. Steel, R. W., Chua, Y. C., Caiazzo, S., Hesping, E., Fernandez-Ruiz, D., Holz, L. E., ... & Boddey, J. A. (2025). Chemovaccination with a novel antimalarial targeting the late liver stage induces durable immunity against malaria. *bioRxiv*, 2025-07.
34. White MT, Griffin JT, Akpogheneta O, et al. Dynamics of the antibody response to Plasmodium falciparum infection in African children. J Infect Dis. 2014;210(7):1115-1122.
35. RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;386(9988):31-45. doi:10.1016/S0140-6736(15)60721-8.
36. Olotu A, Fegan G, Wambua J, et al. Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children. N Engl J Med. 2016;374(26):2519-2529. doi:10.1056/NEJMoa1515257.
37. Stanisic, D. I., Fowkes, F. J., Koinari, M., Javati, S., Lin, E., Kiniboro, B., ... & Beeson, J. G. (2015). Acquisition of antibodies against Plasmodium falciparum merozoites and malaria immunity in young children and the influence of age, force of infection, and magnitude of response. *Infection and immunity*, *83*(2), 646-660.

38. Chandramohan D, Zongo I, Sagara I, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med. 2021;385(11):1005-1017. doi:10.1056/NEJMoa2026330.
39. White MT, Verity R, Griffin JT, et al. Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. Lancet Infect Dis. 2015;15(12):1450-1458. doi:10.1016/S1473-3099(15)00239-X.
40. Dobaño C, Sanz H, Sorgho H, et al. Concentration and avidity of antibodies to different circumsporozoite epitopes correlate with RTS,S/AS01E malaria vaccine efficacy. Nat Commun. 2019;10(1):2174. doi:10.1038/s41467-019-10195-z.
41. Ubillos I, Ayestaran A, Nhabomba AJ, et al. Baseline exposure, antibody subclass, and hepatitis B response differentially affect malaria protective immunity following RTS,S/AS01E vaccination in African children. BMC Med. 2018;16(1):197. doi:10.1186/s12916-018-1186-4.
42. World Health Organization. WHO recommends groundbreaking malaria vaccine for children at risk. Geneva: WHO; October 6, 2021. https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk
44. Alum EU, Ainebyoona C, Egwu CO, Onohuean H, Ugwu OP, Uti DE, Alum BN, Echegu DA. Mitigation of Malaria in Sub-Saharan Africa through Vaccination: A Budding Road Map for Global Malaria Eradication. Ethiop J Health Sci. 2025 May;35(3):205-217. doi: 10.4314/ejhs.v35i3.9. PMID: 40717722; PMCID: PMC12287706.
45. Apanga S, Kumbeni MT, Ayamga EA, et al. Effectiveness of the RTS,S/AS01 malaria vaccine against clinical malaria in Ghanaian children: A case-control study. PLoS One. 2023;18(6):e0287084. doi:10.1371/journal.pone.0287084.
46. Mvamba E, Selemani M, Mwaiswelo RO, et al. Real-world effectiveness of the RTS,S/AS01 malaria vaccine in children aged 6-24 months in Kenya. Vaccine. 2023;41(Suppl 2):S146-S153. doi:10.1016/j.vaccine.2022.12.054.
47. Otieno NA, Otiato F, Nyawanda B, et al. Malaria vaccine effectiveness in preventing hospitalization with severe malaria in young children in a routine immunization program in Kenya. BMC Med. 2024;22(1):89. doi:10.1186/s12916-024-03298-x.
48. Mwenda JM, Mihigo R, Loharikar A, et al. Uptake of the RTS,S malaria vaccine in children in three malaria endemic countries in Africa. Vaccine. 2023;41(Suppl 2):S93-S100. doi:10.1016/j.vaccine.2022.10.013.
49. Otieno P, Otiato F, Odhiambo F, et al. Equity in coverage and access to RTS,S malaria vaccine: analysis of implementation in Kenya. Vaccine. 2023;41(Suppl 2):S101-S108. doi:10.1016/j.vaccine.2022.12.038.
50. Cowling K, Galactionova K, Tediosi F. Seasonal dynamics and the effect of RTS,S/AS01 malaria vaccination on Plasmodium falciparum transmission. Vaccine. 2021;39(41):6209-6217. doi:10.1016/j.vaccine.2021.08.092.
51. Chemba M, Masanja IM, Kamugisha E, et al. Impact of combining malaria vaccine with insecticide-treated nets on malaria incidence in children under five in Tanzania. Malar J. 2022;21(1):316. doi:10.1186/s12936-022-04335-2.
52. Winskill P, Walker PGT, Griffin JT, Ghani AC. Modelling the cost-effectiveness of introducing the RTS,S malaria vaccine relative to scaling up other malaria interventions in sub-Saharan Africa. BMJ Glob Health. 2017;2(1):e000090. doi:10.1136/bmjgh-2016-000090.
53. Datoo MS, Natama MH, Somé A, et al. Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial. Lancet Infect Dis. 2022;22(12):1728-1736. doi:10.1016/S1473-3099(22)00442-X.
54. Klein SL, Shann F, Moss WJ, Benn CS, Aaby P. RTS,S malaria vaccine and increased mortality in girls. mBio. 2016;7(2):e00514-16. doi:10.1128/mBio.00514-16.
55. Hamaluba M, Mugo D, Bett A, et al. Safety monitoring of RTS,S malaria vaccine in the first year of implementation in three African countries. Vaccine. 2023;41(Suppl 2):S118-S125. doi:10.1016/j.vaccine.2022.11.067.
56. Penny MA, Verity R, Bever CA, et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet. 2016;387(10016):367-375. doi:10.1016/S0140-6736(15)00725-4.
57. Galactionova K, Tediosi F, Camponovo F, et al. Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa. Vaccine. 2020;38(48):7511-7516. doi:10.1016/j.vaccine.2020.10.035.
58. Sim SY, Watts E, Constenla D, Brenzel L, Patenaude BN. Return on investment from immunization against 10 pathogens in 94 low- and middle-income countries, 2011-30. Health Aff (Millwood). 2020;39(8):1343-1353. doi:10.1377/hlthaff.2020.00103.

59. Crompton PD, Moebius J, Portugal S, et al. Malaria immunity in man and mosquito: insights into unsolved mysteries of a deadly infectious disease. Annu Rev Immunol. 2014;32:157-187.
60. Warimwe GM, Fletcher HA, Olotu A, et al. Peripheral blood monocyte-to-lymphocyte ratio at study enrollment predicts efficacy of the RTS,S malaria vaccine: analysis of pooled phase II clinical trial data. BMC Med. 2013;11:184.
61. White MT, Verity R, Griffin JT, et al. Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. Lancet Infect Dis. 2015;15(12):1450-1458. doi:10.1016/S1473-3099(15)00239-X.
62. Murungi LM, Sondén K, Llewellyn D, et al. Targets and Mechanisms Associated with Protection from Severe Plasmodium falciparum Malaria in Kenyan Children. Infect Immun. 2016;84(4):950-963. doi:10.1128/IAI.01120-15.
63. Jongo SA, Church LWP, Mtoro AT, et al. Increase of dose associated with decrease in protection against controlled human malaria infection by PfSPZ Vaccine in Tanzanian adults. Clin Infect Dis. 2020;71(7):e395-e404. doi:10.1093/cid/ciaa144.
64. Tan J, Sack BK, Oyen D, et al. A public antibody lineage that potently inhibits malaria infection through dual binding to the circumsporozoite protein. Nat Med. 2018;24(4):401-407. doi:10.1038/nm.4513.
65. Kurtovic L, Agius PA, Feng G, et al. Induction and decay of functional complement-fixing antibodies by the RTS,S malaria vaccine in children, and a negative impact of malaria exposure. BMC Med. 2019;17(1):45. doi:10.1186/s12916-019-1277-x.
66. Ndungu FM, Olotu A, Mwacharo J, et al. Memory B cells are a more reliable archive for historical antimalarial responses than plasma antibodies in no-longer exposed children. Proc Natl Acad Sci U S A. 2012;109(21):8247-8252
67. Murugan R, Buchauer L, Triller G, et al. Clonal selection drives protective memory B cell responses in controlled human malaria infection. Sci Immunol. 2018;3(20):eaap8029. doi:10.1126/sciimmunol.aap8029.
68. Obeng-Adjei N, Portugal S, Holla P, et al. Malaria-induced interferon-γ drives the expansion of Tbethi atypical memory B cells. PLoS Pathog. 2017;13(9):e1006576. doi:10.1371/journal.ppat.1006576.
69. Reyes-Sandoval A, Berthoud T, Alder N, et al. Prime-boost immunization with adenoviral and modified vaccinia virus Ankara vectors enhances the durability and polyfunctionality of protective malaria CD8+ T-cell responses. Infect Immun. 2010;78(1):145-153.
70. Ruterbusch, M., Pruner, K. B., Shehata, L., & Pepper, M. (2020). In vivo CD4+ T cell differentiation and function: revisiting the Th1/Th2 paradigm. *Annual review of immunology*, *38*(1), 705-725.
71. Olotu A, Fegan G, Wambua J, et al. Four-year efficacy of RTS,S/AS01E and its interaction with malaria exposure. N Engl J Med. 2013;368(12):1111-1120.
72. Vorkas CK, Levy O. Immunomodulatory adjuvants for vaccines in early life. Hum Vaccin Immunother. 2021;17(4):1063-1079. doi:10.1080/21645515.2020.1800323.
73. Kollmann TR, Kampmann B, Mazmanian SK, Marchant A, Levy O. Protecting the Newborn and Young Infant from Infectious Diseases: Lessons from Immune Ontogeny. Immunity. 2017;46(3):350-363. doi:10.1016/j.immuni.2017.03.009.
74. Greenwood B. The contribution of vaccination to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130433.
75. Penny MA, Verity R, Bever CA, et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet. 2016;387(10016):367-375. doi:10.1016/S0140-6736(15)00725-4.
76. Neafsey DE, Juraska M, Bedford T, et al. Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine. N Engl J Med. 2015;373(21):2025-2037. doi:10.1056/NEJMoa1505819.
77. Neafsey DE, Juraska M, Bedford T, et al. Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine. N Engl J Med. 2015;373(21):2025-2037. doi:10.1056/NEJMoa1505819.
78. Bejon P, White MT, Olotu A, et al. Efficacy of RTS,S malaria vaccines: individual-participant pooled analysis of phase 2 data. Lancet Infect Dis. 2013;13(4):319-327.
79. World Health Organization. Malaria vaccine: WHO position paper – January 2016. Wkly Epidemiol Rec. 2016;91(4):33-51. https://www.who.int/publications/i/item/WER9104
80. Datoo MS, Natama HM, Somé A, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet. 2021;397(10287):1809-1818. doi:10.1016/S0140-6736(21)00943-0.
81. Laurens MB. The Promise of a Malaria Vaccine—Are We Closer? Annu Rev Microbiol. 2018;72:273-292. doi:10.1146/annurev-micro-090817-062427.

82. Datoo MS, Natama MH, Somé A, et al. Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial. Lancet Infect Dis. 2022;22(12):1728-1736. doi:10.1016/S1473-3099(22)00442-X.
83. Sissoko MS, Healy SA, Katile A, et al. Safety and efficacy of PfSPZ Vaccine against Plasmodium falciparum via direct venous inoculation in healthy malaria-exposed adults in Mali: a randomised, double-blind phase 1 trial. Lancet Infect Dis. 2017;17(5):498-509. doi:10.1016/S1473-3099(17)30104-4.
84. Mordmüller B, Surat G, Lagler H, et al. Sterile protection against human malaria by chemoattenuated PfSPZ vaccine. Nature. 2017;542(7642):445-449. doi:10.1038/nature21060.
85. Didierlaurent AM, Laupèze B, Di Pasquale A, et al. Adjuvant system AS01: helping to overcome the challenges of modern vaccines. Expert Rev Vaccines. 2017;16(1):55-63. doi:10.1080/14760584.2016.1213632.
86. Seth L, Ferlez KMB, Kaba SA, et al. Development of a self-assembling protein nanoparticle vaccine targeting Plasmodium falciparum Circumsporozoite Protein delivered in three Army Liposome Formulation adjuvants. Vaccine. 2017;35(41):5448-5454. doi:10.1016/j.vaccine.2017.02.040.
87. Ewer KJ, O'Hara GA, Duncan CJA, et al. Protective CD8+ T-cell immunity to human malaria induced by chimpanzee adenovirus-MVA immunisation. Nat Commun. 2013;4:2836.
88. Sirima SB, Richert L, Chêne A, et al. PRIMVAC vaccine adjuvanted with Alhydrogel or GLA-SE to prevent placental malaria: a first-in-human, randomised, double-blind, placebo-controlled study. Lancet Infect Dis. 2020;20(5):585-597. doi:10.1016/S1473-3099(19)30739-X.
89. Theisen M, Adu B, Mordmüller B, Singh S. The GMZ2 malaria vaccine: from concept to efficacy in humans. Expert Rev Vaccines. 2017;16(9):907-917. doi:10.1080/14760584.2017.1355246.
90. Kazmin D, Nakaya HI, Lee EK, et al. Systems analysis of protective immune responses to RTS,S malaria vaccination in humans. Proc Natl Acad Sci U S A. 2017;114(9):2425-2430. doi:10.1073/pnas.1621489114.
91. Li S, Rouphael N, Duraisingham S, et al. Molecular signatures of antibody responses derived from a systems biology study of five human vaccines. Nat Immunol. 2014;15(2):195-204.

CITE AS: Namukasa Mugerwa F. (2026). RTS, S Vaccine Efficacy in Sub-Saharan African Children: Long-term Protection Assessment. Research Output Journal of Public Health and Medicine 6(1):78-86. https://doi.org/10.59298/ROJPHM/2026/617886