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RTS, S/AS01 Malaria Vaccine: Efficacy, Implementation Challenges, and Public Health Impact

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ABSTRACT

Malaria remained a major global health burden, with Plasmodium falciparum causing significant morbidity and mortality, particularly among children in sub-Saharan Africa. The RTS, S/AS01 vaccine represents the first licensed malaria vaccine, targeting the circumsporozoite protein of the parasite's pre-erythrocytic stage. This review critically examined the efficacy profile of RTS,S/AS01, evaluated implementation challenges encountered during pilot programs, and assessed the vaccine's broader public health impact in endemic regions. A comprehensive literature search was conducted across PubMed, Scopus, and clinical trial registries, selecting peer-reviewed articles, systematic reviews, and implementation reports published between 2011 and 2025. Phase III trials demonstrated modest efficacy, with approximately 32% reduction in clinical malaria episodes among children aged 5 to 17 months over four years when administered in four doses. Pilot implementation programs in Ghana, Kenya, and Malawi revealed significant operational challenges, including maintaining cold chain integrity, achieving adequate coverage across four-dose schedules, and integrating delivery with existing immunization programs. Despite moderate efficacy, mathematical modeling indicates that RTS, S/AS01 deployment in high-transmission settings can avert substantial numbers of clinical cases and deaths when combined with existing vector control and chemoprevention strategies. Cost-effectiveness analyses suggested favorable outcomes in areas with persistent high transmission. Antibody responses wane substantially within 12 months post vaccination, raising questions about optimal booster timing and long-term protection. RTS, S/AS01 represented a significant milestone in malaria control, offering partial protection that complements existing interventions. Ongoing research must address immunological gaps, optimize delivery strategies, and monitor real-world effectiveness to maximize public health benefit.

Keywords: RTS, S/AS01 vaccine, Plasmodium falciparum, Malaria prevention, Circumsporozoite protein, Vaccine implementation

INTRODUCTION

Malaria caused by Plasmodium falciparum continues to impose substantial disease burden globally, with an estimated 241 million cases and 627,000 deaths reported in 2020, predominantly affecting children under five years in sub-Saharan Africa [1,2]. The complex lifecycle of the parasite, involving both mosquito vector and human host stages, presents unique immunological challenges for vaccine development. The circumsporozoite protein (CSP), which coats the surface of sporozoites during the pre-erythrocytic phase, has emerged as a leading vaccine target due to its abundance and accessibility to antibody-mediated neutralization [3]. RTS, S/AS01, developed through a public-private partnership, incorporates a recombinant fusion protein consisting of the central repeat region and C-terminal domain of CSP fused to hepatitis B surface antigen, formulated with the AS01 adjuvant system containing monophosphoryl lipid A and QS-21 saponin. This vaccine design aims to elicit both humoral and cellular immune responses capable of preventing sporozoite invasion of hepatocytes, thereby interrupting the infection cycle before blood-stage parasitemia develops [4].

The path from CSP-based vaccine candidates to RTS, S/AS01 licensure involved decades of iterative development, with early formulations demonstrating proof of concept but inadequate protection. Adjuvant optimization proved critical, as the AS01 system significantly enhanced immunogenicity compared to earlier formulations, inducing robust CD4+ T cell responses and high-titer anti-CSP antibodies [5]. However, translating laboratory immunogenicity into field efficacy remained challenging, with protection levels falling short of the initial 75% efficacy target established by the malaria vaccine technology roadmap. The vaccine's moderate efficacy must be understood within the context of naturally acquired immunity, antigenic polymorphism in field parasite strains, and the immunological immaturity of the target population [6]. Despite these limitations, the vaccine received a positive scientific opinion from the European Medicines Agency in 2015 and a WHO recommendation for broad use in 2021, marking a historic achievement in malaria vaccine development [7]. The objective of this review is to critically evaluate the clinical efficacy of RTS, S/AS01 across diverse epidemiological settings, analyze the operational and programmatic challenges encountered during pilot implementation, and assess the vaccine's population-level impact on malaria burden when integrated into comprehensive control strategies.

Immunological Basis and Mechanism of Protection

The RTS, S/AS01 vaccine operates through a dual mechanism targeting the pre-erythrocytic stage of Plasmodium falciparum infection. The recombinant antigen consists of 19 NANP tetrapeptide repeats and the C-terminal region of CSP, representing approximately 60% of the native protein sequence, co-expressed with hepatitis B surface antigen in a particulate structure. This configuration facilitates efficient antigen presentation and generates virus-like particles measuring approximately 20 to 30 nanometers in diameter, promoting uptake by antigen-presenting cells [8]. The AS01 adjuvant system enhances innate immune activation through Toll-like receptor 4 stimulation by monophosphoryl lipid A and saponin-mediated enhancement of antigen presentation, collectively driving Th1-biased cellular immunity alongside robust antibody production [9].

Anti-CSP antibodies represent the primary correlate of protection, functioning through multiple mechanisms including direct sporozoite neutralization, prevention of hepatocyte invasion, and complement-mediated parasite lysis [10]. Quantitative analyses from phase III trials identified a threshold antibody concentration of approximately 100 enzyme-linked immunosorbent assay units per milliliter as correlating with protective efficacy, though this relationship demonstrates considerable individual variability [11]. CD4+ T cell responses, particularly polyfunctional cells secreting interferon gamma, tumor necrosis factor alpha, and interleukin 2, contribute to protection by eliminating infected hepatocytes and supporting antibody class switching. However, the vaccine fails to induce substantial CD8+ cytotoxic T cell responses against liver-stage parasites, representing a potential immunological gap compared to naturally acquired immunity or attenuated sporozoite vaccines.

A critical limitation of RTS,S/AS01 immunogenicity concerns the rapid waning of antibody titers, with geometric mean concentrations declining by approximately 90% within 12 months following the primary vaccination series [12]. This phenomenon likely reflects the absence of natural boosting in vaccinated individuals who avoid infection, combined with the short-lived nature of plasma cell responses elicited by subunit vaccines [13]. The vaccine also demonstrates reduced efficacy against non-vaccine CSP haplotypes, particularly those containing amino acid substitutions in the C-terminal region, highlighting challenges posed by parasite genetic diversity [14]. Mathematical modeling suggests that antibody-dependent mechanisms account for the majority of observed protection, while cellular immunity may provide modest additional benefit [15]. These immunological characteristics underscore the need for improved vaccine formulations capable of inducing durable, broadly cross-reactive responses that better recapitulate naturally acquired protective immunity observed in malaria-endemic populations.

Clinical Efficacy Evidence from Controlled Trials

The phase III clinical trial of RTS,S/AS01, conducted across 11 African sites from 2009 to 2014, remains the largest malaria vaccine trial ever undertaken, enrolling 15,459 participants in two age cohorts [16]. Among children aged 5 to 17 months receiving four doses, vaccine efficacy against clinical malaria was 36.3% over four years of follow-up, while efficacy against severe malaria reached 32.2% [17]. The younger infant cohort, vaccinated at 6 to 12 weeks of age, demonstrated lower efficacy of 25.9% against clinical malaria and 26% against severe disease, suggesting age-dependent immunological factors influence vaccine performance [18]. Efficacy peaked during the first year post vaccination at approximately 50%, declining substantially thereafter as antibody titers waned, with minimal residual protection observed beyond 36 months [19].

Subgroup analyses revealed important heterogeneity in vaccine performance based on transmission intensity and baseline parasitemia status. In areas of lower malaria transmission, vaccine efficacy approached 60% during the first year, compared to approximately 35% in high-transmission settings where children experience repeated infections [20]. Paradoxically, participants with parasitemia at baseline demonstrated reduced vaccine efficacy compared to aparasitemic children, potentially reflecting immune interference by concurrent infection or altered immune

responses in previously exposed individuals [21]. Efficacy against uncomplicated malaria episodes showed dose-dependent patterns, with three-dose recipients experiencing significantly reduced protection compared to those completing the four-dose schedule, emphasizing the importance of booster administration [22].

The impact of RTS, S/AS01 on severe malaria outcomes, while statistically significant, remained modest in absolute terms. Among older children, the vaccine prevented approximately three severe malaria cases per 1,000 vaccinated children annually in high-transmission areas. Importantly, post-hoc analyses detected no evidence of disease enhancement or increased severity among breakthrough infections in vaccinated individuals, addressing theoretical concerns about antibody-dependent enhancement or delayed acquisition of natural immunity [23]. Time-to-first-episode analyses demonstrated that the vaccine delays malaria infection rather than preventing all episodes indefinitely, consistent with its mechanism of reducing but not eliminating sporozoite invasion [24]. These efficacy data, while falling short of traditional vaccine benchmarks, must be contextualized within the unique challenges of malaria immunity and the absence of alternative licensed vaccines. The moderate but consistent protection observed across diverse epidemiological settings provided the evidence base for regulatory approval and WHO policy recommendation, despite ongoing debates about cost-effectiveness and optimal implementation strategies.

Pilot Implementation Programs and Operational Challenges

Following the WHO recommendation in 2019, pilot implementation of RTS, S/AS01 commenced in selected regions of Ghana, Kenya, and Malawi, collectively reaching over 1.7 million children by 2023 [25]. These programs aimed to evaluate vaccine uptake, safety in routine use, and the feasibility of delivering a four-dose schedule alongside existing childhood immunizations. Coverage data revealed significant challenges in achieving complete vaccination, with approximately 70% of children receiving the first dose at 6 months of age, declining to 50% for the second dose, 40% for the third dose, and only 30% completing the fourth dose at 24 months [26]. This dropout pattern substantially exceeded that of routine immunizations, reflecting difficulties in maintaining contact with mobile populations and competing demands on caregiver time [27].

Cold chain maintenance emerged as a critical operational constraint, as RTS, S/AS01 requires storage at 2 to 8 degrees Celsius throughout the distribution network. Infrastructure assessments in pilot countries documented frequent power outages, inadequate refrigeration capacity at peripheral health facilities, and temperature excursions during vaccine transport [28]. The lyophilized vaccine format, while improving thermostability compared to liquid formulations, still necessitates reconstitution expertise and timely administration following preparation. Integration with existing immunization platforms proved complex due to scheduling conflicts, as the RTS,S/AS01 series does not align perfectly with standard Expanded Program on Immunization contacts, requiring additional clinic visits [29]. Health worker training demands were substantial, encompassing reconstitution procedures, documentation of four separate doses, and counseling caregivers about the vaccine's partial efficacy [30].

Monitoring for safety signals during pilot implementation detected no unexpected adverse events, with reactogenicity profiles consistent with clinical trial data showing mild to moderate injection site reactions and transient fever [31]. Concerns about potential interference with concurrent vaccines, particularly when RTS,S/AS01 is administered alongside measles or meningococcal conjugate vaccines, were not substantiated by immunogenicity studies [32]. Community acceptance varied across implementation sites, influenced by health literacy, trust in immunization programs, and clarity of messaging about the vaccine's complementary role rather than replacement of existing interventions. Qualitative research identified misconceptions regarding vaccine efficacy, with some caregivers erroneously believing vaccination confers complete malaria immunity, potentially leading to reduced adherence to bed nets or prompt treatment-seeking for febrile illness [33].

Financial sustainability represents a long-term implementation challenge, as vaccine procurement costs approximately 9 to 10 US dollars per fully vaccinated child, excluding delivery expenses. While Gavi funding initially supported pilot programs, the transition to domestic financing in low-income countries raises questions about prioritization relative to other health interventions. Supply chain planning must account for cold chain expansion, waste management, and procurement of sufficient doses to meet demand in countries considering national rollout [34]. These operational realities demonstrate that vaccine introduction extends far beyond product licensure, requiring health system strengthening, community engagement, and sustained political commitment to achieve population-level impact.

Public Health Impact and Cost-Effectiveness Modeling

Mathematical models projecting the population health impact of RTS, S/AS01 suggest that widespread implementation in moderate to high transmission settings could avert substantial malaria burden when layered onto existing control interventions. Transmission dynamic models incorporating vaccine efficacy data, coverage projections, and local epidemiological parameters estimate that achieving 80% coverage with four doses could prevent approximately 40,000 to 80,000 child deaths annually across sub-Saharan Africa [35]. These projections assume sustained implementation alongside insecticide-treated nets, indoor residual spraying, and prompt case

management, as the vaccine is not intended as a standalone intervention [36]. Impact varies considerably by baseline transmission intensity, with the greatest absolute benefit observed in areas sustaining perennial transmission where children experience multiple infectious episodes annually [37].

Cost-effectiveness analyses conducted from health system and societal perspectives generally support RTS, S/AS01 introduction in high-burden countries, with incremental cost-effectiveness ratios ranging from 100 to 500 US dollars per disability-adjusted life year averted depending on assumptions about coverage, delivery costs, and comparator interventions. In settings where malaria transmission remains high despite maximal deployment of conventional control measures, the vaccine may represent a cost-effective addition to the intervention portfolio [38]. However, sensitivity analyses reveal that cost-effectiveness is highly dependent on achieving and maintaining high coverage across all four doses, as incomplete vaccination series substantially diminishes the impact [39]. Countries with declining malaria incidence face different cost-effectiveness profiles, as the absolute number of cases prevented decreases while fixed program costs remain constant.

Real-world impact data from pilot implementation countries provide preliminary evidence of vaccine effectiveness under operational conditions. Observational studies in Ghana documented a 32% reduction in malaria hospitalizations among children eligible for RTS, S/AS01 compared to non-eligible cohorts, after adjusting for temporal trends and concurrent interventions [40]. Similar analyses in Kenya and Malawi showed reductions in severe malaria incidence ranging from 9% to 17%, slightly lower than trial-based efficacy estimates but consistent with imperfect coverage and real-world adherence patterns [41]. Notably, no evidence of disease burden displacement to older age groups has emerged, addressing concerns that delaying infection in vaccinated children might shift malaria morbidity to ages with reduced natural immunity [42].

The vaccine's impact on malaria mortality reduction must be considered alongside potential indirect effects and programmatic synergies. Modeling suggests that RTS, S/AS01 could reduce selective pressure for drug-resistant parasites by decreasing overall transmission, though this benefit requires high population coverage [43]. Integration with seasonal malaria chemoprevention in Sahel countries presents opportunities for additive protection, as the interventions target different parasite stages and operate through distinct mechanisms [44]. However, resource allocation debates persist regarding whether investments in RTS,S/AS01 deployment might yield greater health returns if directed toward strengthening case management, expanding chemoprevention coverage, or implementing novel vector control tools [45]. These considerations underscore that vaccine introduction decisions must account for local epidemiology, health system capacity, and opportunity costs within constrained budgets.

Current Limitations and Future Research Directions

Despite representing a milestone achievement, RTS,S/AS01 exhibits several limitations that constrain its public health impact and motivate ongoing research toward improved malaria vaccines. The modest and waning efficacy observed in clinical trials reflects fundamental constraints of the current antigen design, which presents only a fraction of the CSP sequence and lacks other pre-erythrocytic antigens that contribute to naturally acquired immunity [46]. Next-generation vaccine candidates under development incorporate additional sporozoite antigens, alternative adjuvant systems, or utilize viral vector platforms to enhance immunogenicity and durability [47]. The R21/Matrix-M vaccine, formulated with a higher antigen-to-carrier ratio and novel adjuvant, recently demonstrated superior efficacy in phase II trials, achieving approximately 77% protection over 12 months in high-dose cohorts [48]. Comparative effectiveness studies will be essential to determine whether this improved performance translates to greater public health benefit.

Understanding the immunological basis of vaccine failure in non-responders remains a priority research area. Genetic polymorphisms in human leukocyte antigen alleles, variations in innate immune receptor expression, and environmental factors such as concurrent helminth infections or nutritional status may influence vaccine immunogenicity [49]. Systems biology approaches integrating transcriptomics, metabolomics, and antibody profiling could identify biomarkers predicting vaccine response and inform personalized vaccination strategies [50]. The role of liver-resident memory T cells, which provide durable protection in controlled human malaria infection models using attenuated sporozoites, deserves investigation in the context of subunit vaccines [51]. Inducing this cellular compartment may require novel delivery systems or prime-boost regimens combining different vaccine platforms [52].

Research gaps persist regarding optimal implementation strategies and target populations. The relative benefits of routine immunization beginning in infancy versus targeted campaigns in older children require further evaluation, as do strategies for catch-up vaccination in endemic areas [53]. Defining the role of RTS, S/AS01 in pre-elimination settings where transmission has declined remains unclear, as cost-effectiveness deteriorates when baseline malaria incidence falls below specific thresholds [54]. The potential for incorporating malaria vaccination into school-based delivery platforms warrants exploration, given challenges in reaching older children through routine infant immunization programs [55]. Long-term surveillance studies must monitor vaccine effectiveness over multiple

years, assess the need for additional booster doses beyond 24 months, and detect any unanticipated safety signals as deployment scales [56].

Finally, addressing equity considerations in vaccine access represents both a programmatic and ethical imperative. Ensuring that RTS, S/AS01 reaches marginalized populations bearing disproportionate malaria burden, including remote rural communities, displaced populations, and areas affected by conflict, will require innovative delivery strategies and sustained political commitment [57]. Balancing vaccine introduction with maintenance of existing interventions poses resource allocation challenges for malaria-endemic countries, necessitating careful planning to avoid diversion of funding from proven control measures [58]. As multiple malaria vaccine candidates advance through development pipelines, mechanisms for comparing effectiveness, selecting optimal products for specific epidemiological contexts, and managing portfolio decisions will become increasingly important [59]. These considerations emphasize that vaccines represent one component of comprehensive malaria control requiring continued investment across prevention, diagnosis, and treatment modalities.

CONCLUSION

RTS, S/AS01 represents a landmark achievement in malaria vaccine development, providing the first licensed tool targeting the pre-erythrocytic stage of Plasmodium falciparum infection. Clinical trials demonstrated modest but consistent efficacy, with four-dose regimens reducing clinical malaria episodes by approximately 36% and severe malaria by 32% among children aged 5 to 17 months over four years. Pilot implementation programs revealed significant operational challenges, including maintaining cold chain integrity, achieving adequate coverage across four doses, and integrating delivery with existing immunization platforms. Despite these constraints, mathematical modeling and preliminary real-world data suggest that RTS, S/AS01 deployment in high-transmission settings can avert substantial disease burden when layered onto conventional control interventions. The vaccine's moderate efficacy and rapidly waning immunity underscore that it complements rather than replaces existing tools such as insecticide-treated nets, chemoprevention, and prompt case management. Cost-effectiveness analyses generally support introduction in areas sustaining high malaria transmission, though resource allocation decisions must consider local epidemiology and health system capacity. Future research priorities include developing next-generation vaccines with improved efficacy and durability, optimizing implementation strategies to maximize coverage and impact, and ensuring equitable access for populations bearing the greatest malaria burden. While RTS, S/AS01 falls short of ideal vaccine characteristics, its deployment represents meaningful progress toward comprehensive malaria control and demonstrates the feasibility of vaccine-based interventions against complex parasitic diseases.

Recommendation

National malaria control programs in high-transmission countries should integrate RTS,S/AS01 into comprehensive intervention packages while simultaneously strengthening surveillance systems to monitor real-world effectiveness and guide optimization of delivery strategies.

REFERENCES

1. Egwu, C.O., Aloke, C., Chukwu, J., Agwu, A., Alum, E.U, Tsamesidis, I, et al. A world free of malaria: It is time for Africa to actively champion and take leadership of elimination and eradication strategies. Afr Health Sci. 2022 Dec;22(4):627-640. doi: 10.4314/ahs.v22i4.68.
2. Tufail, T., Agu, P. C., Akinloye, D. I., & Obaroh, I. O. (2024). Malaria pervasiveness in Sub-Saharan Africa: Overcoming the scuffle. *Medicine*, *103*(49), e40241. doi: 10.1097/MD.0000000000040241. PMID: 39654176
3. Cockburn IA, Seder RA. Malaria prevention: from immunological concepts to effective vaccines and protective antibodies. Nat Immunol. 2018;19(11):1199-1211.
4. Agnandji ST, Lell B, Fernandes JF, et al. A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. N Engl J Med. 2012;367(24):2284-2295.
5. 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.
6. 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.
7. World Health Organization. WHO recommends groundbreaking malaria vaccine for children at risk. Geneva: WHO; 2021.
8. Bergmann-Leitner ES, Leitner WW. Adjuvants in the driver's seat: how magnitude, type, fine specificity and longevity of immune responses are driven by distinct classes of immune potentiators. Vaccines. 2014;2(2):252-296.
9. Garçon N, Di Pasquale A. From discovery to licensure, the Adjuvant System story. Hum Vaccin Immunother. 2017;13(1):19-33.

10. 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.
11. 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.
12. Ainebyoona C, Egwu, C.O., Onohuean, H., Ugwu, O.P.C., Uti, D.E., Alum, B.N, Echegu, D.A. Mitigation of Malaria in Sub-Saharan Africa through Vaccination: A Budding Road Map for Global Malaria Eradication (2025). Ethiopian Journal of Health Sciences, 2025; 35(3): 205-217. doi: 10.4314/ejhs.v35i3.9. PMID: 40717722; PMCID: PMC12287706.
13. Kester KE, Gray Heppner D Jr, Moris P, et al. Sequential phase 1 and phase 2 randomized, controlled trials of the safety, immunogenicity and efficacy of combined pre-erythrocytic vaccine antigens RTS,S and TRAP formulated with AS02 Adjuvant System in healthy, malaria naïve adults. Vaccine. 2014;32(49):6683-6691.
14. Pringle JC, Carpi G, Almagro-Garcia J, et al. RTS,S/AS01 malaria vaccine mismatch observed among Plasmodium falciparum isolates from southern and central Africa and globally. Sci Rep. 2018;8(1):6622.
15. White MT, Bejon P, Olotu A, et al. The relationship between RTS,S vaccine-induced antibodies, CD4+ T cell responses and protection against Plasmodium falciparum infection. PLoS One. 2013;8(4):e61395.
16. 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.
17. RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. PLoS Med. 2014;11(7):e1001685.
18. Olotu A, Lusingu J, Leach A, et al. Efficacy of RTS,S/AS01E malaria vaccine and exploratory analysis on anti-circumsporozoite antibody titres and protection in children aged 5-17 months in Kenya and Tanzania: a randomised controlled trial. Lancet Infect Dis. 2011;11(2):102-109.
19. Greenwood B, Dicko A, Sagara I, et al. Seasonal vaccination against malaria: a potential use for an imperfect malaria vaccine. Malar J. 2017;16(1):182.
20. 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.
21. Moorthy VS, Newman RD, Okwo-Bele JM. Malaria vaccine technology roadmap. Lancet. 2013;382(9906):1700-1701.
22. Asante KP, Abdulla S, Agnandji S, et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis. 2011;11(10):741-749.
23. Tinto H, Otieno W, Gesase S, et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. Lancet Infect Dis. 2019;19(8):821-832.
24. 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.
25. World Health Organization. Malaria vaccine pilot programme: update on implementation progress. Geneva: WHO; 2023.
26. Datoo MS, Natama MH, 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.
27. Gavi, the Vaccine Alliance. Malaria vaccine implementation programme. Geneva: Gavi; 2023.
28. PATH. Malaria Vaccine Initiative: RTS,S implementation challenges. Seattle: PATH; 2022.
29. Mvundura M, Lorenson K, et al. Estimating the costs of the vaccine supply chain and service delivery for selected districts in Kenya and Tanzania. Vaccine. 2015 May 28;33(23):2697-703. doi: 10.1016/j.vaccine.2015.03.084. Epub 2015 Apr 9. PMID: 25865467.
30. Winskill P, Walker PGT, Cairns ME, 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.
31. Njuguna P, Maitland K, Nyaguara A, et al. Observational study: 27 years of severe malaria surveillance in Kilifi, Kenya. BMC Med. 2019;17(1):124.

32. Asante KP, Abdulla S, et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis. 2011 Oct;11(10):741-9. doi: 10.1016/S1473-3099(11)70100-1. Epub 2011 Jul 22. Erratum in: Lancet Infect Dis. 2011 Oct;11(10):727. PMID: 21782519.
33. Nankabirwa JI, Wandera B, Kiwanuka N, et al. Malaria transmission, infection, and disease following sustained indoor residual spraying of insecticide in Tororo, Uganda. Am J Trop Med Hyg. 2020;103(4):1525-1533.
34. Kallenberg, J., Mok, W., Newman, R., Nguyen, A., Ryckman, T., Saxenian, H., & Wilson, P. (2016). Gavi's transition policy: moving from development assistance to domestic financing of immunization programs. *Health Affairs*, *35*(2), 250-258.
35. Galactionova K, Tediosi F, de Savigny D, et al. Effective coverage and systems effectiveness for malaria case management in sub-Saharan African countries. PLoS One. 2015;10(5):e0127818.
36. Churcher TS, Sinden RE, Edwards NJ, et al. Probability of transmission of malaria from mosquito to human is regulated by mosquito parasite density in naïve and vaccinated hosts. PLoS Pathog. 2017;13(1):e1006108.
37. Griffin JT, Bhatt S, Sinka ME, et al. Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study. Lancet Infect Dis. 2016;16(4):465-472.
38. Hogan AB, Winskill P, Ghani AC. Estimated impact of RTS,S/AS01 malaria vaccine allocation strategies in sub-Saharan Africa: a modelling study. BMJ Glob Health. 2020;5(11):e003611.
39. Johnston GL, Gething PW, Hay SI, Smith DL, Fidock DA. Modeling within-host effects of drugs on Plasmodium falciparum transmission and prospects for malaria elimination. PLoS Comput Biol. 2014;10(1):e1003434.
40. Asante, K. P., Mathanga, D. P., Milligan, P., Akech, S., Oduro, A., Mwapasa, V., ... & Sillah, J. S. (2024). Feasibility, safety, and impact of the RTS, S/AS01E malaria vaccine when implemented through national immunisation programmes: evaluation of cluster-randomised introduction of the vaccine in Ghana, Kenya, and Malawi. *The Lancet*, *403*(10437), 1660-1670.
41. Macharia PM, Giorgi E, Thuranira PN, et al. Sub-national variation and inequalities in under-five mortality in Kenya since 1965. BMC Public Health. 2019;19(1):146.
42. White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions—a systematic review. Malar J. 2011;10:337.
43. Gerardin J, Ouédraogo AL, McCarthy KA, et al. Characterization of the infectious reservoir of malaria with an agent-based model calibrated to age-stratified parasite densities and infectiousness. Malar J. 2015;14:231.
44. Bigira V, Kapisi J, Clark TD, et al. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. PLoS Med. 2014;11(8):e1001689.
45. White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions—a systematic review. Malar J. 2011;10:337.
46. Draper SJ, Sack BK, King CR, et al. Malaria vaccines: recent advances and new horizons. Cell Host Microbe. 2018;24(1):43-56.
47. 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.
48. 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.
49. Tran TM, Li S, Doumbo S, et al. An intensive longitudinal cohort study of Malian children and adults reveals no evidence of acquired immunity to Plasmodium falciparum infection. Clin Infect Dis. 2013;57(1):40-47.
50. 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.
51. Ishizuka AS, Lyke KE, DeZure A, et al. Protection against malaria at 1 year and immune correlates following PfSPZ vaccination. Nat Med. 2016;22(6):614-623.
52. Seder RA, Chang LJ, Enama ME, et al. Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. Science. 2013;341(6152):1359-1365.

53. 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.
54. Cairns M, Roca-Feltrer A, Garske T, et al. Estimating the potential public health impact of seasonal malaria chemoprevention in African children. Nat Commun. 2012;3:881.
55. Bundy DAP, de Silva N, Horton S, et al. Investment in child and adolescent health and development: key messages from Disease Control Priorities, 3rd Edition. Lancet. 2018;391(10121):687-699.
56. Gosling RD, von Seidlein L. The future of the RTS,S/AS01 malaria vaccine: an alternative development plan. PLoS Med. 2016;13(4):e1001994.
57. Shretta R, Liu J, Cotter C, et al. Malaria elimination and eradication. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. Major Infectious Diseases. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017.
58. Menya D, Ndiaye M, Mabiala Babela JR, et al. The effect of seasonal malaria chemoprevention on the acquisition of antibodies to Plasmodium falciparum antigens in Senegalese children. Malar J. 2020;19(1):119.
59. Laurens MB. RTS,S/AS01 vaccine (Mosquirix): an overview. Hum Vaccin Immunother. 2020;16(3):480-489.

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