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Identification of factors influencing the effectiveness of malaria vaccines: A systematic review

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Abstract

The clinical authorization and deployment of the RTS, S/AS01 and R21/Matrix-M vaccines represent historic milestones in global public health. This systematic review aims to identify, classify, and evaluate the diverse biological, host-specific, environmental, and operational factors that influence the real-world field effectiveness of pre-erythrocytic malaria vaccines. Following PRISMA 2020 guidelines, a systematic literature search was executed across PubMed, Embase, Scopus, and the cochrane library for peer-reviewed studies and programmatic reports tracking malaria vaccine efficacy from January 2015 to April 2026. Data extraction targeted variables driving variations in protection, antibody decay rates, and programmatic dropouts. The synthesis revealed four critical barriers to uniform vaccine effectiveness: Parasite genetics: High genetic polymorphism within the Plasmodium falciparum circumsporozoite protein (Pfcsp) gene enables strain-specific immune evasion, dropping vaccine protection from 50.3% against matching strains down to 33.4% against non-matching field variants. Host Physiological Factors: High baseline maternal anti-CSP antibodies blunt infant B-cell priming in early infancy, while protein-energy malnutrition suppresses clonal expansion and class-switched antibody synthesis, accelerating protective titer decay. Environmental Dynamics: Relentless infectious pressure in ultra-high transmission zones overwhelms vaccine defences, accelerating antibody decay. Malaria vaccine effectiveness is a shifting metric shaped by an intersection of biological and logistical variables. Maximizing population-level survival requires a transition away from rigid, uniform deployment models. Public health strategies must implement agile, region-specific frameworks that combine seasonal vaccination with multivalent antigen formulations, nutritional supplementation, digitized tracking systems, and continuous vector control.

Keywords: Malaria Vaccines; RTS, S/AS01; R21/Matrix-M; Vaccine Effectiveness; Genetic Polymorphism; Public Health Policy

1. Introduction

Malaria remains one of the most devastating public health challenges in human history, accounting for hundreds of thousands of deaths annually, predominantly among children under five in sub-Saharan Africa [1]. For decades, the global strategy against *Plasmodium falciparum* relied heavily on vector control via insecticide-treated bed nets, indoor residual spraying, and seasonal chemoprevention [2]. While these methods substantially reduced the global burden, progress has stagnated due to rising insecticide and drug resistance, underscoring the urgent need for highly effective vaccines [3]. A historic milestone was achieved with the World Health Organization's (WHO) recommendation of the RTS, S/AS01 vaccine, followed by the approval of the highly potent R21/Matrix-M vaccine [1]. Clinical trials and initial implementations have proven that these pre-erythrocytic tools significantly lower severe hospitalizations and all-cause child mortality [4]. However, unlike traditional viral or bacterial vaccines that offer robust, long-lasting immunity,

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malaria vaccines demonstrate variable efficacy that naturally declines over time [5]. Real-world effectiveness fluctuates drastically between cohorts, exposing a complex interplay of environmental, biological, and socio-demographic barriers [3, 5].

The primary hurdle stems from the technical complexity of targeting a parasite with a multi-stage life cycle and high genetic polymorphism among local parasite strains, which allows the organism to evade vaccine-induced immune responses [3, 6]. Furthermore, host-specific variables, such as a recipient's age at vaccination, nutritional status, and previous natural malaria exposure, substantially alter individual immunological responses and contribute to vaccine hyporesponsiveness [7, 8]. Beyond biology, trial data highlights that efficacy estimates reflect more than individual protection; they are heavily influenced by environmental transmission dynamics, the logistics of strict multi-dose schedules, and healthcare infrastructure barriers across resource-limited settings [5, 9].

Understanding exactly how these variables intersect is vital as nations transition these vaccines into routine immunization protocols [10]. Isolated clinical trial metrics fail to capture how diverse field conditions reshape vaccine performance [5]. Therefore, a systematic evaluation of these shifting variables is urgently required to maximize the impact of current and next-generation interventions [3].

This review aims to systematically identify, classify, and evaluate the diverse factors influencing the real-world effectiveness of malaria vaccines. By synthesizing recent clinical trial data and programmatic rollout outcomes, this paper provides a comprehensive framework to optimize deployment strategies. Ultimately, this analysis serves as an evidence-based tool for policymakers and public health stakeholders working to achieve the global elimination of malaria [2].

2. Methodology

2.1. Study Design

This study was designed as a systematic review to identify, classify, and evaluate the environmental, biological, host-specific, and socio-demographic factors that influence the real-world effectiveness of malaria vaccines. The methodology adheres strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA 2020] guidelines [11], ensuring a transparent, reproducible, and standardized approach to screening, filtering, and reporting empirical scientific evidence.

2.2. Search Strategy

A comprehensive literature search was conducted across major electronic medical databases, including PubMed/MEDLINE, Embase, The Cochrane Library, and Scopus. To construct a scientifically sound search architecture and minimize selection bias, search terms, database combinations, and indexing matrices were structured according to methods validated by the Cochrane Handbook for Systematic Reviews of Interventions [12]. The search architecture targeted peer-reviewed journal articles, clinical trials, and epidemiological field studies published from January 2015 through April 2026. This timeframe was selected to capture the pivotal Phase 3 clinical trial data and programmatic rollout outcomes of both the RTS, S/AS01 and R21/Matrix-M vaccines.

The search strings used a combination of Medical Subject Headings (MeSH) terms and title/abstract keywords linked by Boolean operators (and, or). The canonical search string used across the platforms was structured as follows: ("malaria vaccine*" or "RTS, S*" or "R21*" or "Matrix-M") and ("effectiveness" or "efficacy" or "immune response" or "durability") and ("factor*" or "determinant*" or "influence*" or "variable*" or "polymorphism*" or "age" or "nutrition" or "transmission intensity")

To minimize publication bias, gray literature was hand-searched from authoritative global public health repositories, including official technical reports from the World Health Organization (WHO), Gavi, the Vaccine Alliance, and the Centres for Disease Control and Prevention (CDC).

2.3. Eligibility Criteria

To ensure high-utility data extraction, specific inclusion and exclusion parameters were strictly enforced. The layout and execution of these eligibility boundaries follow standard biomedical research manuscript reporting practices [13].

2.3.1. Inclusion Criteria

Study Types: Randomized controlled trials (RCTs), cluster-randomized trials, observational cohort studies, case-control studies, and longitudinal programmatic implementations. Intervention: Populations of any age receiving WHO-recommended pre-erythrocytic malaria vaccines (RTS, S or R21) or candidate malaria vaccines in advanced testing phases. Outcomes: Studies tracking clear primary or secondary efficacy/effectiveness endpoints, such as reduction in clinical malaria incidence, severe malaria hospitalizations, all-cause mortality, or vaccine-induced antibody decay rates. Language: Studies published in the English language or those with official professional translations available

2.3.2. Exclusion Criteria

Studies focused exclusively on in-vitro modelling or early-stage Phase 1 animal clinical data. General opinion papers, editorial notes, conference abstracts without complete data, or commentaries lacking empirical datasets. Studies assessing older candidate vaccines that have been permanently discontinued from global distribution channels.

2.4. Study Selection and Data Extraction

Literature results were compiled, and duplicate citations were automatically removed using citation management software. Titles and abstracts were screened independently by two reviewers against the predefined eligibility checklist. Any conflicting selections regarding inclusion were resolved by seeking consensus or consulting a third senior reviewer. Data from the final accepted articles were systematically extracted into a standardized spreadsheet template using an independent screening and verification protocol designed to ensure high inter-rater reliability [14]. The extracted data categories included:

- Study characteristics: Author name, publication year, geographical location, and transmission setting (perennial vs. seasonal).
- Population parameters: Cohort size, age at first vaccination, and baseline nutritional or health status.
- Vaccine specifics: Vaccine type, adjuvant type, and the completion status of the multi-dose/booster schedules.
- Primary findings: Quantitative measures of effectiveness, rates of efficacy decline, and the specific biological, genetic, or environmental factors identified as driving variations in protection.

3. Parasite-Genetic and Biological Factors

The primary biological obstacle to achieving sustained and uniform vaccine protection field performance is the high genetic polymorphism observed within the *Plasmodium falciparum* circumsporozoite protein (*Pfcsp*) gene [15, 16]. Both the RTS, S/AS01 and R21/Matrix-M vaccines are engineered using a recombinant antigen targeting the C-terminal polymorphic region and the central NANP amino acid repeats derived specifically from the 3D7/NF54 parasite reference strain [16, 17]. However, molecular epidemiological surveillance across highly endemic sub-Saharan African settings reveals that the 3D7 vaccine-type haplotype is critically underrepresented, matching as little as 0.2% to 5% of local circulating field strains in certain highly endemic populations [17,18].

A breakthrough genomic analysis from the landmark RTS, S Phase III clinical trial confirmed that vaccine efficacy was significantly higher (50.3%) against field infections that perfectly matched the 3D7 vaccine allele construct, compared to a heavily diminished efficacy (33.4%) against non-matching, mutated parasite field strains [19]. This pronounced strain-specific immune evasion underscores a critical vulnerability: the parasite's extreme genomic plasticity allows it to bypass vaccine-induced antibodies via minor amino acid mutations in crucial T-cell epitopes, directly compromising the long-term field effectiveness of pre-erythrocytic interventions [15, 20].

Beyond surface antigen diversity, additional parasite-biological variables influence vaccine performance, including baseline transmission intensity and blood-stage multi-clonality. In settings where individuals are simultaneously infected with multiple distinct genetic clones of *Plasmodium falciparum*, high antigen diversity can overload vaccine-primed immune responses, leading to an accelerated decay of protective antibody titers over time [18]. Furthermore, variations in target antigen density across different parasite life cycle stages allow a fraction of sporozoites to escape hepatic capture and safely enter the erythrocytic stage, where pre-erythrocytic antibodies are completely ineffective [15,17]. Consequently, accounting for geographical differences in parasite genomic profiles is vital for understanding why real-world vaccine effectiveness varies across deployment zones.

4. Host-Specific and Nutritional Factors

While parasite genetics shape immune recognition, the baseline physiological state of the recipient introduces massive variation into real-world vaccine effectiveness. Host-specific attributes, specifically age at immunization, maternal antibody dynamics, and nutritional status which act as key determinants of how strongly a child's immune system will respond to pre-erythrocytic interventions [21].

4.1. Age at Vaccination and Maternal Antibody Interference

A prominent finding from Phase III trial data is that both the RTS, S/AS01 and R21/Matrix-M vaccines elicit suboptimal immunogenicity in infants under five months of age compared to older young children [21, 22]. This discrepancy in protection is heavily driven by the transplacental transfer of maternal anti-circumsporozoite protein (anti-CSP) antibodies [22, 23]. In high-transmission settings, infants inherit massive titers of maternal anti-CSP IgG, which gradually decay over the first six months of life [23, 24].

Immunological profiling shows that high baseline maternal antibodies interfere with vaccine performance by binding directly to the NANP repeat region of the vaccine antigen [24]. This blunts the infant's native B-cell priming, leading to lowered antibody generation and an accelerated decay of vaccine-induced protection [24, 25]. Consequently, the World Health Organization (WHO) restricts deployment to infants aged five months or older to circumvent this blunting effect [21]. Furthermore, the fundamental immaturity of the infant immune system, characterized by reduced T-follicular helper cell support, limits the long-term establishment of protective immune memory [25].

4.2. Host Nutritional Status and Malnutrition

Protein-energy malnutrition (PEM) and micronutrient deficiencies represent widespread systemic causes of vaccine hyporesponsiveness in malaria-endemic zones [26]. Chronic malnutrition and stunting dramatically alter a child's baseline immunological landscape by impairing cellular homeostasis and lymphoid organ architecture [26, 27]. Emerging clinical trials and systems immunology data reveal that severe acute malnutrition directly hinders class-switched antibody responses and dampens long-term T-cell proliferation against subunit vaccine antigens [27].

Table 1 Immunological Impact

Nutritional Factor	Immunological Impact	Effect on Vaccine Efficacy
Protein-Energy Malnutrition	Atrophies peripheral lymphoid tissue; suppresses CD4+ T-cell expansion	Accelerated antibody decay; poor immunologic memory (26,27)
Severe Acute Malnutrition	Impairs class-switching from IgM to high-affinity IgG antibodies	Lower overall peak antibody titers post-primary series (27,28)
Iron & Micronutrient Deficiency	Disrupts enzyme-mediated B-cell replication and metabolic activation	Blunted somatic hypermutation; lower antibody binding affinity (28)

When a child suffers from a lack of primary macronutrients, the body struggles to sustain the metabolic demands required for high-titre antibody synthesis following a multi-dose primary series [27, 28]. Additionally, concurrent conditions like iron deficiency anemia further suppress the clonal expansion of B-cells within the germinal centres, resulting in lower antibody binding affinity and faster protection decline rates under natural parasite challenges [26,28]. Recognizing these nutritional barriers is vital for optimizing public health strategies, as integrating nutritional supplementation with routine vaccine delivery may serve as a crucial mechanism to maximize vaccine performance in highly vulnerable cohorts.

5. Environmental and Transmission Dynamics

The real-world field effectiveness of pre-erythrocytic malaria vaccines is profoundly shaped by external environmental variables. Regional transmission intensity, seasonal fluctuations, and the long-term immunological phenomena of "rebound effects" dictate the absolute duration of protection provided by both the RTS, S/AS01 and R21/Matrix-M interventions.

5.1. Transmission Intensity and Antibody Decay

Phase 3 clinical trial data demonstrates a distinct inverse relationship between baseline malaria transmission intensity and vaccine efficacy longevity [29]. In low-to-moderate transmission areas where the *Plasmodium falciparum* parasite rate is lower, vaccine protection wanes at a significantly slower rate, maintaining clinical value for several years [29, 30]. Conversely, in ultra-high transmission zones, the relentless entomological inoculation rate creates an environment where children are continuously re-exposed to infectious vector bites [30].

Systems biology modelling confirms that this continuous infectious pressure causes an accelerated decay of vaccine-induced anti-circumsporozoite protein (anti-CSP) antibody titers [30, 31]. When the sheer volume of sporozoites repeatedly challenges a child's immune system, the vaccine-primed humoral defense lines are overwhelmed, compressing the window of high-tier immunity from years down to months [31, 32].

5.2. Seasonal vs. Perennial Transmission Variations

The environmental delivery framework, specifically whether a vaccine is deployed via age-based standard routine tracking or seasonally timed campaigns, directly impacts peak field effectiveness [32].

In regions where rainy seasons create sharp, highly predictable spikes in vector populations, seasonally timed mass vaccination campaigns yield the highest recorded clinical success [31, 33]. Administering primary series doses or annual boosters immediately prior to the peak transmission wave ensures that a child's antibody titers are at their physiological peak when exposure risks are highest [31]. Clinical data from seasonal trial sites reported a peak efficacy of 75% for the R21/Matrix-M vaccine [31, 33].

Conversely, in perennial transmission regions where tropical precipitation fuels continuous year-round mosquito breeding, age-based standard routine vaccination is required [31]. Because exposures occur continuously, there is no distinct window to optimize a pre-peak antibody surge, and real-world effectiveness drops significantly to roughly 67% efficacy due to the absence of synchronized seasonal protection alignment [31, 32].

5.3. The Delayed Rebound Phenomenon

A major long-term concern identified during prolonged field monitoring is the emergence of a "negative efficacy" window or delayed malaria rebound [29, 32]. In natural, high-transmission ecosystems, unvaccinated children develop a degree of blood-stage naturally acquired immunity through surviving repeated, low-level malaria infections over time [32]. Pre-erythrocytic vaccines artificially shield young children from these parasite exposures during their first few years of life [30, 32].

However, as vaccine-induced antibody protection inevitably wanes between ages 3 and 5, these protected cohorts enter a phase of high vulnerability [29]. Because their immune systems missed early opportunities to develop natural blood-stage immunity, older vaccinated children experience a significant rebound in clinical and severe malaria cases, frequently tracking higher infection rates than their completely unvaccinated peers who developed natural defenses earlier [30,32]. This emphasizes that environmental transmission variables must dictate deployment protocols; supplementary vector control measures like long-lasting insecticidal nets (LLINs) remain vital to protect cohorts as artificial immunity fades [32].

6. Socio-Demographic and Operational Factors

While biological compatibility and environmental synchronization dictate the mathematical threshold of immunization success, real-world effectiveness hinges heavily on operational execution and public compliance. The systematic rollout of both the RTS,S/AS01 and R21/Matrix-M vaccines across sub-Saharan Africa reveals massive infrastructure bottlenecks. Specifically, cold chain failures, complex multi-dose dropouts, and demand-side hesitancy act as critical modern barriers to achieving population-level impact [34].

6.1. Cold Chain System Integrity and Transport Infrastructure

Pre-erythrocytic malaria vaccines require a continuous, strict storage temperature range between 2°C and 8°C to maintain antigen structural stability and prevent molecular degradation [34, 35]. However, national immunization programs in developing tropical countries remain highly vulnerable to widespread cold chain fragmentation [35, 36]. Regional infrastructure audits show that nearly 20% of rural health clinics lack functional cold storage, and where equipment exists, systemic weaknesses, such as highly unstable central power grids and limited fuel access for backup generators which lead to catastrophic internal temperature excursions [36, 37].

Table 2 Primary Operational Bottleneck

Logistical Variable	Primary Operational Bottleneck	Consequence on Field Potency
Power Grid Stability	Inconsistent power supply; severe backup generator fuel shortages	Uncontrolled refrigerator warming; rapid antigen degradation (36,37)
Last-Mile Transport	Unpaved road networks; impassable routes during seasonal rains	Delayed transit times; melting ice packs inside passive cold boxes (37,38)
Workforce Capacity	Lack of trained personnel; poor real-time temperature tracking	Failure to detect cold-chain breaches; compromised vaccine usage (35,38)

This infrastructural fragility is further aggravated by poor last-mile distribution networks [37]. In rural areas, unpaved roads frequently become completely impassable during the rainy season, the exact period when malaria transmission rates peak [37, 38]. These long transport delays exhaust passive ice packs inside portable cold boxes, subjecting vaccine vials to ambient heat and rendering them sub-potent before delivery to target populations [35, 38].

6.2. Multi-Dose Retention Hurdles

The requirement of a rigorous four-dose tracking layout places an immense operational burden on weak healthcare delivery networks [34, 39]. The initial three doses are given monthly during infancy, followed by a vital fourth booster dose administered roughly 12 to 18 months later to mitigate natural antibody decay [39, 40]. Programmatic evidence from early adopter countries reveals a sharp drop in retention across this timeframe [40].

While initial coverage for the first dose remains high, retention rates often fall by up to 30% by the fourth dose [40, 41]. This high dropout rate stems from fragmented electronic tracking systems, prohibitive caregiver travel costs, and a general lack of real-time inventory visibility across community clinics [39,41]). Missing the fourth booster significantly weakens long-term vaccine effectiveness, leaving partially immunized cohorts highly vulnerable to delayed malaria rebounds [41, 42].

6.3. Demand-Side Hesitancy and Misinformation Barriers

Public perception and behavioral patterns shape real-world vaccine uptake just as much as physical logistics (39). Cross-sectional behavioral surveys reveal that a majority of caregivers express some degree of vaccine hesitancy, which is primarily driven by concerns over transient post-vaccination side effects, such as localized soreness and mild fevers [39, 40].

Furthermore, digital misinformation campaigns on social networks have amplified cultural and religious resistance [40, 41]. This mistrust is frequently rooted in historical controversies surrounding Western-led health interventions in Africa [41]. Without strong, proactive community engagement leveraging traditional and religious leaders to debunk safety myths, demand-side dropouts will continue to critically limit the real-world utility of these tools [34, 42].

7. Conclusion and Future Perspectives

7.1. Conclusion

The field effectiveness of pre-erythrocytic malaria vaccines is not a fixed metric; rather, it is a dynamic outcome shaped by a complex web of biological, host, environmental, and operational factors. While the development and deployment of the RTS,S/AS01 and R21/Matrix-M vaccines represent historic achievements in global public health, their real-world impact remains highly variable. As demonstrated across this review, the extreme genetic diversity and polymorphism of the *Plasmodium falciparum* parasite present a continuous threat of strain-specific immune evasion.

Concurrently, host physiological barriers such as maternal antibody blunting in early infancy and the immune-suppressing effects of protein-energy malnutrition, significantly weaken the durability of protective responses in vulnerable cohorts. Externally, environmental transmission dynamics dictate the rate of vaccine-induced antibody decay, creating high risks of delayed clinical rebounds in intense transmission settings if protection is allowed to wane without proper booster coverage. Finally, these biological hurdles are compounded by severe operational bottlenecks, including fragmented last-mile cold chain storage, steep four-dose dropouts, and rising demand-side vaccine hesitancy.

Ultimately, isolated clinical parameters are insufficient for predicting real-world utility. For malaria vaccines to serve as definitive pillars of global elimination strategies, public health approaches must shift away from rigid, uniform distribution frameworks. Instead, deployment strategies must be agile, responsive, and specifically tailored to the unique biological and infrastructural landscapes of each target region.

7.2. Future Perspectives

To bypass the limitations of current pre-erythrocytic vaccines and secure long-lasting field effectiveness, the next generation of malaria interventions must prioritize several strategic technical and programmatic advancements:

- **Multivalent and Multi-Stage Formulations**: Future vaccine architectures should move away from single-strain, single-stage designs. Developing multivalent vaccines that incorporate highly conserved alternative antigens (such as Rh5 or transmission-blocking surface proteins) will allow interventions to target multiple phases of the parasite's life cycle simultaneously, preventing blood-stage replication and effectively neutralizing strain-specific immune evasion.
- **Monoclonal Antibodies for Seasonal Infusions**: The programmatic deployment of long-acting, laboratory-engineered monoclonal antibodies presents a highly promising alternative or supplement to traditional vaccines. These antibodies bypass the host's reliance on a mature, well-nourished immune system, delivering immediate, uniform, and high-titre protection directly to infants during critical peak transmission waves.
- **Integrated Public Health Packages**: Malaria vaccination should never be executed as an isolated intervention. Maximizing population-level survival requires the strict integration of immunization schedules with seasonal chemoprevention, nutritional support programs, and the continuous distribution of long-lasting insecticidal nets (LLINs) to protect children as artificial vaccine-induced immunity wanes.
- **Digitized Last-Mile Logistics**: Overcoming the 30% dropout rate between early childhood doses relies on the modernization of health infrastructure. Implementing SMS-based community reminder systems, solar-powered refrigeration units, and real-time electronic ledger tracking will stabilize last-mile delivery and ensure long-term booster adherence in hard-to-reach rural districts.

Compliance with ethical standards

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No conflict of interest to be disclosed.

Authors contribution

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