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REVIEW ARTICLE

Eradicating Malaria in Africa: Potentials and Challenges of Vaccine Deployment

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Abstract

Background: According to the World Health Organisation (WHO), malaria remains a leading burden of illness in low- and middle-income countries accounting for 94% of cases and 95% of deaths in 2022. As the 2030 Global Goals approach, preventive and chemotherapeutic interventions are necessary to curb the virulence of malaria, making it crucial to review novel approaches to combat this disease.

Objective: This paper aims to review the top two vaccines for malaria prevention, evaluate their efficacy, and examine the potential challenges that may arise in their deployment in lowand middle-income countries.

Methods: A comprehensive review was conducted focusing on the leading malaria prevention vaccines, their effectiveness profiles, and the barriers to implementation in resource-limited settings.

Results: While vaccine usage demonstrates significant potential for malaria prevention, considerable challenges exist in vaccine development and large-scale production in low- and middle-income countries due to limited funding resources. Additionally, misconceptions about vaccines present barriers to acceptance and uptake.

Conclusions: Although malaria vaccines offer promising preventive potential, successful deployment in low- and middle-income countries requires addressing funding limitations for development and production, as well as implementing public enlightenment programs and awareness-raising sessions to combat vaccine misconceptions before deployment.

1. Introduction

Malaria is one of the most burdensome vector-borne infectious diseases in sub-Saharan Africa (SSA), with an estimated 200 million cases and 403,000 deaths in 2020, 80% of which were children under five [1–3]. Despite considerable efforts to eradicate and prevent malaria, it is still a life-threatening disease caused by Plasmodium falciparum and other related species, transmitted to people through the bites of infected female Anopheles mosquitoes. Malaria is the second leading cause of death in the region after

human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) [4]. In addition to the devastating human toll, the disease also incurs significant social and economic costs because of reduced labour productivity. Seven countries, including Nigeria (27%), the Democratic Republic of Congo (12%), Uganda (5%), Angola (3.4%), Burkina Faso (3.4%), and Mozambique (4%), account for half (55%) of all malaria cases globally [5,6]. Unfortunately, the emergence of artemisinin-resistant species and the genetic variability of Plasmodium species have turned malaria into a global public health challenge [7].



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In response, the roll back malaria (RBM) partnership introduced the global malaria action plan (GMAP) in 2010, which advocated the use of insecticide-treated nets, indoor residual spraying, artemisinin-based combination therapy, and rapid diagnostic tests. These interventions have significantly reduced the malaria burden worldwide [8,9]. Furthermore, chemoprevention strategies, such as intermittent preventive treatment of school-aged children (IPTsc) and post-discharge malaria chemoprevention (PDMC), have also helped decrease the burden of the disease, especially in children over five years of age with severe anemia [10]. Despite these successes, the WHO reported that 94% of all malaria cases and 95% of deaths in the African region in 2022 were because of malaria, highlighting the need for continued efforts to achieve the Global Goals target of a 90% reduction in malaria incidence by 2030 [5].

Eradicating malaria is essential for alleviating poverty, enhancing the health of millions and allowing future generations to achieve their full potential. In this mini-review article, we assess the progress made by various medical and pharmacological interventions in addressing malaria in SSA, highlighting the potential for using new malaria vaccines and valuable recommendations to bridge gaps in vaccine accessibility in rural, hard-to-reach areas.

2. Vaccines and Vaccine Development

Vaccines are biological products that safely stimulate immune responses against pathogens, protecting against infection and disease upon subsequent exposure [11]. Vaccines can contain live attenuated pathogens, inactivated whole pathogens, toxoids, or other components of pathogens [12]. Vaccination is considered one of the safest and most effective ways to prevent infectious diseases, accounting for an estimated 2–3 million lives saved annually [13].

Over the last two centuries, vaccination has led to the eradication of smallpox, reduced global child mortality rates, and prevented countless cases of congenital and lifelong disabilities, such as polio-induced paralysis [13]. The effects of vaccination include reducing the medical and socioeconomic burden of disease and synergizing with disease prevalence [2]. Recent advances have dramatically expanded the vaccine landscape. The COVID-19 pandemic accelerated the development and implementation of novel mRNA vaccine technology, demonstrating unprecedented speed from pathogen identification to approved vaccines in less than 1 year [9,14–16]. This technology has shown potential beyond infectious diseases, with promising applications in cancer immunotherapy and the management of autoimmune disease [9].

Despite their successes, the development of vaccines remain challenging because of the limitations of scale-up production and funding resources [17]. The development of vaccines is often capital-intensive, complex, and time-consuming, typically taking 15–25 years to produce a final approved product, by which time the patent has usually expired [17–18]. However, innovations in development

approaches have begun to address these challenges. Structure-based vaccine design using cryo-electron microscopy and computational modeling has enabled more precise targeting of pathogen vulnerabilities [19–21]. The application of artificial intelligence to predict epitopes and model immune responses has streamlined antigen selection, potentially reducing development timelines by years [22].

During the pre-COVID-19 era, only 7% of vaccines under development progressed to human clinical trials from pre-clinical studies, and only 20% demonstrated safety and efficacy [18,23]. The establishment of global platforms like coalition for epidemic preparedness innovations (CEPI) has transformed this landscape by creating infrastructure for rapid response to emerging pathogens. The 100-day mission aims to develop vaccines against novel threats within just over 3 months [24].

In addition to the factors already mentioned, other considerations necessary for vaccine development include stability, storage conditions, the number of injections, route of immunization, optimal dose, scale-up, manufacturing, and global distribution of the vaccine [10]. Significant advances in these areas include the development of thermostable formulations that eliminate cold chain requirements, particularly valuable for resource-limited settings. Novel delivery platforms such as microarray patches and oral/intranasal formulations have shown promise in providing needle-free alternatives that could improve compliance and simplify administration [25,26].

Distributed manufacturing using modular, portable production facilities represents another breakthrough, enabling local production in low- and middle-income countries and reducing global supply chain vulnerabilities [12,27]. These innovations, coupled with improved regulatory harmonization and technology transfer initiatives, are addressing historical inequities in vaccine access while enhancing global pandemic preparedness [28–29].

3. Malaria Vaccines

Malaria vaccines have been developed to address the limitations of antimalarial drugs, insecticide-treated nets, and other preventative measures in combating the adverse effects of malaria. Malaria vaccines are designed to target specific stages of the parasite's life cycle, including transmission-blocking vaccines (TBVs), pre-erythrocytic vaccines (PEVs), and blood-stage vaccines [30,31]. The RTS and R21 vaccines are pre-erythrocytic, while other vaccines are currently being tested in various phases, from preclinical to Phase 2 [31].

3.1. RTS,S/AS01E Malaria Vaccine

The RTS,S/AS01E malaria vaccine represents an improvement over the Mosquirix vaccine approved by the WHO in 2021 [31]. However, the vaccine remains less effective than standard childhood vaccines such as Polio, Measles, Mumps, and Rubella [2]. This vaccine includes virus-like particles produced by expressing the hepatitis B surface

antigen in *Saccharomyces cerevisiae*, fused with the circumsporozoite protein of *P. falciparum*, incorporating repeat regions and a T-cell epitope. The adjuvant AS01E enhances the vaccine's immunogenicity [32]. The vaccine has been introduced for childhood vaccination in Ghana, Kenya, and Malawi because of the high burden of *P. falciparum* malaria in these countries [33].

According to Praet et al. [11] the RTS,S/AS01E malaria vaccination program resulted in a 30% reduction in severe malaria in these countries following a phase 3 study. The vaccine showed an efficacy of 36% in infants aged 5–17 months and 26% in infants aged 6–12 weeks with clinical malaria, who received four doses of the vaccine with a median follow-up period of 48 months [34]. This success resulted in WHO's recommendation for the RTS,S/AS01E malaria vaccine in vaccination programs in several other countries [4]. In July 2023, the WHO, GAVI, and UNICEF announced the allocation of 18 million malaria vaccine doses to 12 African countries [35].

This allocation was initially apportioned to the pilot countries and then administered in early 2024 in Benin, Burkina Faso, Burundi, Cameroon, the Democratic Republic of Congo, Liberia, Niger, Sierra Leone, and Uganda [35]. The vaccine is usually given in a four-dose schedule in children (> 5 months), with over 4.5 million doses administered in the three listed African countries. Using a mathematical model, Hogan et al. [36] estimated an aversion of 5.3 million cases and 24,000 deaths at a dose constraint of 30 million vaccines across several countries. This is helpful, as it will drastically reduce Malaria in several SSA countries.

However, the RTS,S is only partially effective, particularly in endemic areas, as its effectiveness is reduced by 35% at a 4-year interval, termed "age shift" [37,38]. Also, Bharati and Das [37] reported that there were incidences of meningitis in the vaccinated children, and further studies need to identify if there is a correlation with the vaccine.

It is important to note that the RTS,S/AS01E vaccine was specifically designed to target P. falciparum, which is responsible for the most severe form of malaria and the majority of malaria-related deaths globally, particularly in SSA [36] The vaccine's design incorporates the circumsporozoite protein (CSP) specific to P. falciparum, which differs significantly from the CSP of other human malaria parasites such as P. vivax, P. ovale, P. malariae, and P. knowlesi, with no studies showing minimal to no crossprotection against nonfalciparum species [2,11,30,39]. This represents a significant limitation in regions where multiple Plasmodium species co-circulate, particularly in parts of Asia, South America, and some regions of Africa where *P. vivax* is prevalent alongside *P. falciparum* [40,41]. In these areas, even with the successful implementation of the RTS,S vaccine, additional interventions remain necessary to address the full spectrum of malaria infections.

3.2. R21 Vaccine

The R21 vaccine was created to achieve the World Health Organization's (WHO)'s objective of developing a malaria

vaccine with an efficacy exceeding 75% against clinical malaria by 2030 [34]. Developed at the University of Oxford (UK) and produced by the Serum Institute of India (India), the R21/Matrix-M malaria vaccine incorporates virus-like particles derived from the C-terminal of the *P. falciparum* NF54 strain CSP, which is fused to the N-terminus of the hepatitis B surface antigen [42,43]. The vaccine is formulated using the Matrix-M adjuvant [44].

During the clinical trials, no significant safety concerns were identified, and the vaccine demonstrated an efficacy greater than 74% in the two-treatment group after three doses, with efficacy assessed over 6 months.⁴³ Twelve months following the initial three doses, the vaccine's efficacy was 66% [45].

In October 2023, the WHO recommended the R21/Matrix-M vaccine for use in children at risk of malaria, making it the second WHO-recommended malaria vaccine after RTS,S. This recommendation was based on Phase III trial data that showed continued high efficacy, with protection levels maintained at approximately 75% when administered before the high malaria transmission season and followed by annual booster doses [43]. In January 2024, Ghana became the first country to include the R21 vaccine in its routine immunization program, followed by Nigeria and Burkina Faso implementing phased rollouts by April 2024 [46]. The Serum Institute of India expanded its production capacity to meet the growing demand, with plans to produce 100 million doses annually by the end of 2024 [9].

Recent cost-effectiveness analyses published in early 2024 suggested that the R21 vaccine is more cost-effective than the RTS,S vaccine in most endemic settings, primarily because of its lower manufacturing costs and comparable efficacy profile [3]. However, in spite of both being pre-erythrocytic vaccines, the RTS,S and R21 vaccines have not undergone direct comparative clinical studies to determine which is more effective [1]. Predictive mathematical models continue to suggest that the R21 vaccine will have a substantial impact in endemic regions, with potential to avert millions of cases and thousands of deaths annually when implemented at scale [3].

Research efforts are underway to develop vaccines targeting other Plasmodium species, with a particular focus on *P. vivax*, which causes significant morbidity in many regions outside Africa [47]. This is done through targeting the *P. vivax* CSP and the Duffy binding protein, which is critical for its invasion of red blood cells [48]. However, these candidates remain in earlier stages of development compared to the RTS,S/AS01E and RTS vaccines [49]. The species-specific nature of both vaccines highlights the need for continued investment in comprehensive malaria control strategies, including vector control, prompt diagnosis and treatment, and the development of new tools targeting the full spectrum of malaria parasites affecting humans.

4. Challenges

A significant problem confronting vaccine distribution in Africa is improper storage, mainly because vaccines

require a temperature of 2–8°C, which is often impossible because of epileptic power supply. This is not a new challenge and was identified earlier as one of the significant obstacles to the polio vaccination program in Nigeria [50].

Furthermore, the inequitable distribution of vaccines is another pivotal challenge. People living in remote areas are at high risk of being excluded from receiving vaccines because of poor road networks in Nigeria and sub-Saharan countries.

Misinformation concerning vaccines also constitutes another bottleneck. Reports of male sterility, implant tracking, connection to the 5G network, and other religious views have led to misleading information among the public on the efficacy of vaccines [16,28,29].

5. Recommendations

5.1. Integrating Proper Enlightenment Initiatives into the Malaria Vaccination Program

Intensive sensitization programs should be championed by the Federal Ministry of Health in low and middle income countries across Africa and integrated into the malaria vaccination program to demystify wrong myths and negate erroneous beliefs about the malaria vaccine. The Federal Ministry of Health and other government health agencies across LMICs in Africa should also adopt digital media, traditional media, and social media to disseminate information on the potency of malaria vaccines, especially as a protective and preventive mechanism that can contribute to the long-term eradication of malaria This can also significantly enhance the acceptability and uptake of malaria vaccines at various levels in several African countries.

5.2. Initiate Partnerships with Health Professionals and International Agencies

The successful deployment and implementation of vaccines require a collaborative effort at different levels. It is advised that the Federal Ministry of Health, in partnership with the African Centres for Disease Control, should advocate for increased collaboration, funding, and partnership with international agencies such as the United Nations, World Health Organization, and public health professionals within Africa. Such concerted partnerships are crucial in mobilizing not only human resources but also financial resources as well as health products that will foster the availability and accessibility of malaria vaccines to vulnerable regions in African countries.

5.3. Provision of Storage Systems for Malaria Vaccines

Proper storage of vaccines is essential. Hence, the Federal Ministry of Health and its agencies should prioritise the provision of storage systems in primary healthcare facilities nationwide before deploying the malaria vaccines. This will help to preserve the vaccine in good condition.

5.4. Effective Health Data Information Management System

To enhance the efficiency of the malaria vaccination program, the health information database across various primary healthcare facilities in Africa, must be up-to-date and include relevant data. Also, such data should be in electronic form and subjected to different monitoring and assessment levels. This will help track progress in vaccination and also enhance equitable distribution. An effective health data information management system for the malaria vaccination program will also foster budgeting and planning efforts in reaching areas where there are underserved persons.

Authors' Contributions (CRediT Taxonomy)

JOO was in charge of conceptualization, whereas OSO* was responsible for visualization. OSO*, ABA, OSO, OOS, FTO looked into data curation. ABA, OSO*, OSO, OOS, and FTO were in charge of writing of the original draft, whereas OSO*, ABA, OSO, OOS, FTO, and JOO did review and editing. OSO* and ABA also looked into conceptualization.

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Conflicts of Interest

The authors declare no conflicts of interest.

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