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Beyond RTS,S malaria vaccine piloting to adoption and historic introduction in sub-Saharan Africa: a new hope in the fight against the vector-borne disease

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Introduction

Malaria infection remains one of the leading causes of death in sub-Saharan Africa (SSA) (1). The disease has enormous health and economic implications among affected individuals, communities and endemic countries at large (2, 3). The vector-borne infectious disease is caused by *Plasmodium* species and is spread to humans through the bites of infected hosts, by the female *Anopheles* mosquitoes (1). Even though five species of *Plasmodium* exist, *P. falciparum* is the protozoan parasite associated with severe disease and accounts for most malaria deaths in SSA (4).

The World Health Organization (WHO) 2023 World Malaria Report highlighted that, in 2022, there were estimated 249 million cases and 619,000 deaths of malaria globally (5). Between 2019 and 2020, estimated malaria cases increased from 218 million to 230 million and deaths from 552 000 to 604 000. The WHO African Region carries a disproportionately high malaria burden. Around 70% of the global malaria burden is concentrated in 11 SSA countries (5). About 94% of the reported malaria cases in 2022 were in the WHO Africa Region with Nigeria, the Democratic Republic of Congo, Uganda and Mozambique contributing nearly 50% of all the cases (5, 6). The region accounts for 96% of malaria deaths with under-five children accounting for 80% of all deaths in the region (7).

Between 2000 and 2015, the SSA oversaw a 40% reduction in clinical disease and 50% reduction in malaria cases due to mass deployment of control interventions such as indoor

residual spraying, utilization of insecticide-treated nets (ITN), and prompt diagnosis and treatment with effective antimalarial drugs (8–10).

For several years, various measures have been implemented for malaria prevention, including vector control with ITNs and indoor residual spraying and seasonal malaria prophylactics (11). Pharmacotherapy, such as the Artemisinin-based Combination Therapies (ACTs), has been the mainstay for treating uncomplicated and severe *P. falciparum* malaria, including the symptomatic management of malaria complications. The discovery of ACTs led to significant reduction in malaria mortality and morbidity across endemic countries. However, these mainly targets the blood stage of the life cycle (12). The focus on pharmacological agents is being threatened by the ever growing threat of anti-malaria resistance, leading into more deaths (13).

However, over the past few years, malaria control in SSA seems to have stalled, which reflects slow progress of interventions to eliminate the disease and the complex interplay of various other factors that spearhead ongoing transmission of the disease (14, 15). The endemicity, morbidity and mortality due to malaria has moved researchers to seek for more robust preventive measures such as the development of the malaria vaccine. Decades of clinical trials have led up to the WHO recent approval of the groundbreaking four-dose malaria vaccine, RTS, S/AS01 (*Mosquirix*), on October 6, 2021, designed to target the sporozoite (pre-blood) stage of *P. falciparum* before they infect liver cells (16, 17).

Despite its proven effectiveness in reducing the burden of malaria, the malaria vaccine is yet to be introduced in many African nations. Country adoption and approval of the new prequalified vaccines remains crucial toward the success of vaccination programs and eventually the fight against malaria. In this article, therefore, we highlight the state of malaria control in Africa, availability of vaccines and other preventive measures and offer insights into how the RTS, S vaccine offers new hope in the fight against the deadly mosquito-borne disease.

Challenges in malaria control and prevention in Africa

Despite ongoing malaria interventions, malaria remains one of the major health problems in Africa. One of the major challenges faced in the fight against malaria is the development of antimalarial drug resistance (15). Breakthrough drugs such ACTs, which for so long have been frontline, fast-acting drugs have shown increased resistance in the world including in the WHO African Region of Rwanda, Uganda, Eritrea and Tanzania (18). This increases the risk for protracted infections not responding to treatment, severe disease forms and further transmission of the resistant parasites (19).

Another key challenge is limited diagnostic and treatment capacity especially in rural settings in SSA. Most people in African countries travel long distances to access health care and some of the health facilities lack diagnostic equipment such as malaria rapid diagnostic test (RDTs), making it difficult to diagnose and treat malaria cases (15). Additionally, most rural health facilities are poorly equipped, lack appropriate infrastructure, and skilled personnel to detect malaria beyond RDTs as well as to manage severe and life-threatening forms of malaria. As a result, some cases remain either undetected or are detected late with minimal impact of any applied therapeutic interventions.

In addition, the invasion of new species of mosquitoes native to other regions into SSA makes the fight against malaria even harder. For instance, the *Anopheles stephens* is fueling the spread of malaria infections across Africa (20). The species which originated in south Asia was first detected in Djibouti in Africa and it has since been detected in other countries like Ethiopia, Ghana, Kenya and Nigeria. Unlike other species, *Anopheles stephens* is more resistant, hard to detect and thrives in harsh conditions and is therefore difficult to eliminate from the environment (21).

In the recent years, climate change has also been earmarked as another hurdle contributing to the high malaria burden in the tropical regions (22). Warmer climates have been attributed to speeding up the growth cycle of malaria parasites in *Anopheles* mosquitoes (23). Disease burden and malaria transmission is also indirectly impacted by extreme weather events, such as heatwaves and flooding (24). Such adverse natural conditions reduce access to essential malaria services and disrupt supply chain of ITNs, medicines and vaccines.

Furthermore, mutation of the malaria parasites also proves to be another challenge in detection of malaria and treatment. Deletion of the histidine-rich protein genes pfhpr2/3 causes infections to go undetected by histidine-rich protein 2 (HRP2)–based rapid diagnostic tests (RDTs) (25). Naturally emerging deletions of these genes implies that the parasites will remain undetected and become dominant in the environment, thereby increasing the number of missed cases which can progress to severe malaria and death (26). Pfhrp2/3 deleted parasites have so far been reported in most endemic malaria regions including in African countries like Ethiopia, Kenya, Madagascar, and Rwanda (27).

Lastly, the weight of the burden of malaria on a society is determined by a complex interplay of environmental and social factors, including poverty, low awareness and education (28, 29). The most dangerous vectors of malaria thrive mainly within the village environment and transmission is orchestrated by a range of social and behavioral factors including social events mostly occurring outdoors during early morning or late evening hours (30). Other social and environmental factors attributed to high malaria burden include human settlements near the marshlands, irrigation schemes and internal population movement and migrations (29). The dire levels of poverty across SSA with poor quality housing, higher levels of stagnant waters, and swamps promote vector abundance and persistent disease transmission in much of SSA (31, 32). Worse still adoption of the available control methods is largely impacted by social cultural and economic factors (33). For instance, some social beliefs and norms influence ineffective use of ITNs nets in local communities.

Disease immunization and health benefits

Amidst all the aforementioned challenges in the fight against the vector-borne disease, more robust solutions such as immunization remain key in controlling the transmission of the disease. Immunization is a process by which a person becomes protected against a disease through vaccination (30). Vaccines induce artificial immunity which protects the individual from future episodes of illness when they encounter the disease-causing pathogen. In 1974, the WHO founded the Expanded Program on Immunization (EPI), with an aim of providing routine vaccines to all children (31). The EPI includes *diphtheria, pertussis, tetanus, measles, polio, hepatitis B, Haemophilus Influenzae B, and pneumococcal* vaccines. The health benefits of vaccination cannot be overemphasized. The development of safe and efficacious vaccination against disease with high morbidity and mortality has been one of the most successful scientific discoveries of the 21st century (32). Vaccines have led to a significant decrease in the global burden of diseases caused by vaccine preventable microorganisms. For instance, the development of a successful small pox vaccine in 1798 led to the eradication of smallpox which had been affecting people since 1000 BC (33).

Although historically vaccination was intended to prevent deadly infectious diseases, its impact extends to prevention of non-communicable diseases like cancers which are linked to infectious diseases agents (34). For instance, the hepatitis B virus vaccine helps to prevent hepatitis B virus disease which if it becomes chronic can lead to hepatocellular carcinoma. Similarly, this is also the case with Human Papillomavirus (HPV) vaccine which protects against cervical cancer (35).

However, for vaccines to achieve intended benefits, a large proportion of people needs to be vaccinated (36). The massive role of vaccination in infectious disease control is now being put under serious threat due to vaccine hesitancy (37). Among other contributing factors, complacency, low confidence in vaccination and healthcare systems reduces vaccine uptake, making it hard for the population to achieve herd immunity, and hence reduces the potential benefits the vaccines could have had (38).

Malaria vaccines: historical evolutions

Many factors have contributed to the delay in malaria vaccine development, principally due to difficulties to develop vaccines against the parasites (39). This is explained by the unique human immune response to parasites, due to the complicated life cycle and the immune escape mechanisms expressed by different parasites. Malaria vaccines have been under development since the 1960s, with experiments on mice to test irradiated sporozoites (40). In 1967, a study showed that immunizing mice with radiation attenuated *Plasmodium berghei* sporozoites, showed that mice were protected in later challenge with infectious sporozoite. This led to human malaria vaccine trials that delivered irradiated *P. falciparum* sporozoites to humans by mosquito bites.

A study in 1970 demonstrated that humans could be protected after immunization with bites of irradiated mosquitos carrying *P. falciparum* or *P. vivax* sporozoites (41). 11 volunteers from the United States Public Health Service, United States Army and United States Navy were challenged by the bites of irradiated mosquitos harboring infectious sporozoites of *P. falciparum* strain NF54 or clone 3D7/NF54. The weakened sporozoites could travel into the liver and elicit an immune response in the human host, but could not cause the disease. Over a span of 42 weeks, 24 of 26 tests on the volunteers showed that they were protected from malaria. However, this approach was not cost-effective and could not be used on a large scale. Following these studies, scientist gained important insights and continued to explore further potential vaccines targeting different developmental stages of malaria parasite: pre-erythrocytic vaccine, erythrocytic vaccine and transmission-blocking vaccine (42). The new RTS,S vaccine is a pre-erythrocytic vaccine that targets the infectious phase of malaria's life cycle which prevents sporozoites from entering the liver cells (43). The challenge with pre-erythrocytic vaccine is that it gives the immune system less time to eliminate the parasite as sporozoites reach the liver less than an hour after being injected by mosquito.

RTS, S malaria vaccine: a new hope in the fight against malaria in Africa

The RTS,S vaccine is the first malaria vaccine recommended by WHO to prevent malaria in children in October 2021 (44). This pediatric vaccine acts against *P. falciparum*, and reduces the number of times a child gets malaria infection, including severe, life-threatening malaria (17). The vaccine began pilot implementation in 2019 whereby the vaccination initiative reached more than 2 million children in Ghana, Kenya and Malawi (45). Results of phase 1 testing shows that among children aged 5-17 months who received 4 doses of RTS,S, vaccine efficacy against malaria was 36% over 4 years of follow up research resulting in a drop of 13% in all-cause early childhood deaths and a substantial reduction in severe malaria (16, 45).

Following the successful vaccination campaigns from the pilot studies, Cameroon has become the first country to integrate malaria vaccine into routine national immunization in November 2023 (46). With support from the WHO and the Global Alliance for Vaccines and Immunisation (GAVI), 12 African are set to receive a total of 18 million doses of the RTS,S malaria vaccine for the 2023–2025 period (47). This includes Malaria Vaccine Implementation Programme countries Ghana, Kenya and Malawi, where vaccination continues beyond piloting. The other countries which have adopted the introduction of the vaccine and are in the waiting list to receive their consignment includes Benin, Burkina Faso, Burundi, Democratic Republic of the Congo, Liberia, Niger, Sierra Leone and Uganda (47). To capitalize on the proven effectiveness of the vaccine, it is imperative to achieve high coverage rates. However, several constraints threaten to hinder vaccination against malaria.

The first challenge toward malaria vaccination is limited availability of the vaccine in Africa. Africa lacks vaccine

production capacity. The continent is reliant on donor support for vaccines. The WHO and the GAVI have allocated about 18 million doses to 12 African countries (48). This allocation does not cover for the high burden of malaria in the region as some studies report a prevalence of up to 60% among African children under the age of five (49).

Despite some studies reporting a high acceptance rate of the vaccine in some African countries, vaccine hesitancy is a persistent and dynamic public health threat in SSA (50). The SAGE Working Group on Vaccine Hesitancy defines vaccine hesitancy as the delay in acceptance or refusal of vaccination despite availability of vaccination services (50). It is complex and context specific, varying across time, place and vaccines. It is driven by multiple factors in SSA which include low knowledge on vaccination and its schedules, misinformation and concerns about vaccine safety (37, 50). However, there are limited studies investigating the acceptance of the malaria vaccine. Few studies that have been done have demonstrated limited awareness of the vaccine particularly among the general population, which could potentially hinder acceptance among the general public (51–53). Worse still, a study done in Nigeria demonstrated limited awareness of the vaccine among policy makers (53). This could significantly impact adoption of the vaccine at country level.

Addressing the potential barriers to vaccination in SSA requires a multi-sectoral collaborated approach. To begin with, the limited vaccine availability calls for a strong political willpower and commitment to strengthen vaccine production capacity as well as purchase doses equivalent to the high malaria burden in the region. African leaders, health stakeholders and donors need to unite in their efforts to improve the vaccine's availability and accessibility.

Additionally, it is crucial to conduct comprehensive awareness campaigns on the need to vaccinate children against malaria. Multiple avenues of communication could be utilized, including mass media, social media, health facility-based education as well as door-to-door visits conducted by community-based healthcare providers. Equally crucial is the provision of clear vaccination schedules to all caregivers to minimize missing doses. Utilizing existing community leadership structures could also prove essential in promoting awareness of the malaria vaccine and dispelling any conspiracy theories attached to it. The leaders include village headmen, women leaders as well as community leaders.

Nevertheless, malaria control and elimination require an integrated approach. Despite the hope that the vaccine offers, vaccination alone cannot eliminate malaria. All other proven interventions need to be fully utilized. This calls for strengthening the healthcare system at all levels from primary care provision to tertiary care provision to policy making and implementation to enhance vector control, develop diagnostic and treatment facilities, combat antimalarial drug resistance and promote malaria vaccine uptake. Furthermore, there is need for more research to promote the vaccine's acceptability and uptake.

Conclusion

Malaria remains one of the challenging public health problems in Africa, in spite of different interventions going on. The development of highly effective vaccines against the deadly human malaria parasite *P. falciparum* provides optimism against the fight. Therefore, it is of utmost importance to adopt a multi-sectoral collaborated approach to increase the malaria vaccine's availability and increase its coverage in order to achieve the 2030 malaria burden reduction goals.

Author contributions

AL: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. AB: Methodology, Validation, Visualization, Writing – review & editing. CM: Writing – original draft, Writing – review & editing. GC: Writing – review & editing. YM: Writing – review & editing. HN: Writing – review & editing. LK: Writing – review & editing. JP: Writing – review & editing. JC: Writing – review & editing.

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Conflict of interest

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