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CORRESPONDENCE

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Unlocking the potential of novel RTS, S/AS01, and R21/Matrix-M™ malaria vaccines in African nations

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Abstract

Introduction: Mass malaria vaccination, rather than vaccinating only children below age 5, has been proven to have the potential to reduce morbidity and mortality among those vaccinated, both young and old. Addressing vaccine scepticism and misinformation is crucial in African nations to build public trust in malaria prevention. Therefore, including a wider range of demographics in vaccine trials is necessary for equitable representation and achieving herd immunity against malaria.

Aim: This present article aims to identify some of the obstacles that impede malaria vaccination usage and acceptability in African Nations in combating malaria in the region as it continues to pose a significant global public health problem.

Methodology: A literature search was done on the Malaria vaccine between 2000 and 2023. Past and present articles/studies on this topic were consulted on PubMed, Google Scholar, Scopus and Web of Science using the following keywords; "Malaria," "Vaccines," "African Nations," "Obstacles, Strategies," and "Public Health."

Results: The recently approved RTS, S/AS01, and R21/Matrix-M™ Malaria vaccines have the potential to prevent numerous deaths and cases of Malaria in Africa. These vaccines Malaria vaccines are cost-effective in African areas with moderate to high plasmodium falciparum and can be delivered through routine immunization.

Conclusion: To combat malaria effectively in African Nations, African leaders need to set up a comprehensive approach that involves; prevention, healthcare access, implementation research strategies towards adoption and acceptance of malaria vaccines in Africa as well as community engagement with the religious leaders, the market women, community heads, schools, as well as students' union towards the willingness and acceptability of the malaria vaccines among the African populations.

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KEYWORDS
African Nations, malaria, obstacles, public health, strategies, vaccines

1 | INTRODUCTION

The transmission of malaria is usually through the bite of an infected female anopheles mosquito. The infection can present with common early symptoms, including fever, headache, and chills. However, life-threatening complications, including cerebral malaria, severe anaemia, and hypoglycemia, can also occur. Malaria can have implications on pregnancy, putting pregnant females at risk of premature delivery. Despite this severity, malaria is both preventable and curable.[1] In 2021, the global malaria burden reached 247 million cases with 619,000 deaths, mostly concentrated in the World Health Organization (WHO) African Region (95% of cases and 96% of deaths).[1] Children under 5 years old accounted for 80% of malaria deaths in the region. Of course, there is no debate that malaria kills more children than any other age group, however, the presumption that malaria mortality remains uniformly low throughout the rest of the lifespan has recently been debated by researchers worldwide.[2] According to a 2020 article in the American Journal of Tropical Medicine and Hygiene, it was shown that there was a largely unacknowledged malaria burden among adults starting in later middle age in some places with intense transmission.[2,3]

A study in Kenya in 2015 showed a prevalence of malaria of 28.1% in the total adult population of 1190 adults.[4] Female respondents had a 50% higher risk of having malaria compared to males (odds ratio of 1.5, p value of 0.005) with an over 6-month period prevalence rates ranging from around 40%–60% in December, January and February to around 10% between March and June.[4] Nigeria alone represented 27% of global cases and 23% of global deaths in 2021. Despite challenges, efforts have reduced the global burden of severe Plasmodium falciparum malaria since 2000.[5] However, the problem remains in Nigeria, being the most populous African country and the fight against malaria in that country has been and is still facing numerous constraints, including poor living conditions, inadequate infrastructure, underfunding of the health sector, limited access to healthcare, program inconsistency, and lack of oversight. Additionally, political, social, and economic factors further complicate malaria eradication efforts.

2 | JUSTIFICATION AND AIM OF THIS ARTICLE

Mass malaria vaccination, rather than vaccinating only under-5 children, has been proven to have the potential to reduce morbidity and mortality among those vaccinated, both young and old.[2] Gelband et al.[2] argued that under the right conditions, malaria vaccines could materially reduce community transmission by reducing the prevalence of circulating gametocytes throughout the population, and also reduce the evolution and spread of drug resistance to artemisinins by reducing their use and thus exposure of malaria parasites to them. Therefore, if malaria vaccination reduces the number of infections, the infectious reservoir could be greatly reduced.[2] Adults with asymptomatic, low-parasitaemic infections, including most infected individuals, are more likely than individuals with symptomatic higher parasitaemias, and as they are unlikely to be treated, their infections may persist for years.[2] The presence of an adult pool of malaria parasites in Africa represents a key factor in the transmission of parasites to children which is relevant to the malaria eradication agenda in Africa.

Again, global epidemiologists gave approximately 186,318,000 estimated incident cases of malaria across the 12 major African markets (12MM) that is; Burkina Faso, Cameroon, the Democratic Republic of Congo (DRC), Ghana, Kenya, Mali, Mozambique, Niger, Nigeria, South Africa, Tanzania and Uganda in the year. 2022.[6] This data is expected to rise to 211,098,000 estimated incident cases in the year 2027.[6] However, if the COVID-19 vaccination rollout and campaigns can reduce vaccine scepticism in Africa, researchers expect that the estimated incident cases of malaria in Africa will be lower than the current projected estimates over the next 10 years, as the public awareness of the importance of vaccination increases, and more people subsequently engage with vaccination programs, resulting in fewer people being vulnerable to malaria infection.[6] Also, healthcare professionals in Africa believe that the malaria vaccine will help control the spread of malaria in Africa. Having justified the reasons for this topic, the causes, burdens, and challenges associated with malaria prevention and treatment, especially about malaria vaccines must be addressed. The aim of this present article is therefore to identify some of the obstacles that impede malaria vaccination usage and acceptability in African Nations in combating malaria in the region as it continues to pose a significant global public health problem. In writing this article, we searched relevant articles on malaria and vaccine usage from scientific journals and databases.[1–18]

3 | DISCOVERY OF THE NOVEL RTS, S/AS01, AND R21/MATRIX-M™ MALARIA VACCINES

Malaria vaccine development began in 1960.[7] Natural exposure to plasmodium falciparum triggers gradual strain-specific immunity, initially protecting against severe disease and later mild disease.[8] Strategies for vaccine development draw from RTS, S and irradiated sporozoite vaccines, as well as monoclonal antibodies targeting promising epitopes. So far so good, there are two malaria vaccines approved by the World Health Organization's Strategic Advisory Group of Experts (SAGE) and the Malaria Policy Advisory Group (MPAG). The first malaria vaccine approved was RTS, S/AS01(Mosquirix) while the second one was R21/Matrix-M™[9,10] The RTS, S/AS01 (RTS, S) vaccine was the first approved

vaccine in the world to combat a human parasitic disease.[11] The RTS, S/AS01 was launched as a pilot program in Ghana, Kenya, and Malawi and has been met with strong community demand and has been able to reach a significant number of children in a relatively short period.[12] The RTS, S/AS01 malaria vaccine implementation program has been established in Ghana, Kenya and Malawi where participants of the pilot study would receive doses of the vaccine to continue vaccinations in pilot areas in those countries.[12] Allocations were also made for new introductions in other African countries such as; Benin, Burkina Faso, Burundi, Cameroon, Democratic Republic of the Congo (DRC), Liberia, Niger, Sierra Leone and Uganda.[12]

The second vaccine, the R21/Matrix-M™ malaria vaccine which was recently developed by the University of Oxford and the Serum Institute of India aimed to leverage Novavax's adjuvant technology and demonstrates high efficacy with a reassuring safety profile. Experts revealed that the R21/Matrix-M™ vaccine has reached the initial 1-year endpoint in a pivotal large-scale Phase III clinical trial and has been administered to 4800 children across four African countries which include; Burkina Faso, Kenya, Mali and Tanzania, however, the Phase III trial results are undergoing clinical observations before publication.[9] The ability of the R21/Matrix-M™ malaria vaccine to produce the desired result over a year was 75% (95% confidence interval of 71–79; $p < 0.001$) at places with high seasonal malaria transmission and 68% (61–74; $p < 0.001$) at the places with more perennial transmission using standard age-based administration.[9]

Furthermore, higher R21/Matrix-M™ vaccine-induced antibody titres were observed among the participants aged 5–17 months compared to those 18–36 months old ($p < 0.0001$). Researchers at the University of Oxford found that the participants in the younger age category, in whom R21/Matrix-M™ malaria vaccine is most likely to be widely transferred, showed the highest vaccine desired result at both seasonal, 79% (73–84, $p < 0.001$), and standard areas 75% (65–83, $p < 0.001$) in a year.[9]

Following the endorsement and recommendations by the WHO, more regulated approvals are expected to follow within a short period and the two malaria vaccines could be available for use by the end of 2023.[9,10]

4 | IMPORTANCE OF MALARIA VACCINES IN AFRICAN NATIONS

After the provision of clean water and sanitation, vaccination against infectious diseases like malaria has contributed the greatest to public health worldwide, compared with other human interventions. An effective malaria vaccine would be an important tool to tackle the enormous socioeconomic burden caused by this disease in Africa. Malaria vaccines would promote both individual and public health. Malaria vaccines have the potential to prevent numerous deaths and cases. The malaria vaccines have been proven to be cost-effective in areas with moderate to high plasmodium falciparum and can be delivered through routine immunization. For example, the licensed RTS, S/AS01 vaccine shows moderate efficacy against clinical malaria, targeting the pre-erythrocytic stage in the liver thus reducing the number of times a child gets malaria, including severe, life-threatening malaria, and it reduces child mortalities.[9] On the other hand, the R21/Matrix-M™ malaria vaccine is safe and highly effective across several clinical studies.[9] Also, the R21/Matrix-M™ vaccine is easily transferred, cost-effective affordable and ready for distribution in African nations where it is needed most, with the potential to save many people's lives.[9] The good news is that the WHO announced that 12 countries in Africa will be allocated a total of 18 million doses of RTS, S/AS01 for the 2023–2025 period and R21/Matrix-M vaccine could be ready to begin wider roll-out as early as next year 2024. This announcement by the WHO was in response to the high demand for these malaria vaccines.[9]

5 | CHALLENGES

Plasmodium is one kind of blood parasite, with four species; *P. falciparum*, *P. vivax*, *P. ovale and P. malariae P. knowlesi* are considered parasites of humans.[1] However, *P. falciparum* is the deadliest parasite to humans among all Plasmodium species, even if many antimalarials have been developed for Plasmodium treatment, unfortunately, the malaria outbreak could not be prevented in developing countries.[1] In areas with high disease incidence, vaccines are an effective method to prevent the spread of *P. falciparum*. However, malaria vaccination usage and acceptability were impeded in African Nations. We realized that the challenges of malaria treatment and prevention are multi-faceted.[2,14–19] First, drug-resistant parasites undermine antimalarial drugs. Secondly, endemic areas lack quality-assured medicines and diagnostic testing. Additionally, limited access and affordability of mosquito nets and indoor spraying impede protection. Moreover, developing a safe and effective vaccine against the complex parasite is challenging. In general, slower-than-expected uptake of vaccines is a pressing public health challenge across African nations. This has been particularly observed during the rollout of Covid-19 vaccinations in most African countries where the majority of people were sceptical about taking the COVID-19 vaccines.[13]

The majority of African studies proved that African dwellers are hesitant about malaria vaccination because of the failure of the vaccine to protect against malaria while some were afraid of adverse effects following immunization and the handling condition of the vaccine in most African countries.[14–17] Systematic reviews by researchers identified safety concerns, an efficacy profile, and a poor level of awareness as reasons for low acceptance evaluated the acceptability of the malaria vaccine.[18] A low coverage and uptake of the malaria vaccines especially the RTS, S/AS01 malaria vaccine has also been observed in three African countries, Ghana, Kenya, and Malawi since the year 2019.[19] Even though malaria vaccines present the most effective means of preventing malaria, however, their implementation faces various challenges (see Table 1).

TABLE 1 A summary of the challenges that African countries can encounter during the implementation of a vaccine strategy for malaria prevention, updated from the World Health Organization (WHO). Malaria. www.who.int [Internet]. March 29, 2023; available from: https://www.who.int/news-room/fact-sheets/detail/malaria.[19]

Challenges	Description
1. Vaccine skepticism and false information	Fear of negative side effects, historical vaccine myths, and concerns about cost and spouse agreement
2. Vaccine shipment and storage	Inadequate storage facilities, power interruptions, and the need for effective cold chain systems
3. Limited demographic representation in clinical trials	Exclusion of certain subpopulations, limiting the generalizability of trial findings
4. Low awareness among health workers	Insufficient knowledge and understanding of the malaria vaccine among medical staff members
5. Inadequate funding and resource allocation	Limited financial resources allocated to vaccine programs, hindering implementation efforts
6. Infrastructure and logistical challenges	Limited access to healthcare, poor living conditions, and program inconsistency.
7. Educational barriers and community engagement	Lack of public education, misinformation, and challenges in fostering community participation

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6 | CONCLUSION

Although the ability of the malaria vaccines to produce the desired result is about 40%, the vaccines will likely be most successful when used alongside other pre-existing malaria prevention methods like clearing stagnant water, and bushes, use of treated mosquito nets, and spraying houses with insecticides and when there is wide vaccination coverage among affected African populations. Epidemiologists expect that decreased vaccine hesitancy towards the COVID-19 vaccine would likely result in reduced vaccine hesitancy towards the malaria vaccines, and estimated incident cases of malaria will likely decrease over the next 10 years as malaria vaccine coverage increases across African countries.

7 | RECOMMENDATIONS

To combat malaria effectively in African Nations, we recommend all African leaders set up a comprehensive approach that includes prevention, healthcare access, and implementation research strategies through international collaborations with the WHO, the UNICEF, and malaria experts and researchers in the western world towards abundant supplies of these malaria vaccines in their various African countries. These malaria vaccines should be cost-effective and included in the National Program for Immunization (NPI) schedule. Further epidemiological and experimental research on malaria vaccines should be carried out by healthcare providers in Africa to improve the knowledge, attitude, and perception (KAP) of African dwellers about malaria vaccines. Healthcare providers in Africa should also engage in community engagement with the African dwellers including the religious and traditional leaders, the market women, community heads, schools, as well as students' unions towards the willingness and acceptability of the novel malaria vaccines among the African population. This awareness and campaigns could be through mass awareness and campaigns through Newspapers, Television, Radio, and social media platforms such as Facebook, Twitter, etc. in various African community areas. We believe that by addressing these vaccination challenges, we can work towards eliminating malaria in Africa as a global health threat.

AUTHOR CONTRIBUTIONS

Malik Olatunde Oduoye: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Muhammad Usman Haider**: Funding acquisition; Visualization. **Mohammed Dheyaa Marsool Marsool**: Data curation; Formal analysis; Investigation; Software; Writing—review & editing. **Mayowa Odunayo Kareem**: Funding acquisition; Validation; Visualization; Writing—original draft. **Adenike Ebunoluwa Adedayo**: Formal analysis; Funding acquisition; Visualization. **Abdulkarim Surajo Abdulkarim**: Funding acquisition; Visualization. **Abdullahi Adeyemi Adegoke**: Funding acquisition; Visualization; Writing—original draft. **Ikshwaki Kaushik**: Resources; Visualization; Writing—original draft. **Hamza Irfan**: Software; Writing—review & editing. **Hassan Abdullahi Yusuf**: Visualization; Writing—original draft. **Hussain Haider Shah**: Visualization; Writing—original draft. **Karim Arif Karim**: Software; Writing—original draft.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No new data generated for this work.

TRANSPARENCY STATEMENT

The lead author Malik Olatunde Oduoye, Karim Arif Karim affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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