Annals of Medicine and Surgery 81 (2022) 104366

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu



Perspective

# Increasing challenges of malaria control in sub-Saharan Africa: Priorities for public health research and policymakers

ARTICLE INFO

*Keywords*
Malaria control
Sub-Saharan Africa
WHO
Malaria vaccine
Policymakers

ABSTRACT

The ever-increasing cases and mortality due to malaria remains one of the most important public health threats, especially in sub-Saharan Africa—where this burden is considerably high. In 2020, sub-Saharan Africa accounted for about 95% of all cases and 96% of all malaria deaths with about 80% of these deaths reported in children under the age of 5. This review, adopting a public health focus, aimed to understand the challenges of malaria control in sub-Saharan Africa despite ongoing public health interventions. Our review highlights two important findings. First, the increasing resistance of malaria parasites to artemisinin-based combination therapy (ACT) and its partner drugs coupled with increased vector resistance to pyrethroids and insecticides is reversing the progress of public health interventions in keeping malaria under control. Second, the wanning for the efficacy of the WHO-approved vaccine i.e. RTS,S from 60 to 70% following 18 months of observation, and its short-term availability remains an impediment to achieving the WHO target of producing malaria vaccines with more than 75% efficacy by 2030. Our findings underline the need to reassess research priorities with a focus on vaccine production in sub-Saharan Africa. Furthermore, African governments and policymakers must be committed to invest both the political and financial capital in vaccine production and distribution.

## 1. Introduction

Malaria remains one of the most worrisome vector-borne infectious diseases plaguing sub-Saharan Africa (sSA) despite concerted efforts geared towards it and the fact that it is curable and preventable [1]. In 2020, the estimated number of malaria cases worldwide was 241 million (227 million in 2019) with an estimated over 200 million malaria cases and 403,000 deaths in sub-Saharan Africa, of which 80% were children younger than 5 years. Nigeria (27%), the Democratic Republic of Congo (12%), Uganda (5%), Angola (3.4%) and Burkina Faso (3.4%), and Mozambique (4%) accounted for over half (55%) of all malaria cases globally [2]. Malaria case incidence in Africa decreased by 38%, from 363 to 225 per 1000 populations at risk, and the malaria mortality rate decreased by 67%, from 121 to 40 deaths per 100,000 populations at risk from 2000 to 2019 [3]. In 2020, the case incidence increased by 232 per 1000 populations at risk, attributed to the disruption in the provision of malaria services during the COVID-19 pandemic [2]. Between 2000 and 2015, sSA had a reduction in malaria infections by half and clinical disease by 40%, mainly due to mass scale-up of malaria control interventions such as the massive deployment of long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS), prompt diagnosis and treatment with effective antimalarial drugs; with insecticide-treated nets and vector control pivotal to the success contributing to about 68% and 78% of the progress made respectively [4–6].

However, over the past few years, progress has stalled and, in some areas, reversed [3]. Several factors such as widespread and increasing insecticide resistance of pyrethroid-based vector control with substantially higher costs of repurposed insecticides to address resistance [7], the emergence of artemisinin partial resistance [2], and insufficient fund for malaria control and elimination have contributed towards this trend [3]. The global malaria funding reduced from $3·2 billion in 2017 to $3·0 billion in 2019, which is far below the estimated $5·6 billion required annually to remain on track toward the WHO global malaria strategy targets [3].

To eradicate malaria, African countries and the global malaria community must address the constraints that prevent efficient delivery of existing effective key malaria control strategies and forthcoming innovations and tools. Communities must be fully involved in the fight against malaria through effective decentralization and community-level integration of health services to build sustainability [8]. Furthermore, increase political and individual accountability for malaria elimination by strengthening health systems and disease surveillance; promoting multisectoral ownership of health at regional, economic communities, and national levels; supporting advocacy and communication; and addressing social determinants of health, including equitable access to vital health services and commodities as highlighted in the Africa Health Strategy 2016–2030 are key strategies to reduce global malaria incidence and mortality rates to at least 90% by 2030 [8,9]. More so, the recent use of the RTS,S/AS01 (RTS,S) (Mosquirix) vaccine among children living in the sub-Saharan region of Africa (Ghana, Kenya and Malawi) through countries' national immunization programs will further reduce the number of deaths and provide an additional approach in the fight against malaria in addition to other interventions [10].

## 2. Rising threat of malaria in sub-Saharan Africa

Malaria remains one of the most concerning vector-borne infections in sSA despite the national and international initiatives that have been aimed against it in recent years [1,11]. Over 90% of all malaria-related deaths occur in tropical regions in sSA since the disease is virtually

https://doi.org/10.1016/j.amsu.2022.104366
Received 30 July 2022; Accepted 11 August 2022
Available online 18 August 2022

exclusively a problem in poorly developed tropical or sub-tropical regions [11]. In 2019, over 229 million cases of malaria and 409,000 malaria-related deaths were reported globally [1]. The majority of the reported cases, about 95%, were located in 29 countries in sSA, and around 90% of the 409,000 deaths were likewise from sub-Saharan Africa [3]. About 55% of the cases globally were found in countries such as Nigeria (27%), the Democratic Republic of Congo (12%), Uganda (5%), Angola (3.4%), Burkina Faso (3.4%), and Mozambique (4%) [2]. Children under five and pregnant women are typically the most vulnerable groups to malaria; every 2 min, a child under five dies from the disease [12]. Pregnancies exposed to malaria in the WHO African region may result in foetal loss, low birth weights, and other morbidities [3,13].

Malaria is a disease intimately associated with poverty. The prevalent poverty level in sSA, combined with inadequate economic policies, is one of the various factors contributing to the rising threat of malaria in the region [1]. Poor living conditions encourage mosquito vector breeding, and people living in such areas often have little or no access to adequate healthcare [14]. Climatic conditions in sub-Saharan Africa such as abundant rainfall and high temperature create an ideal setting for the reproduction and propagation of female anopheles mosquitoes [15]. In addition to this, there is an upsurge in the resistance of mosquitoes to the pyrethroids used in Insecticide Treated Nets (ITNs), and the resistance of parasites to antimalarial, resulting in difficulty in curbing the diseases [16]. Furthermore, the health system in sSA is attributed to limited access to medical services and products, a deficit of human resources, and a general lack of functioning health facilities [17]. The majority of countries in sSA lack the government backing required for efficient malaria management. Most control strategies in place inevitably lose efficiency due to the failure of governmental bodies to maintain consistent and adequate financial practices [1,17]. The aforementioned conditions, in addition to other factors such as inadequate research facilities, have continuously increased the burden of malaria in sub-Saharan Africa.

## 3. Ongoing interventions used for malaria prevention and challenges

Over the past 2 decades, malaria-endemic sSA countries have adopted different malaria control interventions. This includes vector control, which involves the use of long-lasting insecticide-treated nets (LLIN) and residual indoor spraying; preventive chemotherapy, which involves intermittent preventive treatment of pregnant women (IPTp), intermittent preventive treatment of infants (IPTi), and seasonal malaria chemoprevention (SMC) for under-five children; case management, which involves rapid diagnosis testing kit (RDT) and treatment with Artemisinin combination therapy (ACT) [18]; and recently, the introduction of malaria vaccine (Mosquirix). Although these interventions have been impactful in reducing the malaria burden in sSA, the WHO's African region still fell short of the 2020 Global Technical Strategy milestones for malaria mortality by 25% and morbidity by 20% [3].

### 3.1. Vector control

***Long-Lasting Insecticide-Treated Nets (LLIN)*:** Universal coverage of LLIN is the main tool to prevent malaria and a critical component of the first pillar of the WHO Global Technical Strategy for Malaria (2016–2030), with approximately 2.2 billion nets distributed globally at mid-2020 [3,19]. LLIN generally prevents malaria by minimizing the degree of contact between the vector (*Anopheles* spp) and human populations; thereby reducing the feeding tendencies of mosquitoes and the chances of survival. The early years of the 21st century witnessed a significant increase in the use of LLIN in sSA, with more than 67% of the population having access to LLINs in 2015 compared to <2% in 2000 [11]. According to Paintan and colleagues (2013), the distribution of LLIN between 2010 and 2012 in forty (40) countries of sSA averted more than 350,000 malaria-related under-five mortalities [20]. Despite these gains, the effectiveness of LLIN is threatened by a number of issues, including the emergence of insecticide resistance, exophilic traits of the *Anopheles* vector, operational challenges with the routine distribution of LLINs, and improper use [21,22]. Hancock and colleagues (2020), revealed that there was a significant increase in the resistance rate to pyrethroids and DDT, the main chemicals impregnated into LLINs, throughout sSA between 2005 and 2017, with the mortality rate of *Anopheles* vector after exposure decreasing from almost 100% to below 30% in some regions [23]. In addition to physiological resistance to insecticide, some *Anopheles* spp have modified their feeding patterns by adopting new times or places of bite to prevent exposure to insecticides [24]. For instance, studies conducted in Kenya, Benin, and Senegal showed a change in the vector biting behavior, with *Anopheles gambiae,* which often bites hosts very late in the night (after 12:00 a.m.), began to bite a little earlier before 10:00 p.m. when people are yet to sleep under LLIN [25–27].

To complement LLIN mass distribution campaigns and maintain coverage, the WHO recommends continuous distribution of nets to pregnant women and infants through antenatal care (ANC) and Expanded Programme on Immunizations (EPI) services respectively. However, these channels are underutilized, with only 49 countries distributing LLIN through ANC and barely 29 through EPI [28,29]. Furthermore, pregnancies and births that occur between campaigns represent the vulnerable population that remains unprotected. The limiting factors identified include logistics; programme implementation and human resources; and data collection, management, and use [29]. Beyond having access to LLIN, a range of factors, notably behavioural, sociocultural, and economic factors, also play a significant role in influencing LLIN owners on its proper usage and care [22]. While the WHO recommends a 3-year LLIN serviceable life span, the rife belief, as observed in Ethiopia, Ghana, and Kenya, is that LLINs stopped being effective after 6 months, thereby leading to nets usage for unintended purposes [22]. This practice is particularly common in poverty-stricken regions as McLean and colleagues (2014) observed that about 87% of sampled households in a Tanzanian community called Lake Tanganyika reported the usage of bed nets for fishing, with the inability to afford a fishing net and hunger as the major reason [30]. Similar practices and reasons were also observed in Nigeria, Mozambique, Cameroun, Uganda, and Rwanda [31–34].

### 3.2. Indoor residual spraying of insecticides (IRS)

Currently, IRS is one of the two (2) broadly applicable vector control interventions alongside LLIN, involving the application of long-acting insecticides on the walls and roofs to kill adult *Anopheles* vectors that rest on these surfaces [35]. The primary malaria control method used during the Global Malaria Eradication Campaign (1955–1969) was IRS, with 37 of the 143 targeted countries becoming malaria-free by 1978, and the malaria burden drastically declined in the remaining countries [36]. After this period, there was limited use of IRS in sSA, following the global consensus to replace malaria eradication with a long-term control program, and this contributed to the increase in the malaria burden in the region. However, the recent success of IRS in reducing malaria cases in southern Africa, where IRS continued to be an important pillar of malaria control, by more than 80% renewed interest in IRS as a malaria prevention tool [37]. As a result, in 2006, the WHO reaffirmed and produced a positional statement that IRS should be an integral part of national malaria control strategies in malaria-endemic countries [38]. In 2010, IRS expanded in SA due to the start of the US President's Malaria Initiative (PMI), with coverage increased from <2% of the at risk population in 2005 to 11%, around 78 million people [39,40] IRS was estimated to contribute approximately 10% of the total reduction in malaria cases between 2010 and 2015, with significant reductions in all-cause child mortality and malaria parasite prevalence recorded in several countries, including Equatorial Guinea, Tanzania, Benin, Kenya

and Malawi [5].

Unfortunately, due to the intensification of *Anopheles vector* resistance to pyrethroid—the most popular insecticide used for IRS due to its low cost and longer residual decay rates—IRS has been scaled down in sSA in recent years as alternative insecticides, such as organophosphates, organochlorines, and carbamates, are about 19 times more expensive than pyrethroid, thereby significantly increasing the overall IRS operational cost [41]. Consequently, between 2009 and 2015, there was over a 50% decrease in the number of structures sprayed, with a significant decline seen in Tanzania (68%), Senegal (64%), Zambia (63%), and Madagascar (56%), and PMI suspending IRS activities in Angola, Liberia, and Malawi [41] Furthermore, WHO confirmed that irrespective of population-wide coverage of IRS, outdoor malaria transmission still persists [42]. For instance, an induced exophily rate of about 62% was observed in the Ouémé region of Benin due to the presence of insecticide on the walls [43].

### 3.3. Artemisinin-based combination

Following the widespread resistance to chloroquine, the first-line treatment of uncomplicated falciparum malaria in the second half of the 20th century is Artemisinin combination therapy (ACT), a schizonticidal drug with different mechanisms of action to prevent artemisinin resistance [44]. ACT was introduced in 20 African countries between 2001 and 2004 to curb the threat of chloroquine resistance [45]. Since then, over 81% of ACT regimens deployed worldwide were distributed in Africa, averting over 54% of malaria-related mortality in the region between 2000 and 2013 alongside vector control efforts [42].

However, the success recorded is being threatened by the emergence of artemisinin (ART) resistance. While it is reported that ART resistance emerged from the Greater Mekong sub-region, evidence has shown that it has spread to other malaria-endemic regions, including sSA [2]. Daily and colleagues (2016) ascertained that multiple point mutations in the *Plasmodium falciparum* Kelch 13 gene (*pfk13* gene) account for the clinical ART resistance seen in Southeast Asia and South America. Similar clonal expansion of mutations *pfk13* mutations have been observed in East Africa, particularly Rwanda (R561H) and Uganda (C469Y and A675V) [46]. Although treatment failure remains <10% due to the effectiveness of partner drugs in ACT, it is critical to conduct further studies to assess the degree of polymorphisms of the *pfk13* gene in East Africa [2].

### 3.4. Malaria vaccine

In 2021, the WHO approved RTS,S (Mosquirix) as the first malaria vaccine following the successful pilot studies in three (3) sSA countries: Malawi, Ghana, and Kenya [47]. During the course of the trial, more than 830,000 children were vaccinated with over 40% and 30% reduction in malaria episodes and admission for severe malaria, respectively. Mosquirix population-wide coverage is estimated to save tens of thousands of children annually [2]. However, scaling up malaria vaccination faces recurrent challenges with immunization, such as supply chain, waning immunity, and funding [48].

## 4. Appraisal of malaria vaccines

One of the most important scientific developments of the twentieth century has been the development of safe and effective vaccines against diseases that significantly increase morbidity and mortality [49]. The World Health Organization (WHO) estimated that 2–3 million lives are saved annually by existing immunization programs that were scaled up globally after the World Health Assembly (WHA) established EPI in 1974 [3,50] Various vaccines have been developed for the treatment of malaria, and the safest and currently used vaccine is the RTS, S/AS01 vaccine, a product of 30 years of study and development by GlaxoSmithKline in collaboration with the Program for Appropriate Technology in Health (PATH) organization and assistance from a network of African research institutions. Sequel to the production, funding for the late-stage development was provided by the Bill and Melinda Gates foundation between 2001 and 2015 [51].

RTS,S/AS01, a vaccine that acts against *Plasmodium falciparum*, the deadliest malaria parasite globally and the most prevalent in Africa, this vaccine aims to trigger the immune system to defend against the first stages of malaria when the parasite enters human blood through a mosquito bite and provides adequate protection to the liver, the main region of parasite development [10,52]. To determine its safety, immunogenicity, and efficacy, the vaccine undergoes preclinical research trials in animals and phase 1 to phase 3 clinical trials in humans [53]. The vaccine passed the clinical trials and in July 2015, based on the results of the Phase 3 trial of the vaccine, the European Medicines Agency (EMA) issued a positive scientific opinion on the vaccine under Article 58, concluding that the vaccine had an acceptable safety profile and that the benefits of the vaccine outweighed the risks. The WHO concluded that the vaccine was safe and effective, with the potential to provide an important impact when added to current malaria control interventions [51]. The RTS, SAGE/MPAG Working Group with the WHO recommended that RTS,S/AS01 should be administered at a minimum of 4 doses to reduce malaria disease and burden in children under 5 months of age living in countries in the sSA, especially Ghana, Kenya and Malawi, and this pilot introduction has resulted in the high uptake of the vaccine and has reaffirmed its favorable safety profile [51, 52].

## 5. WHO 2030 malaria target

In 2019, the African region represented 94% of the global burden of malaria mortality and morbidity, with two countries, the Democratic Republic of the Congo and Nigeria, accounting for approximately 40% of all malaria-related morbidity and mortality worldwide [2]. With available data, it is clear that the African region has not been able to achieve the 2020 WHO strategy milestones for reducing malaria morbidity and mortality. Progress has been considerably stalled by some factors, such as rapid population growth and high-impact health emergencies [2].

However, in October 2021, the RTS,S malaria vaccine was recommended for use in malaria-endemic regions by the WHO [51]. This vaccine received positive opinions from the European Medicine Agency, as well as the pilot program conducted in parts of Malawi, Ghana and Kenya in 2019 [51]. Though, wanning efficacy of this vaccine efficacy from its initial 60–70% has been reported [54]. This may hinder the strategic goal of the WHO in producing a malaria vaccine with >75% efficacy by 2030. While the R21 malaria vaccine has shown 71–77% efficacy following its administration in children living in malaria-endemic areas with the seasonal transmission of malaria [55], the protective efficacy in areas with year-round malaria transmission has not been fully understood yet [54]. These vaccines are expected to be an important addition to the existing interventions available in the fight against malaria.

It is also expected that the malaria vaccine will assist to achieve the WHO's global malaria strategy to reduce malaria case incidence and mortality rates by at least 90% by 2030 [2]. However, it is very important to prevent a repeat of the scenario during the COVID-19 pandemic where the lack of manufacturing and financing capabilities, led to unequal access to COVID-19 vaccines [56]. Conclusively, Africa's lack of vaccine production capacity is a serious threat to the WHO 2030 malaria target and must be urgently addressed to help eliminate malaria and other diseases.

## 6. The need to prioritize vaccine development and research in Africa

Africa has the highest incidence of mortality caused by infectious diseases, and remarkably, lacks adequate pharmaceutical

manufacturing capacity to produce vaccines [57]. As a matter of fact, Africa's local pharmaceutical manufacturing is greatly reliant on imported commodities and industrial machinery, and this dependency is a major challenge for Africa's health resilience [56]. For example, In Nigeria, significant attention has not been paid to the local production of raw materials, and due to the lack of domestic production of key inputs such as Active Pharmaceutical Ingredients (APIs), the country is forced to rely on foreign countries like India and China for supply, which causes a hike in prices and foreign exchange difficulties [58]. Furthermore, among the 54 countries in Africa, there are just 8 countries that have industries operating across the vaccine-manufacturing landscape, of which only 1 (Senegal) has the pre-qualification from the WHO to export vaccines [59]. However, a few of the causes of the low local vaccine production in Africa include underinvestment in research and development, inadequate knowledge transfer, and emigration of highly qualified experts [60].

Vaccines constitute an important component of adequate health security and are essential to reduce mortality, improve life expectancy, and promote economic growth [57]. The assistance of donor initiatives and philanthropic groups has been helpful in Africa's efforts to control diseases, however, there are considerable limits to which this assistance can go and Africa must now improve its manufacturing capacity. Moreover, based on previous vaccination and immunization campaigns in Africa, high cost and limited supply of vaccines have posed significant challenges to the successful administration of the vaccination programs [61], and if the demand and supply imbalance between available vaccine production capacity and Africa's population is not addressed immediately, it is likely to worsen in time to come. Strengthening Africa's local pharmaceutical manufacturing capacity will take lots of investment, dedication, advocacy, and sustained cooperation between African governments and other relevant stakeholders – including private, public, and global partners – acting on a regional and continental basis. However, Africa must strive to attain independence and a capacity strong enough to satisfy its population demands, hence; there is necessary to prioritize vaccine development and research in the African region.

## 7. Conclusions and recommendations for future research

To address the increasing prevalence of malaria, and subsequent elimination and control of malaria in sSA, additional interventions are needed. One of these interventions includes the preventive treatment of malaria among school-aged children. In a systematic review and meta-analysis conducted by Cohee and colleagues (2020) [62], it was found that this intervention reduced the risk of malaria transmission among these children and could possibly contribute to the overarching goal of eliminating malaria if considered by relevant stakeholders, including malarial program managers and policymakers.

Attention must also be paid to the effectiveness of mass drug administration (MDA) to control malaria. The lessons of the successful implementation of mass drug administration (MDA) in China's intervention to control malaria should be noted by researchers of sSA, as these strategies could be modified and further developed in innovative ways that would suit the climate of sSA [63]. Furthermore, there is an urgent need to continuously develop effective data modeling and distribution of drugs and other palliatives geared to eliminating and controlling malaria, to manage resources for a successful implementation [64,65].

Although the World Health Organization (2021) has approved the widespread use of RTS,S/AS01 vaccine against *Plasmodium falciparum* malaria infection, most especially to address the growing need to vaccinate children in sSA, one of the greatest impediments in meeting the WHO target of >75% efficacy is wanning of RTS,S vaccine efficacy. In the first 6 months of vaccination in children aged 5–17 months, about 60–70% efficacy was reported. However, by 18 months of observation, the vaccine efficacy declined [54,66]. This may result in failure to meet the WHO malaria target of 2030 as highlighted above. It is important to acknowledge that R21 (a circumsporozoite protein-based subunit vaccine) has shown a 71–77% efficacy in children, and studies are still ongoing to confirm its effectiveness for use [54,55]. As a result, there is a need for the production of highly effective vaccines, especially in sSA where the malaria burden is considerably high to achieve the WHO target of 2030.

Importantly, in addition to the factors affecting the vaccine development process in Africa, other factors include the lack of well-trained scientists and competent early career researchers, as well as technicians required to support technical operations, including the knowledge of vaccine development, formulation, safety, quality control, and pharmacovigilance. This calls for the need to transfer expertise, skills, and medical technologies as well as training of scientists in this region on vaccine production to achieve remarkable vaccine coverage. A poor vaccine learning ecosystem is another challenge facing sSA, and for sSA to witness significant progress in malaria elimination, it is necessary to focus on the teaching of vaccinology in biomedical and public health-related courses in tertiary institutions of learning. This is because the holistic concept of vaccinology is not usually taught in the disciplines such as microbiology, epidemiology, medical statistics, and public health which represents the scientific background for a comprehensive understanding of the vaccine-development process, the clinical aspect of vaccines, the safety and ethics involved [67]. Interestingly, adopting the knowledge, expertise, and capacity of early-career scientists in vaccine-development activities is the key, as such, the teaching of vaccinology will allow for a better understanding of important areas of the vaccine-development process [68]. It is also necessary to develop effective strategies and policies that will bridge the gap between vaccine equity and acceptance within communities in sub-Saharan Africa [69,70].

Stakeholders, governments, and policymakers in Africa must also commit to investing political and financial capital towards the creation of a sustainable ecosystem for vaccine production. In addition to this, the incorporation of technological innovations and the use of home-grown information and communication technologies should also be developed to improve malaria response with regard to epidemiological surveillance and statistical modeling tools, as this will further aid geospatial mapping and vector parasite monitoring to address the growing issues attributed to malaria control [70].

Finally, this growing threat of addressing malaria epidemiological surveillance also calls for the prioritization of holistic approaches to health by African policymakers [71]. This would not only foster effective collaboration among scientists, but also bring about innovative ways to eliminate malaria amid other complex challenges such as climate change. We, therefore, urge researchers to design future projects in line with fostering the holistic approaches to health such as One Health and Planetary Health to achieve multi-disciplinary collaborations in tackling malaria.

## Conflicts of interest

None.

## Sources of funding

None.

## Ethical approval

Not Required.

## Consent

Not required.

## Author contribution

All the authors contributed equally to this paper and approved it for publication.

## Guarantor

Yusuff Adebayo Adebisi.

## Funding

Authors have received no funding

## Declaration of competing interest

The authors declare no competing interest.

## Acknowledgment

None.

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