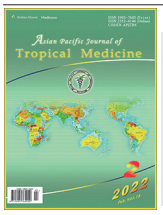

Perspective

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World's first malaria vaccine and its significance to malaria control in Africa

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In October 2021, the World Health Organization (WHO) endorsed the first malaria vaccine, as a complementary tool for widespread use among children in at-risk areas; sub-Saharan Africa and in other regions with moderate to high *Plasmodium falciparum* malaria transmission, including our country, Kenya[1]. The breakthrough followed three decades of clinical trials in seven African countries including Ghana, Kenya and Malawi, where a large-scale pilot programme coordinated by the WHO since 2019, administered 2.3 million doses of Mosquirix, the malaria vaccine, to infants[1].

Malaria, a disease caused by the *Plasmodium* parasite and transmitted by female *Anopheles* mosquitoes[2] tops the list of diseases affecting the African continent and arguably has the greatest impact on African nations' economic and social development. It is reported that 94% of all malaria cases occurred in Africa in 2019 with six countries accounting for approximately half of all malaria deaths worldwide: Nigeria (23%), the Democratic Republic of the Congo (11%), United Republic of Tanzania (5%), Burkina Faso (4%), Mozambique (4%) and Niger (4%)[3]. According to the WHO estimates, malaria is far more deadly than even COVID-19, a disease that has ravaged the world; it killed an estimated 386 000 Africans in 2019, compared with 212 000 confirmed COVID-19 deaths in the past 18 months[4]. Pregnant women and children under the age of five are the most affected[3].

1. The vaccine dosage and safety

The vaccine RTS,S/AS01 (RTS,S) (trade name Mosquirx), is a recombinant protein-based vaccine given in 4 doses to children[5]. The first dose is given at between 5 and 17 months old followed by 2 other doses after every month. The 4th dose is then administered 15-18 months after the 3rd dose[5]. The efficacy is about 40% against malaria cases and 30% against severe malaria[5]. The vaccine has been established to be safe by the WHO Malaria Vaccine Pilot Evaluation (MVPE)[6] where it was used among 800 000 children as part of a pilot implementation programmes and no significant difference in the overall incidence of adverse events was observed in 24 months between RTS,S/AS01 and control groups in children of 5-17 months old[5,6]. The MVPE results showed no evidence of an excess of meningitis, cerebral malaria, or gender-specific mortality comparing age-eligible children living in implementation areas with those in the comparison areas[6]. Besides, the MVPE reports builds on phase 3 trial data that was examined by the European Medicines Agency, which issued a positive recommendation[7].

2. Why did it take so long to create a malaria vaccine?

The most significant reason is that the malaria parasite *Plasmodium falciparum* that causes most cases of malaria is very complex. It exhibits a high degree of genetic polymorphism; it has a genome with more than 5 000 genes[8] (this is far more than the mere 12 genes rattling around inside SARS-CoV-2, the coronavirus behind COVID-19). This makes identification of "essential" proteins that could be used as vaccine candidates difficult. The parasites also display a variety of antigens on their surface[9] which help them escape the immune system and also render vaccines based on

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specific antigens less effective. A vaccine developed against one malaria strain grown in the laboratory generally does not work against many of the malaria parasites that are encountered when bitten by infected mosquitoes[9]. This is also the reason why even though RTS,S/AS01 is a good vaccine, it protects against only 30% of infections.

Another factor that contributed to the delay is that scientists working on malaria vaccines in the early stages lacked an understanding of the specific immune responses associated with protection against the malaria parasite[9]. There was also the lack of typical tools for vaccine development, such as reliable markers of protection, *in vitro* assays that measure protein function, and animal models that mimic human biology, which limited identification of new malaria vaccine candidates[9]. Although much work has gone into generating these tools for vaccine development, none have been proven reliable for human malaria infection and disease, thus hindering the selection of candidates for further evaluation in clinical trials[9].

Further complicating matters, *Plasmodium* goes through multiple life stages as infections spread from the bloodstream into the liver (pre-erythrocytic stage) and then back into the bloodstream, when the parasite infects red blood cells (RBC) themselves (blood stage). Thus, the scientists had to pursue a diversity of approaches: an effective vaccine against the pre-erythroctic stage would be one that elicits immune response to either prevent infection of the liver cells or lead to destruction of the infected liver cells while an effective blood stage vaccine would be the one that either elicits immune response to prevent infection of RBC or decrease the number of parasites in the blood or even reduce the severity of the disease by allowing the body to develop a natural immunity with little risk of getting ill. Another option was to develop a transmission blocking vaccines that would induce antibodies to block maturation of malaria parasites in mosquitoes that fed on vaccinated individuals.

The RTS,S/AS01 vaccine development was based on the pre-erythrocytic stage of the parasites; the sprozoites that first enters the human bloodstream and eventually find their way to the liver[10]. The researchers engineered carrier proteins-a surface protein from the hepatitis B virus that were studded with bits of circumsporozoite protein. These proteins would then self-assemble into microscopic virus-like particles that would trigger the immune system to make antibodies against circumsporozoite protein[10].

The question of safety also played a role in the vaccine delay: the target population for RTS,S/AS01 is young children ages 5 to 18 months, but to prove the vaccine's safety and efficacy, researchers had to start with adult clinical trials and work their way down to younger age groups[10].

Lastly, lack of political will and no real market for a malaria vaccine in resource-rich countries like the Unites states also played a role in the delay as pharmaceutical companies did not have a strong financial incentive to accelerate vaccine development.

3. What does this breakthrough mean for malaria control in Africa?

This announcement is indeed a cause for celebration, as the historic vaccine has been developed in Africa by African scientists. This goes to show that the continent is a fertile ground for innovation in health care and beyond, and convinces that more solutions to fight malaria and other deadly diseases could emerge from here. The vaccine has a great potential to reduce death and illness in high burden areas in sub-Saharan Africa and provides an additional tool to the malaria control tool kit that will make malaria control more efficient[1].

However, it's important to note that the vaccine has modest efficacy and will be most successful if it's a complement to other pre-existing malaria prevention methods like insecticide treated bednets, indoor residual spray, antimalarial drugs and care for the environment[1,3,5]. A study by the London School of Tropical Medicine reported a 70% reduction in hospitalisations and death in children given the mosquirx vaccine before the rainy season plus antimalarial drugs[11]. It is thus advisable that countries stay invested in increasing access to tools such as mosquito nets and antimalarial drugs. The governments should also increase teams of local health workers to respond to cases especially in remote and rural communities for quick detection, diagnosis, treatment and report on malaria cases.

To allow for more tailored and effective malaria interventions, African countries would also need to invest heavily in generation and access to high-quality epidemiological data. This will help to understand where people are most at risk of infections, where insecticide and drug resistance is taking hold, and which tools are working best in local communities.

African countries also need to invest in African scientists and institutions for the continent to gain the upper hand in the fight against malaria. More investment in additional malaria vaccines is necessary to ensure a healthy market. There should also be investment in other much-needed new tools such as genomic surveillance to stay one step ahead of growing drug and insecticide resistance. It has taken a generation to develop the first-ever malaria vaccine thanks to political commitment and financial support from many partners. With more investments and effective tools, this generation could be the one that will end the disease for good.

All in all, it is hoped that the new vaccine will re-invigorate the fight against malaria which had been stagnating in some African

countries like Sudan and Eritrea which have reported significant resurgence in the recent past. It is also hoped that the announcement of this vaccine by the WHO will re-energise the race to find even more efficient malaria vaccines. Recent reports by Oxford University suggested a vaccine: R21/Matrix-M, with up to 77% efficacy against malaria is undergoing trial in Burkina Faso[12]. Similarly, the new vaccine is a proof in concept and is expected to pave the way for the next generation of potentially more effective malaria vaccines using a variety of technologies, like mRNA, which is used for some COVID-19 vaccines. Germany's BioNTech, which has already developed a coronavirus vaccine with US giant Pfizer, has reported that it aims to start trials for a malaria vaccine next year using the same breakthrough mRNA technology.

4. The likely challenges that the vaccine rollout programme could face and how they could be solved

The main challenge will be in ensuring that quality and cheap vaccines are easily accessible to countries with high malaria burden in Africa, taking into account that these countries are some of the world's poorest[4]. GlaxoSmithKline, the main manufacturer of the vaccine, has stated that it will manufacture about 15 million doses of the vaccine anually in addition to the 10 million doses donated to the WHO pilot programmes, up to 2028. It will do at a cost of production plus no more than 5% margin. However, a global market study led by the WHO this year, projected demand for a malaria vaccine would be 50 to 110 million doses per year by 2030; if it is deployed in areas with moderate to high transmission of the disease. The risk of available supplies not meeting the required demand is therefore very high. This could be solved by the GlaxoSmithKline, working with some African countries to decentralize production.

However, Africa lacks the ability to produce vaccines *en masse*. The entire continent has just about ten vaccine manufacturers based across Egypt, Morocco, Tunisia, Senegal and South Africa which mainly carry out packaging and labeling rather than manufacturing and cannot meet the demand.

For Africa to kick-start successful vaccine manufacturing, four key ingredients are at least needed: financing amounting to hundreds of millions of dollars; expanding research capacity; a commitment from governments to purchase vaccines; and regulatory bodies that meet international standards. Most African countries are lacking in all four. It is therefore important that the GlaxoSmithKline, African countries together with their development partners and funders should massively mobilize funding and financing of vaccine production and distribution.

An ambitious plan has already been laid by the African Centers for Disease Control and Prevention (CDC) for Africa to manufacture 60% of its required vaccines within 20 years. The international community is also stepping up to finance and boost vaccine manufacturing capacity in Africa. There are reports that the GAVI vaccine alliance (a global public-private partnership) is already working on how to finance a programme like that offered for COVID-19 vaccine to ensure that all who need the vaccine in malaria endemic zones get quality vaccine. As already witnessed from the COVID-19 vaccine, where there is political will, there is funding available to ensure that vaccines are scaled to the level they are needed. Also, a new African Medicines Agency, under the African Union, is set to launch in November 2021 with the goal of improving safety regulation of medical products in the continent would hopefully establish regulatory pathways to accelerate the development and uptake of safe and effective health products-including vaccines. The African union is also in talks with the WHO on how to get the vaccines to the continent as soon as possible[13].

Finally, there is the challenge of the vaccine facing opposition from antivaxxers just like for the COVID-19 vaccine[14]. African countries and their development partners will therefore need to invest in vaccine awareness campaigns. The countries with high malaria burden will also have to include Mosquirix as part of their national malaria control strategy, maximize vaccine uptake and ensure completion of the four-dose immunization schedule to obtain the vaccine's full benefit.

Conflict of interest statement

The author declares that she has no conflict of interest.

Author´s contributions

EAO conceived and drafted the manuscript. EAO revised critically and prepared the final version of the manuscript. EAO approved the manuscript for publication.

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