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Malaria vaccine: a global problem with a new ally

Sílvia Pimenta[1,2*], Paulo Sousa[2]

[1]Centro Hospitalar de Lisboa Ocidental, Serviço de Saúde Ocupacional. Escola Nacional de Saúde Pública. Lisboa, Portugal.

2Escola Nacional de Saúde Pública. Lisboa, Portugal.

ABSTRACT

OBJECTIVE

Despite the various goals achieved in the last decade, from the collective effort of several countries and institutions, malaria currently remains one of the infectious diseases with the greatest global impact. In this review, we intend to establish the impact of the measures taken in recent years, as well as the effects of the COVID-19 pandemic and the research into vaccines against malaria.

METHODS

This is a review by means of an exploratory study of the scientific literature, which was based on scientific articles and technical guides from international entities.

RESULTS

The prevention and treatment of malaria continue to be the most important measures to reduce the mortality and morbidity associated with this disease. Although the COVID-19 pandemic has brought new challenges regarding the distribution of measures of diagnosis, prevention, and treatment, at the same time, it has shown that with collective and organized effort, remarkable advances can be achieved. The recently recommended vaccine outlines a new direction for malaria, potentially contributing to its eradication.

CONCLUSIONS

There is still a long way to go in the fight against this disease, but with the implementation of measures globally, in particular investment in the poorest countries, and with the new tools available, such as vaccines, it is possible to achieve the objectives defined for the coming decades.

DESCRIPTORS

Malaria, Treatment, COVID-19, Vaccine, Global Health.

Corresponding author:
Sílvia Pimenta.
Médica no Centro Hospitalar de Lisboa Ocidental, Serviço de Saúde Ocupacional. Escola Nacional de Saúde Pública. Lisboa, Portugal.
E-mail: smjsilva@chlo.min-saude.pt
ORCID ID: https://orcid.org/0000-0002-0093-7800.

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INTRODUCTION

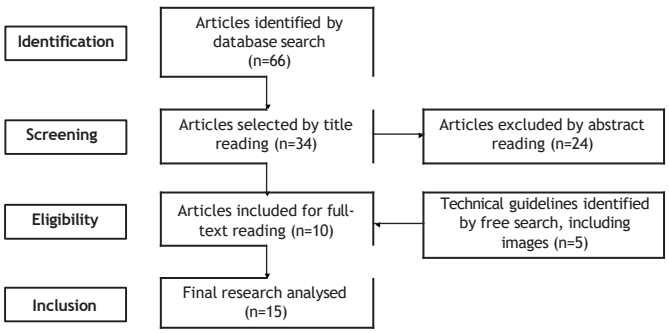
Human malaria is transmitted through the bites of female Anopheles mosquitoes infected with parasites of five species (*Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi*). Major signs and symptoms include fever, chills, sweating, hemolytic anemia, and splenomegaly. Diagnosis is made by identifying *Plasmodium* spp. in peripheral blood slides or using rapid diagnostic tests. Treatment and prophylaxis depend on species and drug sensitivity, with artemisinin-containing combination regimens, the fixed combination of atovaquone and proguanil, and regimens containing chloroquine, quinine, or mefloquine1. Patients infected with *P. vivax* and *P. ovale* are also given primaquine or a dose of tafenoquine to prevent recurrences.

Despite all the efforts made in recent decades, malaria remains one of the deadliest infectious diseases worldwide. World Malaria Day, celebrated annually on April 25th, reminds us that this disease remains a threat to global health. The investment made in recent decades has contributed to a decrease in the incidence and mortality of the disease in many countries, and even to its eradication in some countries, however, many future efforts are still needed to achieve the desired goals, and continuous collaboration around common goals remains fundamental.

METHODS

A literature review was carried out through an exploratory study of the scientific literature, with scientific articles searched in the PUBMED database using the keywords 'Malaria', 'Vaccines', and 'COVID-19', published in the previous five years. As inclusion criteria, studies published up to the date of the research were selected, with any methodological design, that addressed data that responded to the objectives of the study. Technical guides from international entities, namely the World Health Organization, were also consulted. The strategy used to choose the articles is summarized in the Flowchart in Figure 1.

Figure 1. Flowchart: Methodology for selecting the analyzed articles.



RESULTS AND DISCUSSION

In 2019, approximately 4 billion people were at risk of the malaria in 87 countries, with approximately 229 million cases and 409 million deaths2. Most cases were reported in children under 5 years of age (67%) and pregnant women, especially in Sub-Saharan Africa (94%), and Southeast Asia (3%). In 2020, 55% of cases occurred in 6 countries - Nigeria (26.8%), Democratic Republic of Congo (12.0%), Uganda (5.4%), Mozambique (4.2%), Angola (3 .4%), and Burkina Faso (3.4%) - and more than half of the deaths occurred in 4 countries - Nigeria (31.9%), Democratic Republic of Congo (13.2%), United Republic of Tanzania (4.1%), and Mozambique (3.8%)3. In most countries where malaria is endemic, the disease predominantly affects disadvantaged people who have limited access to health care, with difficulty paying for necessary treatment. Of malaria deaths, 30% occur in zones of war, social instability, and natural disasters. Malaria, therefore, is both a cause and a consequence of the poverty and inequality existing in these countries.

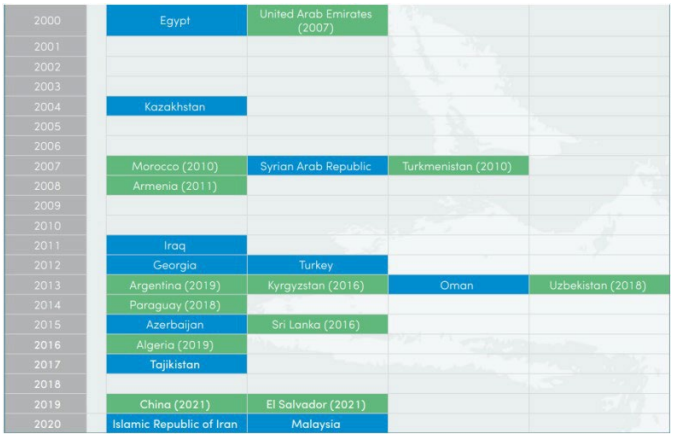
In 2015, the World Health Organization (WHO) announced the *Global technical strategy for malaria 2016-2030*, updated in 2021, which sets four targets by 2030, including reducing the incidence and mortality of malaria by at least 90% (Figure 2).

Figure 2. World Health Organization goals by 2030. Source: Global technical strategy for malaria 2016-2030, 2021 update. World Health Organization, 20212.

GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

Between 2000 and 2020, 23 countries had zero cases of malaria (indigenous cases, excluding imported cases), for three consecutive years, 12 of which were certified as malaria-free by the WHO (Algeria, Argentina, Armenia, China, El Salvador, United Arab Emirates, Morocco, Paraguay, Kyrgyzstan, Sri Lanka, Turkmenistan, and Uzbekistan). In this way, the 2020 goal of eliminating malaria in at least ten countries was achieved, as well as the goal to avoid the re-establishment of the disease in countries that already have no malaria cases (Figure 3). El Salvador was certified as a malaria-free country on February 25, 2021, being the first country in Central America to achieve this result, China was certified malaria free on June 30, 2021, passing from an extraordinary 30 million cases in the 1940s, to zero cases currently3.

Figure 3. Countries that have eliminated malaria since 2000. Countries that have reached zero cases for three consecutive years are represented in blue, and countries certified as malaria-free in green, with the year of certification in parentheses. Source: World malaria report 2021. World Health Organization, 20213.



However, the goal to reduce the incidence and mortality by 40% was not met, with progress stagnating. Although more than half (46) of the 87 malaria-endemic countries are on track to achieve elimination of malaria transmission, these countries are mostly outside the African continent and constitute less than 0.2% of all malaria cases globally. In the remaining countries, mainly in Sub-Saharan Africa, where 94% of malaria cases and deaths occur, the reduction in incidence and mortality rates has slowed down[4]. Several factors have

contributed to this slowdown, such as the increase in population in Sub-Saharan Africa, which continues at a high pace.

The joint effort from the end of the 20th century was decisive for the remarkable progress achieved today. With increasing political and scientific cooperation, there has been investment in prevention, through the availability of insecticide-impregnated mosquito nets, diagnosis with the use of rapid tests, and treatment with the use of various drugs. The most recent drug treatment is artemisinin, which is used in combination with other antimalarials in areas where there is resistance to traditional drugs. Although combination therapies with artemisinin are effective, they are more expensive.

The prevention and treatment of malaria are currently the most effective strategies to combat the disease and reduce its consequences. The expansion of these strategies, driven by *Roll Back Malaria*, has been successful in reducing the incidence and mortality of malaria. Other funds were also created such as the *"The Global Fund to Fight AIDS, Tuberculosis and Malaria"*, and *"US President's Malaria Initiative"*. All the resources allocated have contributed to the avoidance of 7.6 million deaths and 1.5 million cases of malaria in the last twenty years. On January 1, 2016, the United Nations (UN) resolution entitled "Transforming our world: 2030 Agenda for Sustainable Development" was adopted, consisting of 17 objectives (Figure 4), including the eradication of poverty, reduction in inequalities, and guarantee of access to quality health, which also includes the goal of reducing the incidence and mortality of malaria. It is an ambitious agenda that addresses several dimensions of sustainable development and promotes peace, justice, and effective institutions. These goals are based on the progress and lessons learned with the 8 Millennium Development Goals, established between 2000 and 2015, and are the result of the joint work of governments and citizens around the world.

Figure 4. Sustainable Development Goals (SDGs). Source: https://www.undp.org/sustainable-development-goals?utm_source=EN&utm_medium=GSR&utm_content=US_UNDP_PaidSearch_Brand_English&utm_campaign=CENTRAL&c_src=CENTRAL&c_src2=GSR&gclid=Cj0KCQiAgP6PBhDmARIsAPWMq6lNBUwHlLpgEup_T1GrlGlxyfKJgvlVKxHW8r32EI3f87MlhxRE-dEaAkyNEALw_wcB on 07/02/2022.

Simultaneously with the increase in global investment in malaria control, many of the countries where the disease is endemic have also witnessed economic growth and social development, which were essential factors in reducing the incidence of the disease. Since 2000, the GDP of Sub-Saharan African countries has increased by 4% annually and, in the same period, access to electricity in these countries has tripled[5].

Climate change and increasing urbanization in recent years have brought several challenges to global efforts to eradicate malaria. This is a climate sensitive disease, influenced by changes in temperature, rain, and humidity. There is growing concern that these environmental and demographic changes may alter the geographic distribution of malaria and its transmission, expanding the disease to areas where it had already been controlled or to non-endemic areas. This would not be unprecedented, as other vector-mediated diseases have also shifted their distribution from tropical locations to temperate areas, due to the contribution of climate change. *Aedes albopictus* caused several outbreaks of Chikungunya in Europe[6] in the last decade and Ixodes ricinus, which transmits the *Borrelia burgdoferi* (causing Lyme disease), has recently been found at higher altitudes[7]. In order to prevent the spread or re-establishment of malaria in non-endemic areas, it is essential to maintain political commitment and ongoing surveillance at the global level.

With the projected increase in the world's population by 2030, more people living in endemic countries will be at risk of having malaria, putting greater pressure on health systems and on budgets for programs to combat the disease. Continued huge investment is necessary, with the allocation of large financial resources in the various domains of combating the disease. Vector control remains an essential component of malaria control and elimination. The use of insecticide-impregnated mosquito nets is one of the most important preventive measures, however, their use reflects the existing inequity, with greater use of mosquito nets in families with higher economic conditions[8]. The increase in resistance of the *Anopheles* mosquito to insecticides is recognized as a major threat that requires an urgent and coordinated response, and it is also necessary to value the quality and integrity of mosquito nets in the evaluation of the effectiveness of this measure[9].

All patients with suspected malaria must have their diagnosis confirmed by parasite detection methods through microscopy or rapid antigen detection tests. By ensuring the diagnosis of all suspected cases, the use of therapies combined with the use of artemisinin – the first-line treatment for uncomplicated disease – can be instigated, thus reducing the pharmacological pressure on the parasites and the consequent acquisition of resistance to antimicrobials, and contributing to a more effective treatment aimed at the parasite in question. Diagnosis is also important to detect other febrile illnesses besides malaria, which are susceptible to confusion, such as Sleeping Sickness (African Trypanosomiasis). The coexistence of these two infections and their diagnosis is essential for the correct treatment and reduction in mortality[10].

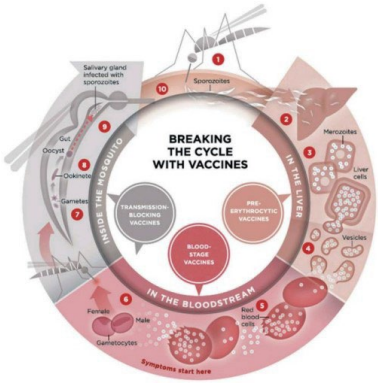
Pharmacovigilance measures and surveillance of the effectiveness of antimalarial drugs are essential to detect unexpected adverse effects and reduced efficacy, in order to implement, in each country, the most appropriate combination of drugs. When treatment fails at a rate greater than 10%, there must be a change in the national antimalarial treatment policy[11]. For now, artemisinin-based combination medications remain highly effective, given the effectiveness of other combination medications. However, caution is needed as the emergence of artemisinin resistance also increases the risk of resistance spreading to the other drugs in the combination. Protecting the effectiveness of artemisinin-based combination therapies and the development of new non-artemisinin-based combinations must be a top priority for both malaria-endemic countries and the global community. In countries and areas where artemisinin and artemisinin combinations continue to be effective, there is a need to promote the use of the recommended drugs and to extend malaria interventions, including vector control, while in countries where artemisinin resistance is reported, intensified measures to control the disease are urgently required, in order to prevent the spread of resistance.

The COVID-19 pandemic has revived the importance of infectious diseases and their enormous economic, health, and social impact. Due to the restrictions imposed and the

confinements, access to means of prevention, diagnosis, and treatment of malaria was affected, contributing to an increase of 14 million cases and 69,000 deaths[3]. The similarities between malaria and COVID-19 in clinical presentation, with symptoms such as fever, difficulty breathing, tiredness, and headache can lead to a misdiagnosis, or even the possibility of co-infection not being considered[12]. However, the pandemic has also brought unprecedented global collaboration, making it possible to study several vaccines to combat SARS-CoV-2 in record time. The internationalization of pharmaceutical companies has provided the ability to ship vaccines to remote parts of the world, despite the huge disparity in access between poor and rich countries. With the emergence of vaccines, the inequity between different countries has become even more evident, requiring a collective and global effort to distribute vaccines where they have not yet been administered.

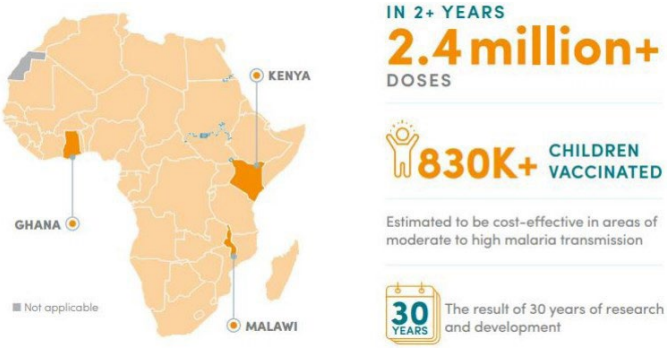
The search for an effective malaria vaccine began more than a century ago. The increase in resistance to antimalarial drugs has highlighted the need to adopt other strategies to reduce the incidence and mortality of the disease. The RTS,S/AS01 vaccine (*Mosquirix*™) provides partial protection against malaria, preventing 4 out of 10 cases and 3 out of 10 serious cases of the disease in children over five months of age. The vaccine was created in 1987 as part of a collaboration between GlaxoSmithKline (GSK) and the *Walter Reed Army Institute of Research* (WRAIR), and so named because it was designed using repeat genes ('R') and the T cell ('T') epitope of the pre-erythrocyte protein of the circumsporozoite of *P. falciparum*, to which the developers added a viral surface antigen ('S') from the Hepatitis B virus, an additional HBsAg (the additional 'S'), and a chemical adjuvant (AS01) to enhance the immune response[13]. *P. falciparum* has a greater relationship with the increase in mortality and morbidity, in relation to other species, in addition to being the most prevalent species in Sub-Saharan Africa. As such, it has been the main research focus for vaccine development. RTS,S acts in the pre-erythrocyte stage, preventing erythrocyte infection and the consequent development of clinical malaria (Figure 5).

Figure 5. Life cycle of the malaria parasite. Source: PATH malaria vaccine initiative. http://www.malariavaccine.org/malaria-and-vaccines/vaccinedevelopment/life-cycle-malaria-parasite[14].



The vaccine was introduced as part of a large study started in 2019 in Ghana, Kenya, and Malawi; showing a high safety profile in children who received the more than 2.4 million doses administered (Figure 6).

Figure 6. Main results of the pilot study of the RTS,S vaccine. Source: The RTS,S malaria vaccine. Geneva: World Health Organization; 2021 (https://www.who.int/multi-media/details/the-rts-s-malaria-vaccinev2[15].



In October 2021, after the assessment by SAGE *(Strategic Advisory Group of Experts on Immunization)* and MPAG *(Malaria Policy Advisory Group)*, the vaccine was recommended by the World Health Organization for the prevention of *P. falciparum* in children living in regions with moderate to high transmission (as defined by the WHO). This is a historic milestone as it is the first malaria vaccine to be recommended, a public health measure that will certainly help fight the disease, reducing thousands of cases and deaths. In December 2021, GAVI *(Global Alliance for Vaccines and Immunizations)* approved an initial investment of US$155.7 million to support the introduction, procurement, and delivery of the vaccine to eligible countries in Sub-Saharan Africa.

There are also other vaccines under study that are candidates for recommendation in the coming years, and BioNTech recently announced its intention to develop a malaria vaccine using the mRNA technique. The goal is that in the near future the vaccine will be a tool to allow the eradication of this disease, providing robust and lasting immunity.

CONCLUSION

The COVID-19 pandemic has shown that the disease targets are achievable, with collaborative, determined, and global efforts; highlighting the importance of tackling the broader determinants of a disease. New tools in the fight against malaria, such as the use of vaccines, may constitute a turning point in strategies, requiring a collective effort based on scientific evidence and experience accumulated over the last few decades. The same commitment applied in the Covid-19 pandemic must now be used to eradicate an ancient endemic disease, not only to save lives, but also to contribute to a healthier and fairer world for all.

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