EXPERTISE FRANCE

Policy brief

L'INITIATIVE SIDA, TUBERCULOSE, PALUDISME

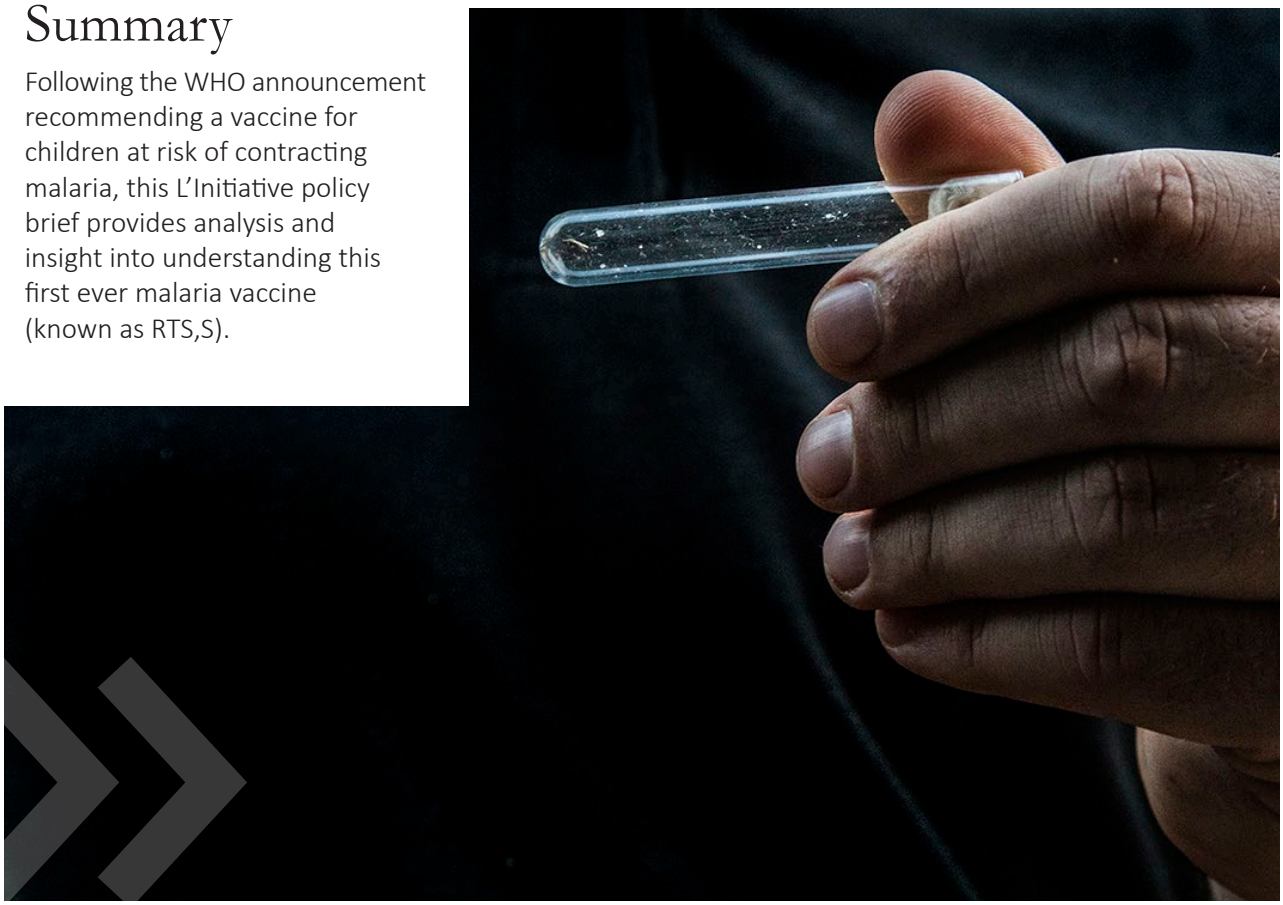
THE MALARIA VACCINE: PROMISING PROGRESS, BUT NOT A SILVER BULLET

Keywords

Malaria, vaccination, integrated approach, arsenal against malaria, financing

Summary

Following the WHO announcement recommending a vaccine for children at risk of contracting malaria, this L'Initiative policy brief provides analysis and insight into understanding this first ever malaria vaccine (known as RTS,S).



On October 6, through a press release[1] that spread quickly around the world, the World Health Organization (WHO) announced its "historic" decision to recommend a "groundbreaking" vaccine for children at-risk of malaria. This style of enthusiastic language, which is unusual for the WHO, hints at a dramatic reality. Children under five are most impacted by malaria, representing 274,000 deaths in 2019, or 67% of global malaria-related deaths[2] : one child dies every two minutes from malaria, primarily in Africa.

1| The missing link in the fight against malaria

The tools to respond to malaria are well known and evidence-based: screening methods, including rapid tests, which are easy to use, including by community actors; treatment that works on parasites, including for use as a prophylaxis, following well-established regimens; vector control tools (i.e. targeting the vector itself: the mosquito) such as long-lasting insecticidal mosquito nets (up to three years), indoor residual spraying of insecticides, and sometimes through targeting breeding sites.

Yet, despite tremendous progress in the global response to malaria in the past 20 years, with a dramatic drop in overall prevalence and the mortality rate reduced by around 60%, progress has slowed in recent years, and many countries where there remains a high malaria burden have fallen behind[3]. Between 2016 and 2017, the number of malaria infections increased by 3.5 million in the ten most affected African countries. With the exception of the WHO South-East Asia region, no other malaria-endemic region in the world is on track to meet the goal of the Global Technical Strategy for Malaria 2016-2030[4] for 2020, to achieve a 40% reduction in the incidence of malaria cases.

This is due to a lack of funding at both international and national levels[5], but also the fact that the arsenal of malaria control tools faces new challenges, such as resistance to insecticides and antiparasitic drugs, and new species appearing in certain regions of the world *(i)*.

Given this very contrasting picture, it is easy to understand why the WHO announcement recommending the mass roll-out of the first malaria vaccine for children living in sub-Saharan Africa received so much attention. Indeed, the development of a vaccine represents the long-awaited missing link in the malaria control arsenal. It is also the first time a vaccine has been developed against a parasite (Plasmodium), which also has a complex life cycle (multiple stages of development in different compartments). This in itself constitutes unprecedented progress, following decades of research.

[1] *https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk*

[2] *https://www.who.int/fr/news-room/fact-sheets/detail/malaria*

[3] *https://reliefweb.int/sites/reliefweb.int/files/resources/World-malaria-report-2020-briefing-kit-fre.pdf*

[4] *https://www.who.int/fr/publications-detail/9789241564991*

[5] *Funding for malaria control and elimination amounted to USD 3 billion in 2019, well below the USD 5.6 billion target in the 2016-2030 Strategy.*

2| A vaccine with limited efficacy and constraints around practical implementation

The RTS,S (or Mosquirix) vaccine was developed in GSK laboratories in 1987. It contains part of a protein from *Plasmodium falciparum*, fused and combined with hepatitis B virus surface antigens intended to increase the immune response, with the aim of blocking the ability of the parasite to infect and mature in the liver. After the first encouraging clinical trials in the early 2000s, phase III trials carried out in seven countries with 15,000 children, concluded that four injections were needed to achieve a 29% reduction in cases of severe malaria in children aged 5-17 months ***(ii)***. This relatively low rate of protection[6] and the high number of injections required, which is difficult to implement on the ground, has given rise to much debate. Particularly as safety concerns have been raised, such as a potential increase in the risk of developing cerebral malaria or contracting meningitis.

Despite these reservations, the European Medicines Agency (EMA) authorized the vaccine for children aged 5-17 months in July 2015. The Strategic Advisory Group of Experts on Immunization and the WHO Malaria Policy Advisory Committee were more cautious, believing that concerns about safety and logistical barriers required further investigation. They therefore recommended a pilot phase to gain a better understanding of the vaccine's impact in a "real life" context. Hence the creation of the *Malaria Vaccine Implementation Programme*, which GAVI and the Global Fund to Fight AIDS, Tuberculosis and Malaria were involved in.

Conclusions drawn from this pilot, which began in 2019 in Ghana, Malawi and Kenya with approximately 800,000 children, informed the recent WHO announcement. The results of this *open label* study rule out the safety concerns which had previously been encountered. However, the results show a relatively moderate efficacy rate over time and the need for four injections. But the feasibility of this rather restrictive vaccination schedule has been demonstrated through Mosquirix being introduced into existing vaccination programs. **There will almost certainly need to be changes to the vaccination schedule in certain countries where malaria is seasonal, in order to ensure optimal protection when the risk of exposure to the disease is high (like the influenza vaccine in autumn in Europe).** These changes are also strongly encouraged by results from a study carried out among children aged 5-17 months in Mali and Burkina Faso, which showed a drastic reduction in malaria when seasonal chemoprophylaxis was combined with vaccinations, and a reduction in mortality of more than 70% *(iii)*. However, the study was not designed to look at potential negative effects in the medium term, such as a rebound of infections in vaccinated children. Nor does the study enable us yet to estimate effects such as a reduced impact of chronic malaria on children's physical and cognitive growth.

3| RTS,S: an additional tool in the fight against malaria

The WHO has set a goal for 2030 to have a malaria vaccine with at least 75% efficacy, yet the pilot project demonstrates that RTS,S has a maximum protection rate of just 30%. It is therefore clear that this vaccine alone will not change the situation. It will nevertheless complement the arsenal of tools that are already in place in the context of what should be called "combination prevention", and may, in certain cases (e.g. seasonal prevention cycles) have a significant impact in high endemic areas.

[6] *This rate is well below the threshold of 75% that the WHO set in 2014 in its program document "Preferred Product Characteristics (PPC) for Malaria vaccines", https://apps.who.int/iris/bitstream/handle/10665/149822/WHO_IVB_14.09_eng.pdf*

In addition, it is reasonable to assume that this immune approach will pave the way for other vaccine-based solutions in the future. In this regard, of the 140 candidate vaccines against malaria under development, including mRNA vaccine projects, of note is the very promising R21 vaccine developed by Prof. Adrian Hill's team from the Jenner Institute at the University of Oxford (United Kingdom). The results of Phase II are very encouraging and show an efficacy rate of 77% *(iv)*. However, this will need to be confirmed at the end of Phase III, which is currently underway with the first data sets expected in 2022. **Limitations are common to both R21 and RTS,S: both require a vaccination schedule of four injections.** But the R21 vaccine was developed 25 years after its predecessor RTS,S, and can therefore benefit from more recent and effective technologies, making it possible, among other things, to reduce the quantity of product required for an injection, and therefore the cost per dose (3 USD for R21 *compared* 5-7 USD for RTS,S).

Funding remains a major issue, which Gavi, the Vaccine Alliance, is looking at in the coming weeks, along with the production and supply challenges that will come with this recommendation for mass roll-out.

Conclusion

Although the WHO announcement surprised some people with its overly enthusiastic tone, the benefit is that it has re-emphasized the need to develop complementary approaches (immune, chemical, technical, etc.) to respond to malaria, which are adapted to the different epidemic, logistical and structural contexts. Vaccines, and in particular a new generation of products that are more effective and perhaps less restrictive in terms of implementation, will play an important role and could constitute a real turning point. However, without a financial commitment commensurate with public health challenges, without strengthening health systems in high-incidence countries, and without community involvement, these tools will have only a limited impact.

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