

# Malaria vaccine: The tale of terror, triumph, tyranny, and trust



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## ABSTRACT

Malaria is an endemic disease in a true sense. It is an acute febrile disease caused due to the parasite *Plasmodium*. However, unlike COVID-19, it failed to raise an international concern or gain the scientific limelight. Most of the 200 million globally affected by malaria, half of them are from Africa. Four of the nations, Nigeria (25%), the Democratic Republic of the Congo (11%), Mozambique (5%), and Uganda (4%), account for half of the world's malaria burden and is the leading cause of illness and death. In 2019, an estimated 5–6 million people died of malaria – most of them are young children in sub-Saharan Africa. Many of the countries affected by malaria have the lowest economic status. In the malaria-endemic region, the most vulnerable groups are young children and pregnant women. The costs of malaria are enormous to individuals, families, communities, societies, and nations. After a struggle for three decades, the much-awaited malaria vaccine, RTS, S (brand name Mosquirix), was finally launched; but it came with its controversies and allegations. This review explored the different angles of this disease, the vaccine development, and the emerging debates.

**Key words:** Africa; Asia pacific; Endemic; Malaria vaccine; Malaria; WHO

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## INTRODUCTION

Malaria caused due to the bites of infected female *Anopheles* mosquitoes is a life-threatening tropical disease usually endemic in sub-Saharan Africa as well as the WHO regions of South-East Asia, Eastern Mediterranean, Western Pacific, and the Americas.<sup>1-4</sup> Caused by *Plasmodium* parasites, these spread to people through the bites of infected mosquitoes, called “malaria vectors.” Unlike flu or tuberculosis, malaria is not contagious and does not spread from person to person. There are a total of five parasite species that can cause malaria in humans; two of these – *Plasmodium falciparum* and *Plasmodium vivax* – seem to pose the greatest risk.<sup>4,7</sup>

As per the WHO, in 2019, there were an estimated 230 million malaria cases worldwide, leading to 409,000 deaths, with children under 5 years most vulnerable to this disease, amounting to 65–70% of all malaria-related death.<sup>8</sup> The WHO African Region is reported to have one of the world's highest malaria incidences, accounting for 95% of all malaria cases.<sup>9</sup> Although a significant amount of funds were invested to cope with the calamity (an estimated US\$ 3 billion in 2019 as part of malaria control and elimination), and the disease is preventable and curable; still it seems to defy all controls, as evident by soaring cases every year.<sup>10</sup> Occurring in five WHO regions, globally, an estimated 3.4 billion people in 92 countries are at risk of being

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infected with malaria and developing the disease (map), and 1.1 billion are at high risk (>1 in 1000 chance of getting malaria in a year).<sup>11</sup> According to the World Malaria Report 2018, there were 219 million cases of malaria globally in 2017 (uncertainty range 203–262 million) and 435,000 malaria deaths, representing a decrease in malaria cases and death rates of 18% and 28% for 2010, respectively.<sup>12</sup> The burden was heaviest in the WHO African Region, where an estimated 93% of all malaria deaths occurred, and in children aged under 5 years, who accounted for 61% of all deaths.<sup>13</sup>

Malaria eradication program worldwide has mixed outcomes. The global Malaria Program (GMP) initiated by the WHO is responsible for coordinating efforts worldwide to eliminate malaria. This is supported by the “Global technical strategy for malaria 2016–2030.” GMP is based on these core principles of reducing the disease burden and maintaining or eliminating it at a reasonably low level from a defined geographical area. These involve (1) effective malaria control: reducing the disease burden to a level that it posed no public health problem, (2) elimination of malaria and mosquito-borne malaria transmission, and (3) malaria eradication globally: permanent reduction to zero of the worldwide incidence of malaria infection.

## TERROR FROM MALARIA

Malaria is quite a severe disease that can be fatal if not diagnosed and treated quickly. Pregnant women, babies, young children, immunocompromised, and the elderly are, particularly at risk. Malaria is usually associated with the following complications.<sup>14,15</sup>

### Anemia and cerebral malaria

The *Plasmodium*-mediated rapid destruction of red blood cells often leads to severe anemia.<sup>16,17</sup> Anemia is a condition, where the red blood cells cannot carry enough oxygen to the body's muscles and organs. A more deadly variant of this is cerebral malaria which affects the brain and could be very lethal. Cerebral malaria often progresses to altered mental status, seizures, and coma and often is the most common cause of mortality in patients, especially in children even with treatment. Other complications involve liver failure, kidney failure, shock, pulmonary edema, splenomegaly, and hematopoietic systems. Clinical deterioration appears within the 1<sup>st</sup> week after the onset of fever. It is estimated that approx. 300–500 million people contract malaria each year globally, resulting in 1.5–2.7 million deaths.<sup>18</sup>

### Pregnancy

Malaria in pregnancy increases the risk of maternal and fetal anemia, stillbirth, low birth weight, pregnancy complications,

spontaneous abortion, and neonatal death.<sup>15,19,20</sup> Malaria during pregnancy, mostly in malaria-endemic regions, has adverse consequences on birth outcomes and a higher incidence of preterm deliveries.<sup>20,21</sup> It is found that erythrocytes infected by *P. falciparum*—express a unique variant surface antigen, VAR2CSA, that mediates sequestration in the placenta.<sup>22,23</sup> *Plasmodium* that interacts with the placental trophoblast cells expresses VAR2CSA proteins that bind specifically to the placental receptor known as chondroitin sulfate A (CSA). Parasite infection reduces the bioavailability of placental growth factor, along with an increased expression of soluble fms-like tyrosine kinase-1 (sFlt-1). sFlt-1 acting like a decoy receptor antagonizes vascular endothelial growth factor function leading to ineffective placental angiogenesis and vascular defects.<sup>24</sup> Infection also leads to an increased level of asymmetric dimethylarginine, a competitive inhibitor of nitric oxide synthase resulting in increased sFlt-1 and NO production affecting placenta blood flow.<sup>25</sup> The malaria parasite also led to heightened immune response through increased production of inflammatory cytokines such as interleukin (IL)1beta and IL6 and reduced anti-inflammatory IL8 and IL10.<sup>26,27</sup> These imbalances lead to sustained inflammation that subsequently contributes to placenta pathology.<sup>28,29</sup>

## MOMENT OF TRIUMPH

Despite the altered cellular physiology due to *Plasmodium* infection, there are moments of encouragement and hopes as well as awareness programs. In addition to the community-based eradication program, a significant breakthrough in malaria control is the development of the waited Malaria vaccine. The only approved vaccine, as of 2021, is RTS, S, known by the brand name Mosquirix.<sup>30-32</sup> It requires four injections. The WHO recommends using the RTS, S/AS01 (RTS, S) malaria vaccine among the children in sub-Saharan Africa regions with moderate to high *P. falciparum* infection. What's amazing is that after almost 130 years of waiting after the discovery of *Plasmodium* parasites as the causative agent of malaria, the first approved vaccine came through only in 2021.

Further, it is speculated that RTS, S could prevent the deaths of 23,000 children a year.<sup>33</sup> Researchers have been developing and testing the RTS, S vaccine – since 1987, investing more than US\$750 million. Funded by the Bill and Melinda Gates Foundation in the USA and the London-based pharmaceutical firm GlaxoSmithKline (GSK), this vaccine was eventually approved for human use by the WHO in 2021.<sup>34</sup> While it's a moment of triumph for the world that finally, after 30 years, a vaccine is in place against malaria, the celebrations were quickly overshadowed by concerns and allegations.<sup>35</sup> Although the vaccine showed

just 50% efficacy against severe malaria in the 1<sup>st</sup> year of the clinical trials, it seems to lose its effectiveness by the 4<sup>th</sup> year, ultimately raising concerns about the whole program.<sup>36</sup> Furthermore, note that the RTS, S vaccine acts only against the *Plasmodium* parasite known as the *P. falciparum* but offers no protection against the other four species such as *P. vivax*, *Plasmodium ovale*, *Plasmodium knowlesi*, and *Plasmodium malariae*, which are prevalent in Southeast Asia, Americas, and Europe even making its usage entirely restricted to few geographical locations. As if there is no end to controversies hereafter. In a recent article by Doshi,<sup>36</sup> citing a serious breach of international ethical standards, it seems the malaria vaccine trials were conducted concealing critical health concerns. It was observed that the rate of meningitis in those receiving Mosquirix were 10 times higher than the control arm, doubling in the risk of death.

The question that also bothers us is the time taken for the development of Malaria vaccine. While it took the world just a year to develop nearly 100 or more COVID-19 vaccine candidates that were also safely inoculated to 700 crore individuals worldwide across 172 countries, it took 30 years to establish the malaria vaccine. The answer lies at several levels that are summarized below.

## SCIENTIFIC ASPECTS

Genome complexity between the two pathogens widely differs. SARS-CoV-2 is a 30 kb genome,<sup>37</sup> while the *Plasmodium* genome is 22.8 megabases (Mb) in size, distributed among 14 chromosomes ranging in size from approximately 0.643–3.29 Mb.<sup>37</sup> While the virus is predominantly an intracellular parasite entirely dependent on host machinery to survive, malaria parasites have a very complex life cycle that is even poorly understood. *Plasmodium* shuttles between its two hosts (mosquito and human) and takes a tour of two different sites in the human host and back to the mosquitoes to complete its life cycle<sup>38</sup> an event that makes it extremely difficult to detect and target. In humans, the parasites grow and multiply first in the liver hepatocytes and then in the erythrocytes.<sup>39</sup> These grow inside the red cells and destroy them in the blood, releasing daughter parasites (“merozoites”) that continue the cycle by invading other red cells.<sup>40</sup> The RTS, S malaria vaccine targets the pre-erythrocytic stage when the malaria parasite enters and replicates in the liver. This vaccine specifically targets amino acids 207–395 of the circumsporozoite protein (CSP) from the NF54 strain of *P. falciparum*.

## POLITICAL AND LOGISTICS ASPECTS

The COVID-19 vaccine has the luxury to be tested on adults, while the malaria vaccine needs to be tested

in children under 5 years of age<sup>41,42</sup> making it very challenging to conduct a clinical trial in this age bracket with extraordinary safety. We also need to consider the fact that malaria affects the part of the world community who are primarily the most marginalized and improvised hailing from the poorest economies in the world. It makes little sense from a corporate point of view to fund research for such a population who otherwise may not even afford to purchase the vaccine. Hence, it took over two decades, with financial assistance from the Bill and Melinda Gates Foundation, involving research collaborations from seven countries across 11 trial sites to finally get this vaccine ready.

## MALARIA VACCINE MECHANISM OF ACTION

The RTS, S/AS01 malaria vaccine targets the pathogen’s CSP, inducing antibodies associated with the prevention of *P. falciparum* infection. RTS, S/AS01 is the first malaria vaccine to be tested in Phase 3 clinical trials. It was found to be the most beneficial in malaria-endemic regions, leading to reductions in malaria cases, hospital admissions, serious complications, and the need for blood transfusions due to anemia.<sup>34</sup>

## TYRANNY TRUST AND BETRAYAL

Although the malaria vaccine is all set toward a success story, it is still not immune to controversies. There had been a polarized political view as far as malaria vaccine development is concerned. Although the global mortality numbers provide a strong reason to fight malaria, its indirect toll on those whom this disease does not kill is so widespread and debilitating that it constitutes a heavy economic drag, more for developing nations with a poor economy. The bioethicist community has criticized it for committing a “serious breach” of international ethical standards, as per reports in The BMJ. It was observed that the rate of meningitis in those receiving the vaccine was 10 times higher than in the non-receivers and a doubling in the risk of death amongst the girls. Further, Western University in Canada bioethicist Dr. Charles Weijer noted a failure to obtain informed consent from parents whose children are taking part in the trials, thereby violating the Ottawa Statement (a consensus statement on ethics of randomized cluster trials). There were allegations that the malaria vaccine trial conducted by the WHO represents a serious breach of international ethical standards. Cluster randomized trials (CRTs), also known as group randomized trials, are place-based or community intervention trials in health and biomedical research. CRTs often involve groups, or “clusters,” of peoples/subjects—rather than individuals and are

randomly allocated. The study outcomes are measured on the individual cluster members.<sup>43</sup> This particular CRT was conducted in Africa (Malawi, Ghana, and Kenya), where 720,000 children will receive the RTS,S vaccine for the next 2 years.

The WHO, however, asserted that the malaria vaccine trial was “conducted in accordance with established and recognized national and international ethical standards” and that there are no violations whatsoever. The WHO critically denies that the malaria vaccine trial in districts in Ghana, Kenya, and Malawi was fundamental research; instead, it was a “systematic evaluation of programmatic implementation.” Further, due to vaccine shortage, the WHO seems to have randomized its use making the study look like a CRT to ascertain its effectiveness, safety, and feasibility. Critiques, however, questioned the intention, because the vaccine manufacturer GSK has donated 10 million doses of RTS,S vaccine, enough to vaccinate entire districts, and every single child. The WHO chief scientific officer Dr. Souminathan argued that there were no violations. The reported imbalance in female mortality in the Phase 3 trial was identified by post-hoc analysis and was likely to be a chance finding, of which no one was aware. Furthermore, the consent protocol for RTS,S is the standard – an “opt-out” approach also called “implied consent,” which means the parents have the last say whether their kids will take this shot or not. The matter is still unsettled with allegations and controversies from both sides.

## KINDLING HOPE: CONCLUDING REMARKS

A country like India carries 2% global malaria case burden and malaria-related death, accounting for nearly 52% of all malaria death outside Africa. It is serious health as well as a socioeconomic crisis for the developing world. To quote Dr. Sutherland from the London School of Hygiene and Tropical Medicine, “The public health impact is not an only severe illness and even death in a relatively small proportion, but chronic or repeated infections leading to anemia, fatigue, poor school attendance, reduced learning opportunity, and also impaired cognition.” Further, vaccine RTS,S, combined with routine seasonal antimalarials seems to reduce the hospitalization and death by around 70%. The watershed moment for malaria management is launching the RTS,S vaccine. This vaccine is the first and the only vaccine that can significantly reduce malaria and life-threatening severe malaria symptoms in endemic malaria regions. Vaccinations began in the three pilot countries in 2019: Malawi on April 23, Ghana on April 23, and Kenya on September 13. It is well known that

African and sub-Saharan nations have been hard hit by malaria despite making tremendous progress in the fight against this disease using the WHO-recommended tools such as mosquito nets, mosquito repellents, insecticides, and indoor spraying as well as antimalarial medications. Even with these strategies, there has been a substantial setback. This is due to the fact the malaria disease has a very complex course that is rather poorly understood. The parasite has evolved a mechanism to avoid host immune surveillance and downplay host immunity such that even the infected subjects do not develop any long-term immunity. There is substantial evidence that both the parasite and the female *Anopheles* mosquito have evolved mechanisms to avoid antimalarials such as artemisinin and anti-mosquito insecticides. Under these circumstances, RTS,S vaccine seems a new paradigm on the horizon with the aim to achieve the vision of a world free of malaria.

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