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Editorial: Current Status of Two Adjuvanted Malaria Vaccines and the World Health Organization (WHO) Strategy to Eradicate Malaria by 2030

Dinah V. Parums, MD PhD

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

e-mail: dinah.v.parums@isi-science.com

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Abstract There is hope that 2023 could bring regulatory approval, licensing, and implementation programs for safe and effective adjuvanted vaccines to prevent malaria. Clinical trials involving the two leading adjuvanted malaria vaccines directed to the *Plasmodium falciparum* circumsporozoite protein (PfCSP) are ongoing. These vaccines are RTS,S/ASO1 (Mosquirix®) and R21/Matrix-M™ (R21/MM). This year, the World Health Organization (WHO) updated its strategy to eradicate malaria by 2030. The hope is that major advances in global health security from effective malarial vaccines could reduce morbidity and save the lives of millions of people living in malaria-endemic countries to achieve the goals recommended by the WHO. This Editorial aims to give an update on recent findings from key clinical trials on the safety and efficacy of RTS,S/ASO1 and R21/MM malaria vaccines and to provide an insight into the importance of key ongoing clinical trials that will report in early 2023.

Keywords: **Malaria • Vaccine • *Plasmodium falciparum* • Editorial**

The most common type of malaria is due to the transmission of *Plasmodium falciparum* by the female *Anopheles spp* mosquito [1]. In terms of human morbidity and mortality, malaria is the most important parasitic disease worldwide, affecting more than 247 million people in 84 malaria-endemic countries in 2021, with 619,000 deaths [2]. Resistance to insecticides and drug treatments has become increasingly challenging to infection control [1].

In May 2015, the World Health Organization (WHO) Assembly met in Geneva to develop the Global Technical Strategy for Malaria 2016-2030 [3]. The WHO Assembly met again in May 2021 to update this global strategic plan [4]. The WHO has defined goals to control, eliminate, and eradicate transmission to reduce malaria incidence to levels that do not threaten public health or are acceptable to communities [4]. Intermittent preventive treatment (IPT) and seasonal chemoprophylaxis have been recommended to reduce malaria risk in high-risk individuals, including pregnant women [4]. Methods of mosquito vector control include the use of long-lasting insecticide-treated nets (LLINs), larval control, and household insecticide residual spraying (IRS) [1,4]. However, the efficacy of mosquito repellents can vary, depending on the mosquito vector [1,4]. Therefore, a successful malaria vaccine that may be used with other control interventions is a critical approach to begin reducing the global malaria disease burden [1,4]. Progress in developing effective malaria vaccines is now becoming a possibility, and with vaccines comes the opportunity to eradicate malaria in the 21st century [4,5]. The *P. falciparum* circumsporozoite protein (PfCSP) is the most abundant antigen on the sporozoite surface and is now recognized as an important target for malaria vaccines [5]. In the past year, two main adjuvanted vaccines to PfCSP are leading the field and are anticipated to be implemented in vaccination regimes in malaria-endemic countries, following the imminent results of further clinical trials (**Table 1**) [4-6].

RTS, S/ASO1 (Mosquirix®)

The RTS,S recombinant fusion protein vaccine, is a first-generation malaria vaccine that was developed in 1987 as part of a collaboration between GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR) and began initial pilot studies in malaria-endemic areas in 2019 [5,7,8]. This vaccine targets an antigen on the surface of the *P. falciparum* sporozoite consisting of a sequence of four amino acids [5,7-9]. Repeat T epitopes (RTS) derived from the PfCSP are combined with the S antigen derived from hepatitis B surface antigen (HBSAg) and the AS01 proprietary adjuvant, which is a liposome-based adjuvant containing two immune stimulants, MPL and QS-21 (RTS.S/AS01) (**Table 1**) [10]. In October 2021, the WHO approved the RTS,S/ASO1 vaccine (Mosquirix®) (GlaxoSmithKline Biologicals, Rixensart, Belgium) for children in

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Table 1. Current status of adjuvanted malaria vaccines to the *Plasmodium falciparum* circumsporozoite protein (PfCSP), as of December 2022 [4,6].

Vaccine	Vaccine type	Vaccine target	Regulatory approval	Key clinical trials	Vaccine characteristics
RTS,S/ASO1 (Mosquirix®) [14]	Adjuvanted recombinant fusion protein	Four amino acids in the PfCSP including the proprietary adjuvant	Approved by the WHO in October 2021 for children in endemic areas, including sub-Saharan Africa [14]	1. NCT00866619. Phase 3 trial of 15,459 infants and children, 5-17 months, with 20-month booster 2. NCT00872963. Phase 3 trial of 447 infants and children, 5-17 months with three vaccine doses [14]	Four-dose vaccine trials are awaited that include a regimen of three vaccine doses, followed by a booster vaccine after one year (NCT05252845)
R21/MM [19]	Adjuvanted protein vaccine	Virus-like particle based on the PfCSP from strain NF54, fused to the N-terminus of HBsAg, manufactured using the Matrix-M, proprietary adjuvant	Not yet approved. First to achieve the WHO-specified goal of 75% efficacy	1. NCT05252845. Phase 2 trial including 450 children age 5-17 months in Burkina Faso 2. NCT04704830. A phase 3 multicnter trial in Africa is ongoing.	Efficacy data beyond 6 months are limited. Currently, it is difficult to compare vaccine efficacy between R21 and RTS,S vaccines

AS01 – a proprietary adjuvant; MM – Matrix-M, a proprietary adjuvant; NCT – National Clinical Trial identifier; PfCSP – *Plasmodium falciparum* circumsporozoite protein; RTS – repeat T epitopes derived from the circumsporozoite protein; S – S antigen derived from hepatitis B surface antigen (HBSAg); WHO – World Health Organization.

sub-Saharan Africa and other endemic regions with high malaria transmission [10].

The RTS,S/AS01 vaccine was the first malaria vaccine evaluated in phase 3 clinical trials in malaria-endemic areas [11,12]. The RTS,S/ASO1 vaccine consists of a recombinant fusion protein antigen of four amino acids based on the PfCSP [11,12]. The repeat T epitopes (RTS) are derived from the PfCSP, the S antigen (S) is derived from the hepatitis B surface antigen (HBSAg), and AS01 is the adjuvant [11,12]. In 2013, the RTS,S/AS01E trial results were reported that included 447 infants and children between 5 months and 17 months of age in Kilifi, Kenya, who received three vaccine doses (NCT00872963) [13]. Vaccine efficacy declined between the first and fourth year of follow-up, from 44% (95% CI; 16-62) to 0 [13].

In 2015, the results from a phase 3 vaccine trial were published that included 15,459 children between 5 months and 17 months of age from 11 centers in seven countries in sub-Saharan Africa (NCT00866619) [14]. The RTS,S/AS01 vaccine produced partial protection from clinical malaria at a median follow-up of 48 months and resulted in protection following a booster at 20 months [14]. However, no significant efficacy against severe malaria was found in the 6-12 week age group, even after a booster vaccine [14]. Studies are ongoing to evaluate children who received four doses of vaccine. It has been observed that the RTS,S/AS01 vaccine provides greater protection against malaria from the *Plasmodium spp.* that matches the protein used in the vaccine [14]. In 2016, the Malaria Policy Advisory Committee (MPAC) and the Strategic Advisory Group of Experts on Immunization (SAGE) made the decision not to recommend widespread vaccination with RTS,S/AS01 vaccine, until the results from further clinical trials were available [15].

In July 2015, the RTS,S/AS01 malaria vaccine received positive scientific support from the European Medicines Agency (EMA), and the WHO recommended the pilot implementation of the vaccine in malaria-endemic areas in children from 5 months of age [16]. The recommended dosing schedule was an initial three doses given at least one month apart, followed by a fourth dose between 15-18 months later [16]. The combination of clinical trials and mathematical modeling of disease transmission support that protection from malaria provided by the RTS,S/AS01 vaccine has the potential to provide a substantial public health benefit when used with other malaria interventions [16]. Also, four vaccine doses in children aged 5 months

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or older give the most significant benefit [16]. These initial findings require future evaluation in real-world settings to identify vaccine safety, the impact on mortality, and the feasibility of delivering a 4-dose vaccination schedule on a large scale in malaria-endemic areas [17]. Further studies are required to evaluate the effects of vaccines on malarial parasites with a PfCSP allele that matches the vaccine target rather than infection with malarial parasites with an allele mismatch [18].

Currently, RTS,S/AS01 is the first and only malaria vaccine to achieve ongoing post-licensing large-scale pilot implementation programs. This year, in malaria-endemic Kenya, Ghana, and Malawi, the RTS,S/AS01 vaccine has been given to hundreds of thousands of infants and children [17].

R21/Matrix-M™ (R21/MM)

During 2022, there has been increasing interest in the R21/MM malaria vaccine. R21 is a virus-like protein based on the PfCSP fused to the N-terminus of the HBsAg, combined with the Matrix-M proprietary adjuvant [19]. This vaccine was developed by created by the University of Oxford, UK, and includes the Novavax proprietary saponin-based adjuvant, Matrix-M (licensed to Serum Institute of India Pvt. Ltd., Pune, India) [19].

In May 2021, the results from a phase 2b investigational study on the safety and efficacy of the R21/MM malaria vaccine were reported NCT03896724) [19]. This phase 2b randomized, controlled, double-blind trial was conducted at the Clinical Research Unit of Nanoro (CRUN) and Institut de Recherche en Sciences de la Santé (IRSS) in Burkina Faso, West Africa, an area with high seasonal malaria transmission [19]. The trial included 450 infants and children between 5 and 17 months of age [19]. The children were randomly assigned to receive either three doses of R21/MM, with either a low dose (5 µg R21 with 25 µg MM) or high dose (5 µg R21 with 50 µg MM), or rabies vaccine as a control [19]. At six months, the vaccine efficacy in the low dose R21/MM adjuvant group was 74% (95% CI; 63-82), and in the high dose R21/MM adjuvant group was 77% (95% CI; 67-84) [19]. No serious adverse events were associated with R21/MM vaccination [19]. At 28 days after the third vaccine dose, infants and children vaccinated with R21/MM developed high titers of malaria-specific antibodies, with doubling antibody titers at the higher adjuvant dose [19]. There was a high level of vaccine efficacy in infants and children of 77% [19]. Also, a vaccine booster dose at one year following a primary three-dose R21/MM vaccination regime, boosted antibody titers to levels similar to peak antibody titers [19]. The efficacy and safety profile of the R21/MM malaria vaccine, and the possibility maintaining immunity with annual vaccine boosters has given new hope to the possibility of controlling endemic malaria [20]. Notably, the high-level of vaccine efficacy of 77% identified the R21/MM malaria vaccine as the first to achieve the WHO-specified efficacy goal of 75% [21].

The phase 2b trial was funded by the European and Developing Countries Clinical Trials Partnership 2 (EDCTP2) program supported by the European Union (EU), the Wellcome Trust, and National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre, and has been extended for a further two years to assess the efficacy of additional vaccine booster doses [19]. The results of an ongoing clinical trial will be reported in early 2023 of the safety and immunogenicity of R21/MM in adults in Thailand (NCT05252845) [22]. The trial investigators, based at the University of Oxford, are conducting a safety and immunogenicity trial of R21/MM in Thai adults, which also aims to determine whether the combined use of antimalarial drugs has any effects of the immunogenicity of the vaccine [22]. This trial includes a pharmacokinetics evaluation of the absorption and pharmacokinetics of the antimalarial drugs piperaquine and a single low dose of primaquine (SLDPQ) when administered with the R21/MM vaccine [22]. It is hoped that the high levels of malaria vaccine efficacy and immunogenicity identified in infants and children may also be achieved in adults.

Also, the results from an ongoing large-scale phase 3 safety and efficacy licensing trial that includes 4,800 infants and children between 5 months and 36 months in four African countries, including Burkina Faso, Kenya, Mali and Tanzania, are expected in early 2023 [23]. Should the findings from these ongoing clinical trials support the regulatory approval of the R21/MM malaria vaccine in 2023, this will be a major advance in global health security that may save the lives of millions of people.

Conclusions

There is anticipation that 2023 could bring regulatory approval, licensing, and implementation programs for safe and effective adjuvanted vaccines to prevent malaria, following the findings from ongoing clinical trials on the two leading adjuvanted malaria vaccines RTS,S/ASO1 (Mosquirix®) and R21/Matrix-M™ (R21/MM). The hope is that major advances in global health security from effective malarial vaccines could reduce morbidity and save the lives of millions of people living in malaria-endemic countries.

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