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Malaria vaccines for children: and now there are two

In 2021 nearly half of the world's population lived at risk from malaria, with over 600,000 deaths annually, of which over 95% occur in WHO's AFRO region and 80% of these in children aged less than 5 years[1]. WHO recommends several preventive and curative interventions, that when used together can greatly reduce malaria illness and death, including effective vector control, chemoprevention, prompt diagnosis and treatment and since October 2021 malaria vaccines, the first of which is RTS,S/AS01. Malaria, specifically *P.falciparum*, is the first human parasite for which vaccination has proved possible. This took over 40 years of development since the identification of the circumsporozoite (CSP) antigen as a functionally important antigen. A key recent finding was the successful demonstration of programmatic feasibility, effectiveness, and safety, of RTS,S/AS01 in very large pilot implementations in 3 African countries. Demand for malaria vaccines is unprecedented, with 18 countries already approved for Gavi support to introduce in 2024. However, supply of RTS,S/AS01 is severely constrained, with only 18 million doses available between 2023 and 2025 – whereas the annual demand is anticipated to exceed 80 to 100 million doses. Inventors at the University of Oxford, in partnership with the Serum Institute of India (SII), have now developed a second, CSP-based vaccine similar in construct to RTS,S/AS01, known as R21/Matrix-M. SII has a track record of supplying other WHO recommended vaccines at very large scale, at relatively low cost, and of meeting WHO's Prequalification standards on vaccine quality, safety and efficacy. Like RTS,S/AS01, the R21/Matrix-M vaccine targets the CSP antigen, It is formulated with a saponin-based adjuvant, Matrix-M, which is distinct from the AS01 adjuvant of RTS,S.

The Phase 3 trial of R21/Matrix-M, reported in this issue of The Lancet, enrolled 4800 children aged 5-36 months in 5 sites in 4 sub-Saharan African countries. The study population were children in mostly moderate and low transmission intensity sites. In this trial 75% efficacy (95%CI 71-78) is reported against all episodes of malaria during 12 months follow-up when the vaccine is given in 3 doses just before the malaria season in areas where malaria is highly seasonal, with a booster dose sustaining efficacy in the following malaria season. This is similar to the efficacy of RTS,S/AS01 when it was provided in the same way[2]. When R21/Matrix-M was administered according to age of the children rather than for seasonal administration slightly lower, 67% (95%CI 59-73), but still substantial, efficacy was reported over 12 months of follow-up. Too few children were included in the trial to assess reliably the protection against severe malaria but it is reasonable to assume this will similar to that demonstrated for RTS,S/AS01.

The efficacy and safety results from the R21/Matrix-M vaccine Phase 3 trial have provided critical evidence for a WHO recommendation for its use, and for becoming the second WHO recommended malaria vaccine[3]. WHO prequalification review is underway - a critical next step to allow GAVI financing and UNICEF procurement. Two key advantages of R21/Matrix-M are the price, which is expected to be substantially lower than the current RTS,S/AS01 price, and the much higher near-term supply capability. The two vaccines have not been tested in a head-to-head trial. There is no evidence to date showing the effects of the vaccines are materially different. Together with prompt diagnosis and treatment, vector control and chemoprevention, both vaccines will have an important role in malaria control.

More than 2 million children have now been vaccinated with RTS,S/AS01 in three African countries, yielding substantial impact during the 46 months of vaccine scale-up, including a 13% reduction in all-cause mortality in children eligible for vaccination[4] at 65-75% vaccine coverage. The impact could be expected to be even greater as vaccine coverage improves. It is expected that similar gains will be seen when R21 is widely deployed. While R21 appears safe from the data so far presented, it, together with the Matrix-M adjuvant, has been used in far fewer children than RTS,S/AS01, and it will be critical that safety monitoring for R21/Matrix-M continues, as is done for all newly introduced vaccines. A post-licensure evaluation of the vaccine's effectiveness and durability in high perennial transmission settings will also be informative, as these were not included in the Phase 3 trial.

Next generation malaria vaccines are still needed, particularly those that block transmission of *P. falciparum* from human to human. This use case for malaria vaccines is important for the aspiration to dramatically reduce malaria mortality and eliminate *P. falciparum* from many more African countries. The malaria vaccine community has learned many lessons from the Malaria Vaccine Implementation Programme[5], which forged a pathway for the development and deployment of future malaria vaccines; including on deliverability, acceptability, safety, and how a malaria vaccine can protect children not reached by other malaria preventive interventions,. The malaria vaccine community also has the benefit of a strategic framework in the form of the malaria vaccine technology roadmap, and agreement on the priority use cases, and preferred product characteristics (PPCs) for these use cases[6].

WHO prioritizes the use of malaria vaccines in moderate to high transmission settings because this is where the impact will be greatest[3]. In these areas, it will be important to ensure that the malaria vaccines are integrated into the existing package of WHO recommended high impact measures for malaria control. Already it has been shown that the preventive effectiveness of RTS,S/AS01 plus seasonal malaria chemoprevention (SMC) is higher than that of either intervention alone[2,78]. Effective malaria control depends on the strategic deployment of a mix of partially effective interventions, including vaccines. Financing for malaria vaccines must be additive to, and not replacing existing WHO recommended malaria control measures if the unacceptable burden of malaria mortality is to be curtailed.

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[1] https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022 Accessed 31 October 2023

[2] D Chandramohan, I Zongo, I Sagara et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. *N Engl J Med* 2021; **385**:1005-1017

[3] https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization Accessed 31 October 2023

[4] American Society of Tropical Medicine and Hygiene, 2023, conference presentation. KP Asante.

[5] Malaria vaccine implementation programme (who.int)

[6] https://iris.who.int/bitstream/handle/10665/362694/9789240057463-eng.pdf

[7] Dicko A., Ouedraogo J.B., Zongo., et al. Seasonal vaccination with RTS,S/AS01E vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial. *Lancet Infect Dis* 2023 Published Online August 22, 2023 https://doi.org/10.1016/
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