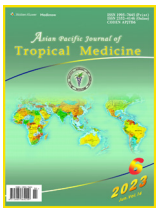

Perspective

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R21 vaccine: A ray of hope for malaria elimination

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The steady decline in malaria cases and deaths in recent years is a step ahead toward elimination; however, an increasing number of reports of antimalarial and insecticide resistance highlight the importance of having newer approaches to achieve the goal in the stipulated time frame. Therefore, having an effective and durable malaria vaccine is extremely crucial, which can complement the tools currently in use. Although the malaria vaccine development efforts initiated in the 1910's with the first attempts to develop a malaria vaccine involved inoculating humans with live, attenuated strains of the malaria parasite but the efforts have been intensified over the previous decade, resulting in several significant developments. Based on the field implementation trial in three African countries (Ghana, Kenya, and Malawi), the World Health Organization (WHO) in 2021 recommended the RTS,S vaccine for use in moderate-high transmission settings for malaria prevention and control. RTS,S vaccine, administered in 4 doses, demonstrated vaccine efficacy of 36% after 48 months of follow-up among 5-17 months old children[1]. RTS,S vaccine demonstrated the feasibility of use of malaria vaccine in the endemic areas; however, certain points needed consideration: reduction in the concentration and representation of HBsAg (currently 4:1) in virus-like particle (VLP); a mechanism to reduce the high antigenic competition with HBsAg, and thus high seroconversion rates for HBsAg, and finally having a vaccine with improved efficacy to meet the WHO goal of having a malaria vaccine with an efficacy of 70% or more in preventing clinical malaria by 2030[2]. Thus, the need for improvement in the existing vaccine was realized, and it is always preferable having multiple vaccines against malaria for meeting the demands.

The R21 vaccine, an improved version of the RTS vaccine, was designed and developed at the Jenner Institute in 2012, at the University of Oxford. It consists of a circumsporozoite protein (CSP) *C*-terminus fused with the HBsAg *N*-terminus. Unlike RTS,S, R21 used an advanced vector system (*Pichia pastoris*) for expressing fused CSP-HBsAg proteins. The expressed R21 VLP is ~22 nm in size. A preclinical study by Collins *et al*. tested the immunogenicity of R21 with a range of adjuvants in mice[2]. The accessibility of CSP and HBsAg was tested, and the study confirmed CSP as fairly accessible and HBsAg as having decreased accessibility, and the low antibody titter to HBsAg echoed this finding. Thus, R21 has the potential to generate a greater immune response towards malaria antigen, in contrast to RTS/AS01, as anti-NANP (part of CSP) is an immune correlate of protection against malaria. Further, anti-NANP, being an immune correlate of protection, should lead to greater efficacy of the vaccine. Matrix-M (MM), a saponin-based adjuvant manufactured by Novavax and recently used in COVID-19 and influenza vaccines, is the adjuvant for R21[3].

The R21 vaccine Phase 1a study was conducted from October 2015 to January 2017 among 31 healthy adults at the University of Oxford. The study participants were randomized to four groups and received either 2/10/50 mcg of R21 alone or mixed with MM. Based on the interim findings of Phase 1a, the Phase 1b study was initiated in Burkina Faso in August 2016 and enrolled 13 participants who were randomized to receive either 10 mcg R21 along with MM or placebo[4]. The anti-NANP responses to the R21 (10 mcg each) dose were similar to the response attained by three RTS (50 mcg each) doses, highlighting the requirement of a relatively lower antigen dose in the case of R21, thus being cost-effective for vaccine production. Based on Phase 1 results, Phase 2b was initiated in May 2019 in Burkina Faso, before the onset of the malaria season[3]. In this, 450 children aged 5-17 months were randomized to either group 1 (5 mcg R21 and 25 mcg MM) or group 2 (5 mcg R21 and 50 mcg MM) or the control group. The children received 3 doses of vaccine 4 weeks apart. The anti-NANP titters were assessed using ELISA before the 1st dose of the vaccine and at frequent intervals thereafter. The vaccine efficacy was 74% in group 1 at 6 months and 71% at 12 months, and 77% in group 2 both at 6 months and 12 months[3].

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Thereafter, the booster dose was administered to 409 children in 2020. Group 2 (higher adjuvant dose) retained an efficacy of 77%. The geometric mean of antibody titters increased till 28 days after 3rd dose and then decline, however, the levels again rose after the fourth dose (booster dose). Further, anti-NANP antibodies showed a negative correlation with malaria episodes, thus it can be considered as a correlate of protection for the R21 vaccine. Phase 3 trial was initiated in Burkina Faso, Kenya, Mali, and Tanzania with a sample size of 4 800 children[5] and the investigators have submitted the results for regulatory approvals, though the results are not available in public in the form of scientific literature.

The immunobridging study can be conducted in malaria-endemic areas for generating evidence for the safety and immunogenicity of the R21 vaccine[5]. For vaccines showing effectiveness in one setting, immunobridging studies are mainly conducted to infer effectiveness in another setting. In immunobridging studies, an immune correlate of protection, *i.e.*, seroconversion rate or antibody titters are compared between two settings using appropriate statistical tests. The immunobridging studies have been conducted earlier for COVID-19 vaccines. It is an effective approach for generating relevant data in a shorter time period.

R21, an improved version of the RTS,S vaccine has shown promising results in Phase 2 trial, and Phase 3 trial results are awaited. Now, Ghana and Nigeria's governments in April 2023 have provided the regulatory clearance and approved its use for malaria control. In the WHO, the prequalification process for the R21 vaccine is being undertaken. There are some impending questions: 1) How the vaccine will perform in areas of low transmission? 2) Will it be cost-effective? 3) How the vaccine will perform if administered around the year or irrespective of the season, as currently, the vaccine efficacy results are available for the seasonal administration of the vaccine? 4) If approved by the WHO, do countries still need to test the vaccine in a trial setting or immunobridging studies will suffice? 5) Long-term safety data of the vaccine; 6) Need of booster doses, if yes, the interval and age till which booster should be given? 7) Impact of human and parasite genetic diversity on the effectiveness of the vaccine. In addition, Phase 4, *i.e.*, post-marketing surveillance should be prioritized, by strengthening pharmacovigilance in the countries opting for wider use of the vaccine in public health settings. Despite some unanswered questions, the R21 vaccine with efficacy exceeding 75%, the WHO's target, has the potential to revolutionize malaria prevention, thus reducing malaria morbidity and mortality, and finally eliminating malaria. For effectively eliminating a disease, or for efficient control and prevention, as has been shown for COVID and polio, the role of vaccine is prominent. For mass-scale use in a field setting, an uninterrupted supply of vaccines is very crucial and, being manufactured by the Serum Institute of India, has assured delivery of 200 million doses of R21 vaccine per year which may meet the demands. With the commitment towards eliminating malaria, it is hoped that the vaccine may be instrumental for this in malaria-endemic communities globally.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

NN and SN did the literature search and drafted the manuscript; NN, and PKB gave intellectual comments, reviewed the final version.

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