Indian Academy of Pediatrics (IAP)

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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial

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BASED ON ARTICLE

Mehreen S Datoo, Hamtandi Magloire Natama, Athanase Somé, et al. Lancet Infect Dis. 2022;22:1728-36.

ABSTRACT

Background: Malaria is a leading cause of morbidity and mortality worldwide. This group previously reported the efficacy of the R21/Matrix-M malaria vaccine, which reached the WHO-specified goal of 75% or greater efficacy over 12 months in the target population of African children. Here, they report the safety, immunogenicity, and efficacy results at 12 months following administration of a booster dose of same vaccine.

Methods: This double-blind phase 1/2b randomised controlled trial was done in children aged 5–17 months in Nanoro, Burkina Faso. Eligible children were enrolled and randomly assigned (1:1:1) to receive three vaccinations of either 5 μg R21/25 μg Matrix-M, 5 μg R21/50 μg Matrix-M, or a control vaccine (the Rabivax-S rabies vaccine) before the malaria season, with a booster dose 12 months later. Children were eligible for inclusion if written informed consent could be provided by a parent or guardian. Exclusion criteria included any existing clinically significant comorbidity or receipt of other investigational products. A random allocation list was generated by an independent statistician by use of block randomisation with variable block sizes and provided to the pharmasists. All vaccines were prepared by the study pharmacists by use of the same type of syringe, and the contents were covered with an opaque label.

Vaccine safety, efficacy, and a potential correlate of efficacy with immunogenicity, measured as anti-NANP antibody titres, were evaluated over 1 year following the first booster vaccination. The population in which the efficacy analyses were done comprised all participants who received the primary series of vaccinations and a booster vaccination. Participants were excluded from the efficacy analysis if they withdrew from the trial within the first 2 weeks of receiving the booster vaccine. This trial is registered with ClinicalTrials.gov (NCT03896724), and is continuing for a further 2 years to assess both the potential value of additional booster vaccine doses and longer-term safety.

Results: Between June 2, and July 2, 2020, 409 children returned to receive a booster vaccine. Each child received the same vaccination for the booster as they received in the primary series of vaccinations; 132 participants received 5 µg R21 adjuvanted with 25 µg Matrix-M, 137 received 5 µg R21 adjuvanted with 50 µg Matrix-M, and 140 received the control vaccine. R21/Matrix-M had a favourable safety profile and was well tolerated. Vaccine efficacy remained high in the high adjuvant dose (50 µg) group, similar to previous findings at 1 year after the primary series of vaccinations. Following the booster vaccination, 67 (51%) of 132 children who received R21/Matrix-M with low-dose adjuvant, 54 (39%) of 137 children who received R21/Matrix-M with high-dose adjuvant, and 121 (86%) of 140 children who received the rabies vaccine developed clinical malaria by 12 months. Vaccine efficacy was 71% (95% CI 60 to 78) in the low-dose adjuvant group and 80% (72 to 85) in the high-dose adjuvant group. In the high-dose adjuvant group, vaccine efficacy against multiple episodes of malaria was 78% (95% CI 71 to 83), and 2285 (95% CI 1911 to 2568) cases of malaria were averted per 1000 child-years at risk among vaccinated children in the second year of follow-up. Among these participants, at 28 days following their last R21/Matrix-M vaccination, titres of malaria-specific anti-NANP antibodies correlated positively with protection against malaria in both the first year of follow-up (Spearman's ρ –0·32 [95% CI –0·45 to –0·19]; p=0·0001) and second year of follow-up (–0·20 [–0·34 to –0·06]; p=0·02).

Interpretation: A booster dose of R21/Matrix-M at 1 year following the primary three-dose regimen maintained high efficacy against first and multiple episodes of clinical malaria. Furthermore, the booster vaccine induced antibody concentrations that correlated with vaccine efficacy. The trial is ongoing to assess long-term follow-up of these participants and the value of further booster vaccinations.

COMMENTARY

Malaria is still a life-threatening disease – in year 2021 number of Malaria deaths stood at 619000. WHO African region accounted for 96% of this mortality and children under 5 contributed 80% of all malaria deaths[1].

We know that RTS,S/AS01 a vaccine against Malaria manufactured by GSK has shown moderate protective efficacy against clinical malaria (39%), severe malaria (31.5%), and malaria-related hospitalizations (37.2%) at 4 years of follow up after a phase 3 trial in children 5-17 months of age at first vaccination. . At six months following the 4th dose, vaccine efficacy was 42.9%. Vaccine was endorsed by SAGE as no other candidate vaccine was available2. The Malaria Vaccine Implementation Programme (MVIP) was conceived, designed and initiated to act on the 2016 WHO recommendation to pilot the RTS,S/AS01 malaria vaccine in routine immunization programmes.

Since October 2021 WHO recommendedbroad use of the RTS,S/AS01 malaria vaccine among children living in regions with moderate to high P. falciparum malaria transmission along with preventive chemotherapy (MVIP)3. Through April 2021, 24 months of data after the MVIP started, the DSMB concluded that the MVPE findings demonstrated effectiveness of RTS,S/AS01 vaccine against severe malaria, with a 30% reduction in severe malaria, and a 21% reduction in hospitalization with

malaria parasitemia.

According to European Medicines Agency these studies showed modest efficacy, however, possible safety signals of increased incidence of meningitis, cerebral malaria cases, and increased female mortality in malaria vaccine groups were also observed.There remains an urgent need to identify and develop improved vaccine candidates that could achieve the WHO goal of 75% efficacy against clinical malaria.

New candidate vaccine R21 is a novel pre-erythrocytic candidate malaria vaccine developed by Oxford University, UK and now manufactured by Serum Institute of India. R21 has more vaccine antigen and lacks the excess HBsAg found in RTS,S leading to focused immune response towards the malarial antigen rather than HBsAg. Following preclinical studies of R21 plus multiple adjuvants, Matrix-M (R21/MM) was selected for clinical development based on high immunogenicity. It is a saponin-based adjuvant that stimulates both humoral and cellular immune responses to vaccines. Initial findings with the new R21/MM vaccine candidate appear to improve on the efficacy in children of all other malaria vaccines[4].

In the initial phase 1/2b trialsin Burkina Faso,children aged 5–17 months were randomly assigned (1:1:1) to three groups at the start of the trial from arandom allocation list, by use of block randomisationwith variable block sizes. Group 1 received 5 ìg R21 adjuvanted with 25 ìg Matrix-M, group 2 received 5 ìg R21 adjuvanted with 50 ìg Matrix-M, and group 3 was the control group and received the Rabivax-S rabies vaccine4. Analyses of vaccine efficacy included all participants who received a booster vaccination. Outcomes of asymptomatic malaria infection at 12 months following the booster vaccination were analysed by use of a log binomial model, including randomised group as a covariate. Relative risks and 95% CIs were reported, comparing groups 1 and 3 and groups 2 and 3. They analysed further secondary outcomes of vaccine safety,immunogenicity (measured by ELISA), and efficacy over the 12 months following the first booster vaccination and over the 24 months following the primary series of vaccinations. There was no safety issue in any of the groups.

Vaccine efficacy according to the primary case definition from 14 days following booster vaccination to 12 months was 70% (95% CI 59–78; p<0·0001) in group 1 and 80% (72–85; p<0·0001) in group 2 (table 2). Further adjustment for use of seasonal malaria chemoprevention (at least one monthly course of three doses) resulted in a vaccine efficacy of 81% (95% CI 74–87; p<0·0001) in group 2. Efficacy was further assessed at 24 months (range 660–731 days) following the primary series of vaccinations. A lower efficacy was observed in group 1 compared with group 2 participants in the first and second year of follow-up. After 2 years, vaccine efficacy in group 1 dropped to 70% (95% CI 59–78). This was significantly lower than in group 2, where vaccine efficacy was 80% (95% CI 72–85; p<0·0001), consistent with lower vaccine immunogenicity in group 1.

This study was done in an area of highly seasonal malaria transmission. These findings show that R21/Matrix-M has reached the WHO-specified efficacy goal of 75% or greater over 24 months in the target population of African children. This trial is now fully enrolled and evaluating vaccine safety and efficacy in 4800 children at five sites in East and West Africa, including sites with perennial malaria

transmission. We are very hopeful that Phase III trials of the vaccine will be very encouraging and will meet the goal of 75% efficacy.

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