Topic: Parasites — Malaria/Plasmodia: Vaccines and Immunotherapeutics

RH5.1/Matrix-M™: Efficacy of a standalone blood-stage vaccine against clinical *P. falciparum* malaria in 5-17 month old children; a Phase 2b randomised trial in Burkina Faso

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Two pre-erythrocytic vaccines (R21/Matrix-M™ and RTS,S/AS01) are now approved for *P. falciparum* (*Pf*) malaria prevention in children. However, neither vaccine induces blood-stage immunity against parasites that emerge from the liver. The most advanced blood-stage *Pf* vaccine candidate is a full-length protein (RH5.1) that targets the conserved and essential reticulocyte-binding protein homologue 5. RH5.1 induced the highest levels of *in vitro* growth inhibition activity (GIA, a correlate of protection in non-human primates) in 5–17-month-old children when administered with Matrix-M™ in a Phase 1b trial in Tanzania. Here we assess efficacy against clinical malaria in an area of seasonal transmission in Burkina Faso in a Phase 2b, double-blinded, randomised, controlled trial (NCT05790889). Healthy children aged 5-17 months were recruited at the Siglé site and randomised to receive either three intramuscular 10 µg doses of RH5.1 with 50 µg Matrix-M™ (two groups of N=120) or three doses of a rabies control vaccine (two groups of N=60), given as a monthly 0-1-2 or a delayed third dose 0-1-5-month regimen. Primary endpoints were: i) efficacy against clinical malaria at 6 months (starting from 14 days post dose 3), defined as the presence of axillary temperature ≥37.5°C and/or history of fever within the last 24 hours AND *Pf* asexual parasitaemia >5000/µL; and ii) vaccine safety and reactogenicity. Vaccinations started in April 2023 and completed by mid-September 2023. A total of 122, 119 and 120 children were enrolled in the control, delayed and monthly dose RH5.1/Matrix-M™ groups, respectively. RH5.1/Matrix-M™ was well tolerated with no safety concerns or serious adverse events at 12 months of follow-up post first dose. Vaccine efficacy at 6 months as per the primary case definition was 55% (95% CI 20-75, *P*=0.007) in the delayed group and 40% (95% CI -0.03-65, *P*=0.065) in the monthly group. A 0-1-5-month regimen of RH5.1/Matrix-M™ appears safe, highly immunogenic, and shows the first promising efficacy of a RH5-based blood-stage vaccine when used alone, supporting further clinical development within a multi-stage vaccine strategy for *Pf* malaria.

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