Commentary

Addressing the bottleneck at clinical testing of candidate malaria vaccines

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Invited Commentary on 'Preerythrocytic and Blood-Stage Malaria Vaccines Can Be Assessed in Small Sporozoite Challenge Trials in Human Volunteers', Roestenberg et al., Journal of Infectious Diseases, 2012.

Vaccines are a very effective health care intervention but are not available for many diseases, including malaria. Potential candidates have been identified in preclinical research studies and some have progressed through preclinical development to clinical trials (http://www.who.int/vaccine_research/links/Rainbow/en/index.html). However, the vaccine development pathway is long and expensive and there is a major bottleneck at the stage of clinical testing. For malaria, only a single candidate has advanced to Phase 3.¹ Moreover, rodent malaria models exist but protection against challenge with the causative parasites of human malaria can only be assessed in humans, and there are no known correlates of protective immunity to malaria. Candidate vaccines that fail to meet defined go/no-go criteria in animals during development may nonetheless exhibit efficacy in humans. The testing of a larger portfolio of vaccine candidates in small numbers of volunteers in clinical research studies would be valuable.

Controlled human malaria infection of malaria-naïve human volunteers with *Plasmodium* sporozoites administered via the bites of laboratory-reared *P. falciparum* infected mosquitoes is routinely performed at two institutions in Europe (University of Oxford, United Kingdom; Radboud University Nijmegen Medical Centre (RUNMC), The Netherlands) and three institutions in the United States (US Military Malaria Vaccine Program, Silver Spring; University of Maryland, Baltimore; Seattle Biomedical Research Institute, Seattle).² A comparative analysis of safety and parasitological data from trials performed at three of these institutions has

confirmed the safety profile and demonstrated that parasite growth rates are highly reproducible between institutions.³ There is increasing interest in controlled human blood-stage malaria infection, pioneered at the Queensland Institute of Medical Research, Australia.⁴ One limitation of those studies, however, is that vaccinees are treated by curative anti-malarial treatment at very low parasite densities providing little opportunity to assess the efficacy of blood-stage malaria vaccines.

As detailed in the accompanying commentary by Stoute,⁵ the typical readout of sporozoite challenge studies is via Giemsa-stained blood smears but more sensitive and informative readouts are now available with advances in technology including the development of quantitative PCR techniques. In their recent article, Roestenberg and colleagues⁶ specifically looked at the impact of qPCR readouts by analysing qPCR data and parasite kinetics from 48 volunteers in seven sporozoite challenge studies of pre-erythrocytic and erythrocytic malaria vaccine candidates conducted at RUNMC over an 11-year period. It was assumed that pre-erythrocytic stage vaccines would reduce the geometric mean parasitemia of the first cycle only but not impact the parasite multiplication rate, whereas erythrocytic stage vaccines would reduce the parasite multiplication rate from the first cycle onwards. The authors concluded that sporozoite challenge trials with 6–7 subjects per group are sufficiently powered to detect vaccine-induced biological effects potentially associated with clinical protection. Sensitivity may be enhanced by increased frequency of qPCR monitoring and more complex data analysis methodologies.

One caveat is that the authors do not describe the blood-stage vaccines included in the analysis but state that only two erythrocytic candidate vaccines, AMA1 and MSP1, have been subjected to sporozoite challenge. However, both AMA1 and MSP are also expressed in *Plasmodium*-infected hepatocytes^{7,8} so any vaccine-induced biological effects may be directed at pre-erythrocytic as well as asexual erythrocytic stages. Indeed, the geometric mean parasite density in the first cycle was not significantly different between any of the vaccine trials analysed, implying all vaccines had an effect at the pre-erythrocytic stage. It is likely that sporozoite group challenge sizes for candidate blood-stage vaccines where the component antigen is not expressed in the pre-erythrocytic stage

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may need to be larger than those for candidate vaccines targeting only the pre-erythrocytic stage or both pre-erythrocytic and erythrocytic stages.

The study of Roestenberg *et al.*⁶ advances the case for clinical research addressing, in part, the current bottleneck in the malaria vaccine pipeline. Small sporozoite challenge trials would allow for preliminary evaluation of the efficacy of pre-erythrocytic and asexual erythrocytic stage malaria vaccine candidates and down-selection for efficacy testing in the field.

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