Antibody titre as a surrogate of protection of the first malaria subunit vaccine, RTS,S/AS01

The RTS,S/AS01 vaccine is the first effective malaria subunit vaccine tested in a phase 3 trial.1,2 The target antigen of the vaccine is circumsporozoite protein, a surface protein expressed only in sporozoites, the invasive stage of the malaria parasite, which are transmitted by infected mosquito bites to human beings and develop to other stages in the liver. The RTS,S/AS01 vaccine acts solely at the pre-erythrocytic stages. In the phase 3 trial, the vaccine provided significant efficacy against clinical malaria in different age groups in different transmission settings. Previous reports suggest that anti-circumsporozoite protein antibodies and circumsporozoite protein-specific CD4-positive T cells were associated with protection from *Plasmodium falciparum* infection and clinical malaria.3,4 However, the duration of protection and determinants of immunogenicity after vaccination are unclear because of the lack of long-term follow-up in the phase 2 trials.

In-depth analyses of the duration of protection is important for both the application of RTS,S/AS01 in Africa and for efforts to develop the next-generation of malaria vaccines based on circumsporozoite protein. In *The Lancet Infectious Diseases*, Michael White and colleagues report analyses of the determinants of immunogenicity induced by RTS,S/AS01, given with or without a booster, using data from 8922 African children aged 5–17 months and 6537 African infants aged 6–12 weeks in the pivotal phase 3 trial.6 To our knowledge, this is the first comprehensive analysis of the determinants of protective immunity of RTS,S/AS01.

By comparison of anti-circumsporozoite protein antibody titres over time with individual follow-up data for episodes of clinical malaria, White and colleagues showed that the efficacy profile of RTS,S/AS01 can be informed by measurements of anti-circumsporozoite protein antibodies, enabling estimation of the duration of protection. They estimated that an anti-circumsporozoite protein antibody titre of 121 EU/mL could prevent 50% of infections. Waning antibody titres predict the duration of efficacy against clinical malaria across different age categories and transmission intensities, and efficacy wanes more rapidly at higher transmission intensity. The immune responses induced by RTS,S/AS01 vaccination and by natural infection are distinct. In low transmission areas, efficacy against clinical malaria wanes because of the reduction in anti-circumsporozoite protein antibody titres. In high transmission areas, efficacy against clinical malaria wanes more rapidly because of both the reduction in antibody titres and the lesser blood-stage immunity in vaccinated participants compared with control individuals. White and colleagues concluded that anti-circumsporozoite protein antibody titres are a surrogate of protection for the magnitude and duration of RTS,S/AS01 efficacy.

The relation between anti-circumsporozoite protein antibody titres and efficacy can be used to assess future iterations of RTS,S and second generation anti-circumsporozoite protein vaccines. Why antibody titres are not maintained is unknown, but could relate to the inability of sporozoites to naturally boost vaccine-induced antibody responses and the subsequent exposure to few sporozoites, or the polymorphic nature of the T-cell epitopes on the circumsporozoite protein.7 This work shows the limits of anti-infection vaccines and highlights the importance of a blood-stage malaria vaccine that prevents disease caused by the blood-stage parasite. Blood-stage vaccines induce protective immunity that is boosted by repeated natural parasite infection and the allelic polymorphism that hampered vaccine efficacy in candidates such as apical membrane antigen 1 could be overcome by the identification of highly conserved blood-stage vaccine targets. Therefore, to improve the efficacy of malaria vaccines, we suggest that addition of a conserved blood-stage vaccine component to RTS,S/AS01 as a multistage malaria vaccine is of paramount importance.
Comment


5. White MT, Ventry R, Griffin JT. Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. Lancet Infect Dis 2015; published online Sept 1 http://dx.doi.org/10.1016/S1473-3099(15)00339-X.

