Commentary

Malaria Sporozoite Challenge Model Comes of Age

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Invited Commentary on 'Efficacy of 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.

For decades a small group of laboratories have been quietly but steadily testing experimental malaria vaccines in human volunteers and confirming their efficacy by exposing these volunteers to the bite of infected mosquitoes. A few days following the bite of the mosquitoes the volunteers are followed closely for onset of symptoms and for the presence of the parasite in the peripheral blood by preparing blood smears that are examined microscopically. The requirements for a successful challenge that infects 100% of non-immunized volunteers, such as the number of mosquito bites and the length of time the mosquitoes are allowed to feed, were worked out empirically initially.¹ The sample size of these sporozoite challenges also was driven by limitations in logistics as well as by ethical concerns about the safety of volunteers.² Despite these limitations, the cumulative observation through the years has been that the results of these trials accurately predicted success or failure in the field. The advent of quantitative PCR has allowed a more accurate estimation of the parasitemias in these individuals than was ever possible microscopically as well as the calculation of the parasite multiplication rates, making it possible to determine the effect of immunization on these parameters. This is important because pre-erythrocytic vaccines which just target sporozoites and liver stages of the parasite would only have an impact on the first wave of parasitemia coming out of the liver. On the other hand, blood stage vaccines that target merozoites are not predicted to impact the first wave of parasitemia but would affect the multiplication rate in blood. Thus, the addition of quantitative PCR has allowed scientists to determine the effect of a vaccine on the parasite load in the liver and on the multiplication rate in blood. One recent example of the usefulness of this approach was the finding that the AMA-1 vaccine resulted in a reduction of the first

wave of parasites.³ A subsequent preliminary trial in Africa also seemed to suggest that this vaccine can offer some protection against vaccine strain parasites.⁴ With the use of statistical simulation, Roestenberg *et al.*⁵ have estimated that with the addition of quantitative PCR sporozoite challenge studies, although small, do have sufficient power to detect clinically relevant differences between immunized volunteers and controls such as 90% or greater inhibition of parasitemia or multiplication rate. Some have argued that blood stage vaccines that target the red cell invasive form of the parasite should be tested in the field in order to better observe the effect of vaccine-induced immunity over a period of time. However, the limited published experience and now the analysis by Roestenberg *et al.*⁵ seem to argue that the sporozoite challenge model can provide a window into the likelihood that these vaccines can confer protection. The results of Roestenberg and colleagues are welcome news in an era when resources and funding for large field trials are very limited. This is illustrated in the accompanying commentary by Doolan.⁶ They support the paradigm of subjecting all malaria vaccines to sporozoite challenge trials prior to committing to large field studies.

Reference List

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