Mechanistic Correlates of Protection for SARS-CoV-2 Vaccines

To the Editor:

The rapid development of COVID-19 vaccines from bench to bedside is an unprecedented feat made possible by pre-existing vaccine candidates against the SARS-CoV and MERS-CoV viruses and the use of neutralizing antibodies against the SARS-CoV-2 virus as a potential correlate of protection.[1] Although currently approved vaccines were licensed after efficacy studies of immunogenic vaccine candidates, the possibility of reinfection and escape variants, although uncommon, may necessitate the update of the vaccine.

This has led to calls for the establishment of correlates of protection for COVID-19 vaccines and a growing number of studies to investigate protective immune responses against the SARS-CoV-2 virus after infection and vaccination.[2] For example, in a recent publication from the SIREN study, it was estimated that prior infection reduced the risk of (re-)infection with SARS-CoV-2 by 84%.[3] This is reassuring for the prospects of control of COVID-19 through mass vaccination, and a return to normality. Krammer[2] discussed the importance of establishing neutralizing antibodies as a correlate of protection—that is, an immune marker that is associated with individual protection against infection or disease. As Krammer recognized,[2] it is important to identify immune markers that have a mechanistic role in protection.[4,5]

On additional examination of the SIREN report,[3] we estimated that 9.8% (1,704/17,383) of the SARS-CoV-2 negative cohort were infected. The SIREN study used an assay which can detect antibodies that bind to the SARS-CoV-2 spike protein and nucleocapsid.[3] In the SARS-CoV-2 positive (previously infected) cohort, the comparative proportions were 1.7% (127/7,551) among the antibody-positive members and 4.0% (23/582) among the antibody-negative members. Comparison of these proportions suggests that antibodies play a role in protection against reinfection while indicating that other immune markers, for example cellular immunity,[6,7] might also be involved. Studies of immune responses to SARS-CoV-2 infections and COVID-19 vaccines indicate that immune markers of both humoral and cellular immune responses could be detected following an infection or vaccination.[8] These markers include neutralizing antibodies, T-cell responses, and antibody-mediated immune responses such as antibody-dependent complement deposition.[8]

Further analysis of these immune markers such as antibody titer and immune cell responses, with adjustment for potential confounders and follow-up duration, could provide a refined comparison of what might be lesser protection by reinfection without persistent immunity in the form of circulating antibodies or pathogen-specific immune memory. However, such analyses require comparisons between infected individuals with and without detectable levels of the immune marker of interest, or between persons with different levels of the marker if it is a quantitative marker. For example, in the SIREN report,[3] there were relatively few antibody-negative but previously infected individuals which could be used to determine the potential mediating role of antibodies in the protection provided by prior infection. Although this suggests that large sample sizes may be needed to establish and distinguish correlates and mediators of protection for SARS-CoV-2 with traditional study designs such as randomized controlled trials as well as cohort or case–control studies, methodologic and statistical advances are needed to overcome these challenges.[8]

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