COMMENTARY

SEROLOGIC TESTS FOR COVID-19 INFECTIONS AND VACCINATION

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We are accustomed to obtaining antibody tests to a variety of pathogens to determine whether the infection has taken place or vaccines have been previously given. For example, a positive test for measles antibody indicates either prior infection or vaccination, with the proviso that young infants may possess passive maternal antibodies from their mothers. The situation for severe acute respiratory syndrome (SARS)-2 coronavirus is considerably more complex and an antibody result requires a deeper understanding of the biology of infection.

Similar to other pathogens, the usual reason for testing someone for antibodies to SARS-2 is confirmation of prior infection or vaccination. The difficulty is that the tests to be employed differ from the simplicity of other pathogens owing to the construction of the virus and the variation of its antigens. The principal antigens of the SARS-2 virus are the spike protein on the surface of the virus particle and the nucleoprotein that is internal. Although infection usually induces antibodies both to the spike and the nucleoprotein, only current whole virus inactivated vaccines contain the nucleoprotein. Thus, in an individual who has received an mRNA or adenovirus-vectored vaccine spike antibodies will be produced, but a positive test for nucleoprotein antibodies confirms prior infection.[1] Of course, in the absence of prior vaccination, a positive test for spike antibodies also confirms prior infection, although those antibodies may disappear with time after mild infections.[2,3]

Separate use of antibody testing is confirmation of response to vaccination. Inasmuch as all vaccines against SARS-2 use spike protein to induce neutralizing antibodies, a serologic test for those antibodies can confirm the likelihood of resistance to infection. There are several tests available to show antibodies to the spike protein, including ELISA to detect binding antibodies and neutralization to show an effect on infectivity.[4] The ELISA antibody test is the most widely used, which measures binding to the spike protein. Neutralization and pseudo neutralization assays test the ability of antibodies to prevent infection of cell cultures by the virus. The higher the neutralizing antibodies in a vaccine, the lesser the likelihood of symptomatic infection, although asymptomatic infection may still occur.[5,6] Coronavirus infections are essentially mucosal infections of the respiratory tract, although secondary infection of cells outside the respiratory tract can cause complications. However, coronavirus disease 2019 is not a viremic infection such as measles, meaning that levels of antibody in the serum have variable protective effects, and no level of antibody is an absolute guarantee of protection.[7]

To interpret antibody levels, one must understand that antibody levels are predictive of protection against infection, but that a completely protective level does not exist. Moreover, there is a great variation of SARS-2 strains, such that antibodies to the original Wuhan strain have limited value in predicting individual protection against newer variants such as omicron. Nevertheless, antibody titers in a population do have a high predictive ability in predicting protection in a population, as long as the antibody test uses the prevalent strain as the antigen.[8]

Thus, the commonly used tests for antibodies in vaccinees will inevitably show lower levels of antibodies to the omicron variant than antibodies to the original SARS-2 strain, which will justifiably lower predicted efficacy against omicron. Moreover, any evaluation of vaccine efficacy should be made after the third dose, for the immune response to have reached its peak and greatest breadth.[9]

Unfortunately, although a laboratory standard developed in the UK is available, most articles reporting on the immunogenicity of vaccines compare antibody responses to the vaccine with responses to infection. Roughly speaking, a titer equivalent to convalescent sera will give efficacy of about 60%. Lower titers are associated with lesser efficacy, but whether that efficacy is attributable to the low antibodies or to T cell responses is unclear. However, it is quite clear that antibodies at levels several times those of convalescents give about 80% protection and levels that are numerically in the thousands give 90%–95% efficacy. The relevance of those titers is confirmed by the fact that protection decreases with time postvaccination in proportion to decreasing antibodies.[10,11] A legitimate question is with regard to the interpretation of falling titers after vaccination. Unfortunately, it appears that antibody declines with time postvaccination and that correlates with falling efficacy. Accordingly, the determination of titers is useful to predict the likelihood of protection in vaccinated individuals, although as mentioned there is no absolute threshold for efficacy.[12]

In view of the above, what antibody test should one order and for what reasons? Neutralization or pseudo neutralization tests give the best biological information, but ELISA binding antibodies by and large give similar information and are more widely available. Certainly, the clearest indication is to determine if an immunosuppressed individual has responded to vaccine or needs still another dose of vaccine. Second, in the absence of vaccination, a spike antibody test performed after an illness will confirm a SARS-2 infection. Third, if the patient has been vaccinated, antibodies to the nucleoprotein as well as the spike will confirm infection. Fourth, while third doses are recommended for all patients to obtain the maximum height and breadth of antibody responses, the need for the fourth dose can be evaluated by antibody tests 4 months or more after the third dose.

The last indication is the most controversial. On the one hand, as stated above, the risk of infection decreases in proportion to the height of the antibody response, but there is no level that gives certain 100% protection. On the other hand, each vaccine dose carries with it the risk of reactions. The best advice appears to be that 3 doses given over 6 months (2 with the J&J vaccine) are essential for the broadest immunity and that one should follow the advice of public health authorities that a fourth dose is recommended for high-risk groups such as the elderly or people with comorbidities. It is possible that in the future booster vaccination against SARS-2 will become annual, perhaps with the use of vaccines in development that stimulate broad antibodies against all beta coronaviruses.[13]

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