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Antibody testing for coronavirus disease 2019: not ready for prime time

The tests need work, and fundamental questions remain about immunity

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The development of serology testing to detect antibodies to the virus responsible for coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported by Zhu and colleagues,[1] and followed soon after by many others, has been enthusiastically hailed as the key to monitoring and responding to the pandemic, including the restart of economic activities. This enthusiasm reflects the hope that antibodies to SARS-CoV-2 will provide protective and long lasting immunity and allow recovered individuals to resume their daily lives. Unfortunately, we do not yet know what the presence of detectable antibody signifies, either for an individual or for a population, how durable it will be, or how much serologic variation to expect among different groups, such as those who had an asymptomatic infection.

Not good enough

In a linked paper, Bastos and colleagues (doi:10.1136/bmj.m2516) provide a much needed review of the performance of serological assays to accurately detect antibodies to SARS-CoV-2.[2] They meta-analyzed 40 studies according to type of antibody test (enzyme linked immunosorbent assays (ELISAs), lateral flow immunoassays (LFIAs), and chemiluminescent immunoassays (CLIAs)), and for each type, determined the average or pooled sensitivity and specificity and assessed the studies for risk of bias. Only four of the 40 studies included outpatients and only two studies assessed LFIAs at the point of care.

The pooled sensitivities had a wide range, with higher sensitivity in the CLIAs (97.8%) and lowest in the LFIAs (66.0%) and were higher with increased time after symptom onset. The range for specificities was narrower, from 96.6% to 99.7%. The risk of patient selection bias affected nearly every study.

It is important to keep in mind that pooling sensitivities makes it difficult to determine how well tests perform at detecting antibody early or late in the course of illness (reported as 26.7% for samples collected during the first week versus 78.4% for samples collected beyond the third week for ELISAs). Pooling also hinders the ability to identify individual tests that might perform well in testing algorithms, described below. Ideally, test performance should be compared according to the viral antigen used in each assay, such as the N nucleocapsid or the S spike protein, since antibodies against the spike protein are thought to correlate with neutralizing titers.[3] Nonetheless, the key message of the review aligns with the conclusion of another systematic review[4] published last week: serologic assays for SARS-CoV-2 antibodies, especially point-of-care tests, are not ready for widespread use by clinicians, the general public, or policy makers.

It is unlikely that any single serologic test will provide the kind of reliable and accurate information that are needed to fully understand the current pandemic. As Bastos and colleagues and others have indicated,[5] tests with low specificity provide more false positives than true positives in low prevalence settings, resulting in unacceptably low positive predictive values. To overcome the poor performance of a single serologic test, an algorithm should be considered that combines two or more tests (eg,[6]). For example, in a 5% prevalence setting, screening with one of the more sensitive ELISAs reviewed by Bastos and colleagues (96.0% sensitivity, 99.2% specificity)[7] and then using a more specific test (85.0% sensitivity, 100% specificity)[8] as the confirmatory test would increase positive predictive value from 55% to 100%.[9] Such an algorithm would still fail to identify antibodies in samples collected within the first 14 days of symptom onset and require follow-up testing at a later date (more than three weeks after symptom onset).

Independent evaluation

In the early months of the outbreak, the global market was flooded with antibody tests of unproven test performance, and various governments, including those of the UK and India, purchased large quantities of ineffective antibody tests.[10-12] In the US, the Food and Drug Administration reversed course in May and mandated emergency use authorizations for all commercially available serologic test kits with a test performance of 90% or more sensitivity and 95% or more specificity,[13] but the damage had been done and contributed to surveillance data of uneven quality. Critical independent evaluations of antibody tests are currently underway by the FDA and other organizations[14-16] to provide researchers, public health officials, and others with better data for decision making. Ideally, these evaluations should all use the same specimen panels containing reverse transcriptase polymerase chain reaction confirmed SARS-CoV-2 positive and negative plasma. Such specimen panels are a valuable tool for both test kit developers and evaluators, and global health institutions should make them widely available.

As this review makes clear, there is more work to do on serologic testing. Assays must be optimized further, independently validated, and used in an algorithm format to achieve the highest possible accuracy for decision making, especially at an individual level.

High quality antibody tests have the potential to provide important information about prior infection, and the prevalence of antibodies in a population might help us to understand the extent of the epidemic and the role of transmission from asymptomatic individuals. Further research is needed to address fundamental questions about the presence of antibodies and the degree and durability of protection. Until then, even the most optimal serologic test will be of limited utility.

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