

AACC Recommendations for SARS-CoV-2 Serology Testing

This AACC statement seeks to provide clarity and guidance on serology testing and to raise awareness of its utility and limitations in the management of the COVID-19 pandemic.

There is broad recognition that the unprecedented COVID-19 pandemic requires clinical laboratory testing as part of the worldwide response to this health crisis. To detect SARS-CoV-2—the virus that causes COVID-19—in infected individuals, the primary laboratory tool has been molecular diagnostic tests. While these tests inform clinicians of individuals who are currently infected by identifying the presence of SARS-CoV-2 genetic material, there is a need to gain insight into the prevalence of SARS-CoV-2 in the general public. Serologic testing, which looks for antibodies specific to SARS-CoV-2, can identify individuals who have been infected and may assist in epidemiologic initiatives and contact tracing. Clinical laboratory professionals are invaluable for the evaluation, use, and interpretation of these clinical tests and can help policy makers and public health officials develop strategies to constrain the pandemic.

Utility of Serology Testing in COVID-19

Serology tests are blood-based tests that can be used to determine whether people have been infected by particular pathogens. The immune system recognizes pathogens as foreign and mounts a protective response involving the development of antibodies. The presence or absence of SARS-CoV-2 specific antibodies can determine whether a person has been infected by the virus.

Diagnosis and management

Serologic testing may play a role in vaccine development and identification of recovered patients who can donate blood to help others fight the infection. Serologic testing may also be a useful diagnostic tool in patients who have a longer (i.e. greater than 1-2 week) history of COVID-19 symptoms but have a negative molecular test. In such cases, the patient may have stopped producing virus and therefore may no longer be infectious. **Serologic testing may be complementary to PCR-based diagnostic testing for management of SARS-CoV-2 infection.**

Surveillance and prevalence

Serologic testing has limited utility for surveillance and identification of the prevalence (i.e. the percent of people infected within a population) of disease. The time required for antibody production after infection by SARS-CoV-2 must be considered when surveillance testing is utilized. **While serologic testing can provide insight into the level of SARS-CoV-2 exposure within our communities, there are limitations for its use, and test results must be interpreted judiciously.**

Limitations of Serology Testing

Serologic testing should not be used as a primary method of diagnosing an acute infection or exclusion of SARS-CoV-2 infection when a patient is experiencing symptoms. SARS-CoV-2 can be detected in infected individuals before antibodies are detected. While research into the course of SARS-CoV-2 infection is ongoing, it is known that antibodies take time to be produced by the immune system. Serology tests that are performed too early during infection will likely be negative, despite the presence of active infection.

Most importantly, it is unclear whether the antibodies produced after infection by SARS-CoV-2 result in lasting protective immunity. Research is underway to elucidate the protective effects of SARS-CoV-2 antibodies and duration of immunity.

SARS-CoV-2 Testing Performance

Serologic test performance, like all laboratory tests, can be evaluated using the following metrics:

Cross Reactivity

Ideally, serological tests detect only the antibodies for the particular virus being tested, in this case SARS-CoV-2. However, there are many viruses, including other coronaviruses, that people may have been infected with in the past. Some serological tests may not be able to distinguish between antibodies produced against these viruses versus the antibodies specific to SARS-CoV-2. This phenomenon is called cross-reactivity and can cause false positive results. Clinical laboratories play a critical role in the evaluation of serological tests to safeguard against these limitations and minimize false positive results that may undermine disease prevention strategies.

Sensitivity and Specificity

The sensitivity of a test refers to how frequently a test correctly identifies the presence of antibodies following infection (i.e. does detect the antibodies when they are there). Specificity indicates the frequency with which a test correctly identifies the absence of antibodies in a person who has not been infected (i.e. does not mistakenly detect antibodies that are not there). A test that has high sensitivity may have reduced specificity, resulting in some degree of false positive results.

Predictive Values

Positive and negative predictive values are two essential calculations that provide insight into the accuracy of positive or negative test results within the population tested. These values are based on the test sensitivity and specificity, but also incorporate and are dependent on the prevalence of SARS-CoV-2 in the population.

Positive predictive value (PPV) indicates the number of positive cases that a test accurately identifies out of the total number of positive cases within a given population. Negative predictive value (NPV) defines the accurate detection of negative cases. PPV increases with increased disease prevalence, whereas NPV decreases with increased disease prevalence.

Serology tests are manufactured by many companies that report a wide range of sensitivity and specificity values. If a serologic test that is 95% sensitive and 95% specific is used to test a population of 10,000 people in which 20% (2000) of individuals have antibodies, the test would correctly identify antibodies in 1,900 of those 2000. However, it would incorrectly identify antibodies in 400 people of the remaining 8000 who do not have antibodies. If that same test is used to test a population of 10,000 people in which only 5% (500) have antibodies, the test would correctly identify antibodies in 475 of those 500. However, it would also incorrectly identify the presence of antibodies in 475 people among the 9,500 individuals who do not have

them. In the first situation out of the 2300 people who tested positive, 82% would actually have antibodies, whereas in the second situation, out of the 950 who tested positive, only half would have antibodies.

Until a clear picture emerges regarding prevalence, serologic test results should not be used as the sole basis for clinical or public health policy decisions.

Regulatory Aspects

Clinical laboratory tests are regulated to ensure that they provide accurate results. A number of commercially produced serological tests for SARS-CoV-2 antibodies have received FDA Emergency Use Authorization (EUA) for clinical use and some laboratories are now beginning to use these tests. Other laboratories are choosing to develop their own serologic assays as laboratory developed tests (LDTs). **It is AACC's position that clinical laboratories should only use assays that have received an EUA by the FDA, or LDTs that have been developed and clinically validated by a laboratory certified to perform high complexity testing.** Clinical laboratories are responsible for validating and implementing all tests, regardless of FDA EUA status or LDT and AACC does not support at-home serology testing at this time.

There is significant interest in using rapid response tests broadly in hospitals, clinics, and physicians' offices, particularly in medically underserved areas. In these settings, a test performed at the point of care (near patient) by non-laboratory personnel requires designation as a waived test. As of May 5, 2020, there are no FDA EUA serologic tests for SARS-CoV-2 that may be used in a waived setting. At this time, all rapid response tests must be performed within a moderate or high complexity setting of a certified clinical laboratory.

In summary, serology testing is complementary to molecular diagnostic testing in managing the COVID-19 pandemic. It may play an important role in assessing the prevalence of the disease and may support epidemiological efforts such as contact tracing while research into anti-viral therapies and vaccines continues. **Although there are many various serologic tests coming to market, their accuracy, reliability, and interpretation must be evaluated by laboratory medicine professionals before these tests can be used effectively.** The FDA continues to adapt its guidelines based on real-world experience and new data to balance the risks and benefits of granting test authorization. AACC commends the FDA for its continued diligence in holding manufacturers accountable for their tests and marketing practices.

Our understanding of COVID-19 and the tests used to detect and manage infection will increase as our global scientific and clinical communities work together to understand this novel virus. Laboratory professionals play an indispensable role in developing and performing diagnostic and serologic tests and providing guidance in their proper use and interpretation.

AACC supports the efforts to expand testing in an evidence-based manner as this pandemic continues to unfold. The association advocates for vigilance in implementing serologic testing to provide better patient care through laboratory medicine. ■