American Clinical Laboratory Association

Supporting a Comprehensive, Nationwide Response to COVID-19: The Role of Serologic Testing

Overview

As the administration, federal policymakers and state and local officials consider the range of economic and health interventions necessary to address COVID-19, there is broad recognition that clinical testing is a critical element of our national response. To date, COVID-19 molecular tests have been the primary mechanism to detect the virus. The introduction of serologic testing, or serology, provides another valuable tool to inform broader prevention, containment and mitigation strategies against infection with SARS-CoV-2.

When used appropriately, serologic testing may help determine the number of individuals who actually have been infected with SARS-CoV-2. By supporting screening for individuals using serology, health workers can provide a more detailed assessment regarding the true rate of infection and gain a better understanding of the case fatality rate to help inform public health strategies. Serologic testing also potentially could be used to support future vaccine development and contact tracing to stop the spread of the infection in the community.

While serology can help broaden our understanding of the reach and scope of exposure to SARS-CoV-2 within our communities, it has limitations. For example, serologic testing should not be used as a primary method of diagnosing COVID-19 in an acutely ill patient. Relying on serologic tests too soon after infection can yield false negative results. When a patient is symptomatic and experiencing the greatest viral replication, a molecular test is most useful for detecting the virus and determining a course of treatment.

This paper outlines a number of key considerations related to the use of serology in clinical management and preventive measures in response to the COVID-19 pandemic. As many leading public health experts have noted, serologic testing cannot stand on its own as the primary health intervention in response to COVID-19, but it is a valuable tool in a comprehensive response to this global pandemic.

Serologic Testing Methodology and Laboratory Capacity

Serologic testing is used to analyze blood specimens for the presence of proteins, called antibodies, made in response to an infection. The presence of specific antibodies indicates that an individual has been infected by that specific pathogen.[1] For many infectious diseases, serology is used retrospectively to confirm prior infection and/or to indicate that an individual has developed an immune response to the pathogen. While this immune response suggests immunity from re-infection, the duration of such protective immunity varies depending on the infectious agent and is unknown for some pathogens.

Laboratory-based serology testing requires a blood sample from venipuncture, usually acquired by a licensed phlebotomist, a nurse or another qualified health care professional. It is placed in an appropriate specimen container, stored at room temperature and then transported to the performing laboratory. The person performing phlebotomy must wear the appropriate personal protective equipment (PPE) for collection and handling of blood samples of this type. The laboratory needs to have all the necessary supplies and

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[1] There are different subclasses of antibodies, including IgM, IgA and IgG. While IgM and IgA frequently appear earlier in the disease course compared to IgG antibodies, their presence can overlap. Additionally, early studies suggest that IgM and IgG antibodies develop approximately at the same time, limiting the utility of IgM antibodies as a marker of recent infection.

consumables (*e.g.*, PPE, blood collection tubes, reagents) to perform the test and report it to the ordering physician. As has been the case with SARS CoV-2 molecular diagnostic tests, supply constraints will undoubtedly limit the availability of serologic testing. Fingerstick based blood samples will also be potential specimens for serology testing. This approach does not require phlebotomy and can be performed by individual consumers.

Reference laboratories perform serologic testing using basic chemistry analyzers that are commonly available in major commercial laboratories and hospital laboratories. Currently, a number of in-vitro diagnostics manufacturers are working with the U.S. Food and Drug Administration (FDA) to bring reagent kits to market pursuant to Emergency Use Authorization. Not every manufacturer's kit can be run on every chemistry platform, but in most cases, the manufacturer's reagent kits are not specific to one platform. It is expected that there will be broad availability of platforms that would allow this testing to be accessible throughout the United States, and manufacturers are scaling up their production of reagent kits now.

Test methodologies – and possibly the reliability of test results – differ depending on the setting in which the testing is performed: a reference laboratory or at the point-of-care. For COVID-19 testing at the point-of-care, lateral flow devices are used and require a small amount of specimen – a single drop of blood – to be placed into a plastic device, after being pipetted from a venous blood draw or transferred from finger stick via capillary tube. This type of point-of-care testing is not as quantitative as laboratory-based testing and is not yet designed for the consumer or home setting, and FDA guidance for serology testing explicitly excludes home use.

Given the rapid speed of development and market introduction, comprehensive data on the comparative reliability from point-of-care serologic testing for SARS-CoV-2 and testing performed in a reference laboratory are not available yet. However, early assessments identified both false positives (cross reactivity) and false negatives as issues with these point-of-care devices, and evidence suggests that the incidence of false results for point-of-care testing is higher than those processed in a reference laboratory.

Use of Serology in COVID-19 Clinical Management

The use of serology may help determine the number of individuals who actually have been infected with SARS-CoV-2. Antibodies against SARS-CoV-2 should be detectable in individuals who were infected and have since recovered – even those with mild disease or who are asymptomatic.

Around 8 to 11 days after peak viral replication, detectable levels of IgG antibodies are developed with the majority of individuals becoming antibody-positive by 14 days after the onset of symptoms. At this point, a serologic test becomes useful to inform clinical management. Based on early studies, serologic testing may play a role in the retrospective diagnosis of COVID-19 in patients presenting at least 11 days post-symptom onset whose SARS-CoV-2 molecular test results are negative.

Because serologic testing only assesses the presence of antibodies post-infection, it is not recommended nor should it be used to diagnose COVID-19 in an acutely ill patient. When a patient is symptomatic and is experiencing the greatest viral replication, a molecular test is most useful for detecting the virus. Relying on serologic tests too soon after infection can yield false negative results. During this time period, the virus likely is still present in the individual during the first one-to-two weeks after the onset of symptoms and the patient still may be contagious.

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Use of Serology in Public Health

Serologic testing may be especially helpful to identify frontline health care and other essential workers who have been exposed to the virus. Although the level and duration of protective immunity against SARS-CoV-2 remains unknown, early data suggests that following a primary infection, re-infection is unlikely. Thus, individuals who test positive for IgG with a serologic test and negative for the virus with a molecular assay could be allowed to return to work with reduced risk to the individual and others of SARS-CoV-2 transmission.

Serologic testing also could be used for mass screening of individuals to determine whether a population has attained "herd immunity," which occurs when a sufficient portion of the population is immune to the infectious agent. When enough people are immune, it makes it difficult for further infections to occur, and this protects those who have not yet developed immunity. The percentage of individuals that must be immune for there to be herd immunity depends on multiple factors, including the infectiousness or transmissibility of the infectious agent: the more transmissible the agent, the higher the percentage of the population that needs to be immune for herd immunity to be effective. The precise threshold for what percentage of the population would need to be immune to SARS-CoV-2 for herd immunity to be effective currently is not known.

It is important to note, however, that no test is perfect. It is expected that there will be a limited number of false positive serologic test results. This means that some individuals could go back to work believing that they are protected from developing COVID-19 when they may not be. It's important that any national testing strategy account for required confirmatory or repeat testing to inform any return to work efforts nationwide.

Use of Serology in the Development of Treatments and Vaccines

Serology also may be a component in the development of treatments for COVID-19 and a vaccine for SARS-CoV-2. One potential treatment for COVID-19 is the use of convalescent plasma. Individuals who have recovered from COVID-19 and have antibodies against the virus (as determined by a serologic test) can donate blood, which can then be used to treat someone else. On March 25, 2020 the FDA authorized the compassionate use of convalescent plasma for the treatment of patients with COVID-19. This treatment strategy is currently under review in clinical trials (www.ccpp19.org).

In the future, it may be possible to use convalescent plasma to prevent infection in high risk individuals or to provide post-exposure prophylaxis. Additional research is needed before the strategies can be deployed. In addition to screening potential blood donors, serologic assays will be an important tool to evaluate the efficacy of candidate SARS-CoV-2 vaccines.

Prioritizing Use of Serology as a Mechanism for Return-to-Work Protocols

There are a number of factors that state and federal policymakers and officials must consider when making decisions about return to daily life for Americans and their families. Serology is one tool that can inform decisions about whether it may be safe to lift stay-at-home orders or provide a timeline for safe returns to the workplace, schools and other common areas.

Just as the demand for diagnosing SARS CoV-2 has exceeded supply, the demand for serologic testing will be high, if not universal. Serology testing will be especially critical for health care workers and those on the

frontlines of the pandemic but will be equally essential for businesses to open and remain open, for people returning to work and for students returning to school.

There has been early interest in return-to-work protocols for use with health care workers to determine whether it is safe for them to be exposed to COVID-19 patients and what level of PPE is required for them, given the resource constraints in some health care settings. Additionally, a variety of population surveillance sampling techniques have been proposed and initiated to determine the background levels of antibody presence in populations.

In light of the recent experience with diagnostic testing and expected demand, supply shortages are likely to occur. Therefore, the use of serology for public health purposes should focus initially on health care workers, public servants and other workers involved directly in the pandemic response. Only with adequate supplies can SARS CoV-2 serology be used more broadly. Evidence-based approaches for optimal use and interpretation of serologic testing are still under development by the Centers for Disease Control and Prevention for clinical, administrative and population-based indications.

Payment for SARS CoV-2 Serology

The federal government's stake in the widespread success of SARS CoV-2 serology is considerable, and it should invest the financial resources to ensure that serologic testing is widely available and that a wide array of laboratories, hospitals and health care providers have the necessary resources to perform the testing. Therefore, the federal government should fully assume the cost of SARS CoV-2 serologic testing. Estimates suggest that to provide serologic testing to nearly 70 million Americans, including frontline health workers, the non-health care workforce, college students and military service members would cost at least $25 billion.

In light of the scope of this public health emergency, a full commitment from the federal government is needed to allow clinical laboratories to scale capacity to meet the demand for SARS-CoV-2 serologic testing. Laboratories' recent experiences with payment for molecular diagnostic tests for COVID-19 is informative. Under normal circumstances, payment for lab tests is established laboratory by laboratory, payor by payor. As a result, laboratories performing COVID-19 diagnostic testing have been forced to wrestle with each payor individually to try to obtain reimbursement for molecular diagnostic tests for COVID-19 that covers the cost of the testing – and their efforts have been in vain with a large number of payors, some which set reimbursement rates that cover only a fraction of the cost of performing the test.

Laboratories would face the same roadblocks with SARS-CoV-2 serologic testing as they have with COVID-19 diagnostic testing. Reimbursement rates may be just a fraction of the cost to perform the testing. Yet, a laboratory that loses money on every test it performs is not likely to offer the test at all.

The U.S. government has brought considerable resources to bear to help slow the spread of SARS CoV-2 transmission in the community. To ensure that the U.S. can reopen and stay open for business, the federal government must play the leading role in scaling up and financing widespread SARS CoV-2 serologic testing.