IDSA COVID-19 Antibody Testing Primer
Updated: April 22, 2020

As serological testing for SARS-CoV-2 advances, there are multiple issues that need to be addressed, from test quality to interpretation. Unlike molecular tests for COVID-19 (e.g., PCR), antibody tests may be better suited for public health surveillance and vaccine development than for diagnosis. The current antibody testing landscape is varied and clinically unverified, and these tests should not be used as the sole test for diagnostic decisions. Further, until more evidence about protective immunity is available, serology results should not be used to make staffing decisions or decisions regarding the need for personal protective equipment.

The sections below outline the current state of antibody testing for SARS-CoV-2, along with research questions and additional testing and policy considerations. This information will be updated regularly as new research, tests, and increased public health capacity become available.

BACKGROUND ON ANTIBODY TESTING FOR SARS-CoV-2 INFECTION
- The antibody response in infected patients remains largely unknown, and the clinical values of antibody testing have not been fully demonstrated. Seroprevalence data will be important in understanding the scale of the pandemic and future vaccine utility.
- Potential utility of serology in SARS-CoV-2:
    - Detection of PCR-negative cases, especially for patients who present late with a very low viral load below the detection limit of RT-PCR assays, or when lower respiratory tract sampling is not possible;
    - Identification of convalescent plasma donors;
    - Epidemiologic studies of disease prevalence in the community;
    - Verification of vaccine response once antibody correlate(s) of protection identified.
- Potential drawbacks if serological assays are not well-validated:
    - False negative risks if performed early in disease course, especially in mild disease;
    - False positive risks, particularly with tests for Immunoglobulin M (IgM) and potential cross-reactivity with common cold coronaviruses (e.g. HKU1, NL63, OC43, 229E).

TEST QUALITY & INTERPRETATION
- There are a multitude of different antibody tests for COVID-19 with variable performance. Tests vary in the viral antigen(s) they target, e.g., nucleoprotein (N protein) or spike protein (S protein). It is not yet clear which antibody responses, if any, are protective or sustained.
- The Foundation for Innovative New Diagnostics (FIND), a global non-profit organization driving innovation in the development and delivery of diagnostics, is conducting an independent [evaluation](#) of performance data for SARS-CoV-2 immunoassays to help inform procurement and implementation decisions for countries and health programs. The dataset could also help inform clinical validation studies for these tests.
- A "positive" test is exceptionally difficult to interpret because the performance of these tests is not well known. For some assays both sensitivity and specificity may be poor, or at the very least undefined.

- Clinical laboratories will need to perform validation studies of commercial reagents.
- **Some FDA-authorized COVID-19 antibody tests are estimated to have 96-98% specificity, which would mean that a positive test result is more likely a false-positive result than a true positive result if the [prevalence](#) or pretest probability is 5% or less.**

ADDITIONAL CONSIDERATIONS
- No universal standard for reporting is available and test detection limits are variable. Some assays provide semi-quantitative results and others are designed to be qualitative (i.e. antibody detected or not).
- Combination IgG/IgM tests can provide unclear value given the potential for cross-reactivity with other coronavirus antibodies and the often-poor specificity of IgM.
- Currently available commercial assays do not have titers, and without this information it is unclear how to identify "qualified" individuals for plasma donation.
- Nucleic acid amplification tests (NAATs) perform differently than antibody testing, and this has implications for interpretation. The NAATs that were developed for SARS-CoV-2 are very specific. In patients with signs and symptoms of infection, a positive NAAT result has a very high positive predictive value (PPV) for true infection. Conversely, both the negative and PPV of antibody testing are likely to be lower, given the low prevalence of prior exposure to SARS CoV-2 in the U.S. population and imperfect sensitivity and specificity of the test.
- As a result, antibody tests will be most useful as surveillance tools to estimate (with surrounding confidence intervals) relative proportions of different populations that have been exposed to SARS CoV-2. They will have less utility as diagnostic tools for individual patient assessment.
- Privacy concerns: As we roll out antibody tests, the federal government should clarify several key questions regarding privacy: Who will collect antibody samples? How might they be saved and used in the future (i.e. by government, by law enforcement)? Will there be federal privacy protections for patient samples? What type(s) of applications are intended?
    - Applications must mitigate concerns about privacy violations and hacking; advertiser tracking; potential test error; and faulty phone/wireless signals.

OUSTANDING RESEARCH NEEDS
- While extrapolation from other coronavirus infections allows us to be optimistic that detection of an IgG response will likely confer at least some protection to most people, we have no direct evidence of this for SARS-CoV-2.
- Understanding which antibodies (if any) are protective is required for vaccine development. There are many different SARS CoV-2 IgG antibodies that may be produced, and each may have a different role. This should also be a consideration in assessing the clinical utility of tests designed to target specific antibodies.
- Determine limits of protective immunity (e.g., antibody amount, duration, and efficacy) and correlations with disease severity.
- Address concerns about potentiation of cytokine release syndrome (CRS) by a vaccine or hyperimmune plasma administration: Patients with COVID-19 infection can develop CRS about day 7-10 of illness, which often leads to death. There is some concern that a vaccine against the "wrong" antigens or infusion of hyperimmune plasma from COVID-19 survivors could worsen the inflammatory immune response in patients with COVID-19 infection. This immune enhancement is seen for some flaviviruses such as dengue.

- Development of accurate serologic tests that can be used with fingerstick capillary blood would be ideal for seroprevalence field studies. Most commercial assays require venipuncture blood draw to obtain serum or plasma.

POLICY CONSIDERATIONS: ADDITIONAL FUNDING PRIORITIES
- Increased research, public health, and laboratory funding for test development, supplies, and PPE, and for the routine application of serological testing, once available and well-validated, in the diagnosis and management of COVID-19 patients.
- Federal funding for longitudinal studies of immune response and risk of re-infection

ADDITIONAL RESOURCES
- [10,000-participant NIH "serosurvey" planned to quantify undetected COVID-19 cases](#) (*NIH*)
- [Antibodies for COVID-19 vaccine design](#) (*Science*)
- [Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19)](#) (*CID*)
- [The convalescent sera option for containing COVID-19](#) (*JCI*)
- [The Importance of Antibody Testing in Addressing COVID-19](#) (*Mayo Clinic*)
- [Virological assessment of hospitalized patients with COVID-2019](#) (*Nature*)
- [FDA Letter to Health Care Providers re: Serological Testing for COVID-19](#)
- [FDA FAQs on Diagnostic Testing for SARS-CoV-2](#)
- [FDA Fact Sheet - Serological Testing for Antibodies to SARS-CoV-2 Infection](#)