Interim Guidelines for COVID-19 Antibody Testing

Interim Guidelines for COVID-19 Antibody Testing in Clinical and Public Health Settings

Updated Jan. 24, 2022

Summary of Recent Changes

Updates as of January 24, 2022

Added language for people that are up to date with their vaccines and quarantine and isolation recommendations.

View Previous Updates

Who this is for:

Healthcare providers considering antibody testing of persons with a history of possible COVID-19 or public health officials and other researchers conducting investigations involving antibody tests.

Key Points:

Serologic methods have public health value for monitoring and responding to the COVID-19 pandemic, and clinical utility in providing care for patients.

- Antibody testing does not replace virologic testing and should not be used to establish the presence or absence of acute SARS-CoV-2 infection.
- Antibody tests can vary in their individual performance characteristics; tests that have received Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) may be used for public health and clinical purposes.
- Antibody tests yielding qualitative, semi-quantitative, or quantitative results have been issued EUAs; there currently is no recognized public health or clinical indication for preferential use of semi-quantitative or quantitative tests.
- Virus-based neutralization assays are currently not authorized for emergency use by the FDA, although an enzyme-linked immunosorbent assay (ELISA)-based competitive neutralization test for qualitative detection of total neutralizing antibodies has been issued an EUA. Neutralization assays currently are being used as possible surrogates of protection in epidemiological and clinical studies.
- Antibody testing is not currently recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination, to assess the need for vaccination in an unvaccinated person, or to determine the need to quarantine after a close contact with someone who has COVID-19.
- Everyone should stay up to date on their vaccines (which includes additional doses for immunocompromised individuals and booster doses at regular time points) and take steps to protect themselves and others from COVID-19, including people who have previously been infected and have detectable antibodies.

Background

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initiates a cell-mediated and humoral immune response that produces antibodies against specific viral antigens such as the nucleocapsid (N) protein and spike (S) protein. These include anti-S protein antibodies that target the spike's S1 protein subunit and receptor binding domain (RBD). Antibody tests can detect the presence of these antibodies in serum within days to weeks following acute infection. However, antibody testing should not be used to diagnose acute SARS-CoV-2 infection. Antibody tests can identify persons with resolving or past SARS-CoV-2 infection and thereby help scientists and public health experts better understand the epidemiology of SARS-CoV-2. Although the immune correlates of protection are not fully understood, evidence indicates that antibody development following infection likely confers some degree of immunity from subsequent infection for at least 6 months (1, 2). However, it is not known to what extent SARS-CoV-2 variants could impact protection from subsequent infection (3).

Development of Antibodies and Immunity

Infection

Data indicate that nearly all immunocompetent persons develop an adaptive immune response following SARS-CoV-2 infection, triggering antiviral humoral and cellular immune responses via B and T cell-mediated immunity (4–6), respectively. Our understanding of the immune response to SARS-CoV-2 is rapidly advancing. In humans, the humoral response includes antibodies directed against S and N proteins. The S protein contains two subunits, S1 and S2. The S1 subunit contains the RBD that mediates binding of virus to susceptible cells. RBD is the main target for neutralizing antibodies. Antibodies—including IgM, IgG, and IgA—against S and its subunits can be detected in serum within 1-3 weeks after infection (7, 8). IgM and IgG antibodies can arise nearly simultaneously (7); however, IgM (and IgA) antibodies decay more rapidly than IgG (7, 9). The clinical significance of measuring serum IgA in SARS-CoV-2 infection is not known; however secretory IgA plays an important role in protecting mucosal surfaces against pathogens by neutralizing respiratory viruses, including SARS-CoV-2 (10).

IgG antibodies, including IgG against the S and N proteins, persist for at least several months in most persons, but the precise duration of time that antibodies persist after infection is unknown (11). Loss of previously detectable SARS-CoV-2 antibodies (seroreversion) has been reported among persons with mild disease (12). Persons with more severe disease appear to develop a more robust antibody response with IgM, IgG, and IgA, all achieving higher titers and exhibiting longer persistence (12, 13). The observed persistence of antibodies can vary by assay (14), and some studies have found that approximately 5%–10% of people do not develop detectable IgG antibodies following infection (15, 16). Although neutralizing antibodies might not be detected among patients with mild or asymptomatic disease (17), the humoral immune response appears to remain intact even with loss of specific antibodies over time because of the persistence of memory B-cells (18). SARS-CoV-2 neutralizing antibodies that inhibit viral replication *in vitro* mainly target the RBD (5, 6). Efforts to better understand antibody kinetics, longevity of humoral immune responses, correlation of binding antibody levels to neutralizing antibodies, and serological surrogates of immune protection are dependent on wider availability of quantitative binding antibody assays that are standardized and traceable to an international standard (19).

SARS-CoV-2 reinfection has been documented (20, 21); however, studies indicate that persons with SARS-CoV-2 antibodies are less likely to experience subsequent infection or clinical disease than persons without antibodies. Investigations of outbreaks among people on a fishing vessel and at a summer camp in the United States found that persons with pre-existing SARS-CoV-2 antibodies were correlated with protection from subsequent infection (22, 23). In sequential outbreaks among staff and residents of two British nursing homes, persons who tested antibody-positive following the first outbreak were approximately 96% less likely to become infected during the second outbreak four months later (24). In a British prospective cohort study of persons with and without SARS-CoV-2 antibodies, the adjusted incidence rate ratio for subsequent infection was 0.11 among persons followed for a median of 200 days after a positive antibody test, compared with those who tested negative for SARS-CoV-2 antibodies (2). Another British cohort study found an 84% reduction in SARS-CoV-2 infection incidence over a seven-month period among persons who had tested antibody positive for SARS-CoV-2 or had prior infection documented by reverse transcription polymerase chain reaction (RT-PCR) (1). A large study in the United States of commercial laboratory results linked to medical claims data and electronic medical records found a 90% reduction in infection among persons with antibodies compared with persons without antibodies (25), and another study of U.S. military recruits found that seropositive persons had an 82% reduction in incidence of SARS-CoV-2 infection over a 6-week period (26). Experiments on non-human primates support the above observations in humans. Experimentally infected rhesus macaques that developed humoral and cellular immune responses were protected against reinfection when re-challenged 35 days later (27). Another study found that transfer of purified IgG from rhesus macaques infected with SARS-CoV-2 was effective in protecting naïve rhesus macaques from infection, and the threshold titers for protection, based upon binding and neutralizing antibodies, were determined. Analyses of data from two vaccine trials found that higher titers of neutralizing and anti-S binding antibodies correlated with more effective protection from infection.(28, 29)

Taken together, these findings in humans and non-human primates suggest that SARS-CoV-2 infection and development of antibodies can result in some level of protection against SARS-CoV-2 reinfection. The extent and duration of protection have yet to be determined. While life-long immunity has not been observed with endemic seasonal coronaviruses (30), studies of persons infected with the SARS-CoV-1 and Middle East Respiratory Syndrome (MERS-CoV) coronaviruses demonstrated measurable antibody for 18–24 months following infection (31, 32), and neutralizing antibody was present for 34 months in a small study of MERS-CoV-infected patients (33). It is not known to what extent persons re-infected with SARS-CoV-2 might transmit SARS-CoV-2 to others or whether the clinical spectrum differs from that of primary infection.

Vaccination

SARS-CoV-2 infection begins when the RBD of the S protein of the virus binds to the angiotensin-converting enzyme 2 (ACE-2) receptor site in human cells, the initial step in viral entry into human cells. Preventing SARS-CoV-2 from binding with ACE-2 receptors in the respiratory tract of humans can prevent infection and illness (34). This interaction between the S protein of SARS-CoV-2 and the ACE-2 receptor sites has been the major focus of vaccine development. The vaccine candidates that have received EUA or approval from FDA or are in late-stage development aim to elicit neutralizing antibodies against the S protein or the RBD (35). Data from two phase III mRNA vaccine efficacy trials and cohort studies demonstrated up to 95% efficacy following a two-dose vaccination series (36–38). It is unknown whether infection confers a similar degree of immunity compared to vaccination.

SARS-CoV-2 infection results in antibody development against viral proteins including the N and S proteins. Vaccine-induced antibody development has implications for antibody testing. Before vaccine introduction, a SARS-CoV-2 antibody test that detects any of the N, S, or RBD antibodies could be considered to indicate previous exposure to SARS-CoV-2. A vaccinated person could test positive by serologic tests for the vaccine antigenic target (S and S subunits, including RBD) but not against other non-target proteins (39, 40). Thus, history of vaccination and/or prior SARS-CoV-2 infection must be considered when interpreting antibody test results.

Currently available antibody tests for SARS-CoV-2 assess IgM and/or IgG to one of two viral proteins: S or N. Because COVID-19 vaccines are constructed to encode the spike protein or a portion of the spike protein, a positive test for S IgM and/or IgG could indicate prior infection and/or vaccination. To evaluate for evidence of prior infection in a person with a history of COVID-19 vaccination, a test that specifically evaluates anti-N IgM/IgG should be used. Testing for antibodies that indicate prior infection could be a useful public health tool as vaccination programs are implemented, provided the antibody tests are adequately validated to detect antibodies to specific proteins (or antigens). Although an antibody test can employ specific antigens, antibodies developed in response to different proteins might cross-react (i.e., the tests might detect antibodies they are not intended to detect), and therefore, might not provide sufficient information on the presence of antigen-specific antibodies. For antibody tests with FDA EUA, it has not been established whether the antigens employed by the test specifically detect only antibodies against those antigens and not other antigens. Although current EUA indications do not preclude the use of these tests in vaccinated individuals, none of the currently authorized tests have been specifically authorized to assess immunity or protection of persons who have received a COVID-19 vaccine.

Considerations for public health and clinical practice

Accumulating evidence suggests that the presence of antibodies following infection offers some level of protection from reinfection. Evidence includes the following: (1) reduced incidence of infection among persons with SARS-CoV-2 antibodies followed for 3 months or longer; (2) findings from outbreak investigations that pre-existing detectable antibody correlates with reduced incidence of infection (22, 23, 26, 41); (3) challenge experiments in primates passively immunized with convalescent plasma demonstrating prevention of infection (42); (4) viral neutralization demonstrated with serum from persons following infection (5, 6); (5) data demonstrating that vaccination, which also results in antibody production, can reduce the incidence of illness (36, 37); and (6) decreased disease severity, and even prevention, of infection associated with administration of monoclonal antibodies (43, 44).

While it remains uncertain to what degree and for how long persons with detectable antibodies are protected against reinfection with SARS-CoV-2 or what concentration of antibodies are needed to provide such protection, cohort studies indicate 80%–90% reduction in incidence for at least 6 months after infection among antibody-positive persons (1, 2, 25). Longitudinal patient follow-up studies are ongoing to measure antibody levels before and after vaccination or infection to identify an association between responses below a certain threshold and vaccine failure or reinfection. These longitudinal patient follow-up studies are expected to elucidate the relationship between antibodies and protection from reinfection. In addition, T-cell-mediated adaptive immunity following infection, although not fully understood, likely contributes to protection from subsequent exposure to SARS-CoV-2 (45). It is also not known whether, and to what extent, viral evolution and the emergence of new SARS-CoV-2 variants could impact immunity from reinfection. One study in the United Kingdom found that among people with primary infections >180 days prior to reinfection, the risk of reinfection with the Delta variant was increased compared to reinfection with the Alpha variant (46).

Current Status of Antibody Testing in the United States

Antigenic targets

While S protein is essential for virus entry into cells and is present on the viral surface, N protein is the most abundantly expressed immunodominant protein. Multiple forms of S protein—full-length (S1+S2) or partial (S1 domain or RBD)—are used as antigens for antibody tests. The protein target determines cross-reactivity and specificity because N is more conserved across coronaviruses than S, and, within S, the RBD is more conserved than S1 or full-length S. The choice of antigenic targets might help address different aspects of immune response. Antibody detection against RBD is considered to have higher correlation toward functional aspects like ability to neutralize virus (6). Differential reactivity of S and N specific antibodies might be used to help differentiate previous infection from vaccination in serologic studies, particularly for vaccines that produce antibodies only against S protein (1, 25, 40).

Types of antibody testing

Different types of assays can be used to determine different aspects of the adaptive immune response and functionality of antibodies. The tests can be broadly classified to detect either binding or neutralizing antibodies.

- **Binding antibody detection:** These tests use purified proteins of SARS-CoV-2, not viable virus, and can be performed in lower biosafety level laboratories (e.g., BSL-2). With specific reagents, individual antibody types, like IgG, IgM, and IgA, can be differentiated. Both SARS-CoV-2 IgM and IgG antibodies may be detected around the same time after infection. However, while IgM is most useful for determining recent infection, it usually becomes undetectable weeks to months following infection; in contrast, IgG is usually detectable for longer periods. IgA is important for mucosal immunity and can be detected in mucous secretions like saliva in addition to blood; although, its significance in this disease is still to be determined. Depending on their complexity, some binding antibody tests can be performed rapidly (in fewer than 30 minutes) in a field setting or in a few hours in a laboratory.

  Tests that detect binding antibodies fall into two broad categories.

  - **Point-of-care (POC)** tests are diagnostic tests performed at or near the place where a specimen is collected and can provide results within minutes rather than hours. Antibody POC tests generally are lateral flow devices that detect IgG, IgM, or total antibody in fingerstick whole blood.
  - **Laboratory tests** use lateral flow, ELISA, or chemiluminescent immunoassay (CIA) methods for antibody detection in serum, plasma, whole blood, and dried blood spots, which, for some assays, might require trained laboratory scientists and specialized instruments. Based on the test, total antibody (Ig) can be detected, or IgG and IgM can be detected separately. While most tests detect antibodies against either S or N proteins, some tests can detect antibodies against both immunodominant proteins (multiplex assays).
- **Neutralizing antibody detection tests** determine the functional ability of antibodies to prevent infection by SARS-CoV-2 *in vitro*. These tests monitor inhibition of viral growth in cell culture when incubated with serum or plasma.

  There are three types of neutralization tests:

  - **Virus neutralization tests (VNT),** such as the plaque-reduction neutralization test (PRNT) and microneutralization, use SARS-CoV-2 or recombinant SARS-CoV-2 expressing reporter proteins. These tests may take up to 5 days to complete. There are currently no EUA- VNTs.
  - **Pseudovirus neutralization tests (pVNT)** use recombinant pseudoviruses (like vesicular stomatitis virus [VSV] or lentiviruses) that incorporate the S protein of SARS-CoV-2. These reporter-based tests can be performed in BSL-2 laboratories depending on the virus strain used. There are currently no EUA pVNTs.
  - **Competitive neutralization tests** (cVNT) have also been developed, and one has been authorized under an EUA by the FDA. These are binding antibody tests designed to qualitatively detect potentially neutralizing antibodies, often those that prevent interaction of the RBD with the ACE-2 receptor. The test mimics the interaction of the RBD with ACE-2 in an ELISA format (similar to the RBD on a virus particle binding to a cell surface ACE-2 receptor) and the ability of RBD specific antibodies to interfere with the interaction detected using a decrease in signal based on the reporter-fused RBD. These tests can be conducted in BSL-2 laboratories because they do not require viable virus.

Performance of antibody tests

FDA requires commercially marketed antibody tests for SARS-CoV-2 to receive Emergency Use Authorization (EUA) or approval. Multiple agencies—including FDA, the National Cancer Institute/National Institutes of Health (NCI/NIH), CDC, and the Biomedical Advanced Research and Development Authority (BARDA)—are collaborating with members of academia and the medical community to evaluate the performance of antibody tests independently using a well-characterized set of clinical specimens (serum and plasma) collected before and during the current COVID-19 pandemic. Independently evaluated test performance and the approval status of tests are listed on an FDA website . Only one test has received an EUA as a quantitative assay (providing a measured and scaled assessment of antibody levels). All other currently authorized tests are qualitative (providing a result that is positive, negative, or indeterminate) or semi-quantitative. The World Health Organization has developed international standards for SARS-CoV-2 antibody tests that can serve as the foundation for the calibration of tests that quantify antibodies. Both laboratory and point-of-care antibody tests have received EUA from the FDA. Antibody testing technologies include single-use lateral flow tests where the presence of antibody is demonstrated by a color change on a paper strip (similar to a pregnancy test) and laboratory-based immunoassays that allow for processing of many specimens at the same time. The EUA letter of authorization includes the settings in which the test is authorized, based on FDA's determination of appropriate settings for use during the public health emergency.

Interim Recommendations for Use of Serologic Tests

Acute infection from SARS-CoV-2 is determined best by diagnostic testing using a nucleic acid amplification test (NAAT) or antigen test. Resolving or past infection is best determined by serologic testing that indicates the presence of anti-N antibody. Accumulating evidence suggests that infection with SARS-CoV-2 with subsequent development of antibodies could confer some level of immunity for at least 6

months. However, the robustness and durability of immunity following infection and how it compares with vaccine-induced immunity remain unknown. These recommendations will be updated as new information becomes available.

Choice of antibody test and testing strategy

- Tests issued an EUA by FDA are recommended for clinical and public health purposes. Numerous antibody tests for SARS-CoV-2 have been issued an EUA by the FDA. EUA tests include both qualitative and semi-quantitative tests. The list of SARS-CoV-2 antibody tests granted an EUA by the FDA can be found on FDA's website .
- Antibody tests with very high sensitivity and specificity are preferred since they are more likely to exhibit high positive and negative predictive values when administered at least 3 weeks following onset of illness.

- Additional considerations when selecting an antibody test include:
  - IgG levels appear to decrease more slowly over time than levels of other classes of antibody. Therefore, assays that measure total antibody or IgG could have higher sensitivity as the time between infection and antibody testing increases.
  - IgM antibody can persist for weeks to months following infection, though its persistence appears to be shorter than IgG's; therefore, detection of IgM could suggest relatively recent infection.
  - Persistence of detectable antibodies could vary by the test used.
- FDA has issued an EUA for a competitive neutralization test (cVNT), a qualitative binding assay that detects antibodies that block the interaction between the virus and the cellular virus receptor (ACE-2). Although the cVNT exhibits correlation to a plaque reduction neutralization test (PRNT), the clinical or public health applicability has not been established.
- The clinical and public health applicability of semi-quantitative tests has not been established.

Indications for antibody testing and interpretation of results

- Antibody testing is not a replacement for virologic testing and should not be used to establish the presence or absence of acute SARS-CoV-2 infection. Persons suspected of having COVID-19 who test positive by direct viral detection methods for SARS-CoV-2 (e.g., NAAT or antigen detection tests) typically begin to develop measurable antibody 7–14 days after illness onset, and by 3 weeks most persons will test positive for antibody. During this interval, the sensitivity of detecting infection using nucleic acid detection or antigen detection testing is decreasing and the sensitivity of serologic testing is increasing. Antibody testing may be useful to support the diagnosis of COVID-19 illness or complications of COVID-19 in the following situations:
  - A positive antibody test at least 7 days following acute illness onset in persons who had a previous negative antibody test (e., seroconversion) but did not receive a positive viral test might indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests.
  - A positive antibody test can help support a diagnosis when patients present with complications of COVID-19, such as multisystem inflammatory syndrome or other post-acute sequelae of COVID-19.
- SARS-CoV-2 antibodies, particularly IgG antibodies, might persist for months and possibly years. Therefore, when antibody tests are used to support diagnosis of recent COVID-19, a single positive antibody test result could reflect previous SARS-CoV-2 infection or vaccination rather than the most recent illness.

- Antibody testing can be used for clinical, occupational health, and public health purposes, such as serologic surveys, to help differentiate past infection from vaccination by using tests that measure antibodies against different protein targets. Although current EUA indications do not preclude the use of these tests in vaccinated individuals, none of the currently authorized tests have been specifically authorized to assess immunity or protection of people who have received a COVID-19 vaccine, including immunocompromised people. Whether the test has been validated to specifically detect antibodies against the antigens employed by the test and whether the antigens cross react with antibodies to antigens that are not employed by the test should be considered. The results of available anti-SARS-CoV-2 IgG antibody tests may be interpreted in the following way:
  - In a person never vaccinated:
    - Testing positive for antibody against N, S, or RBD indicates prior infection.
  - In vaccinated people:
    - Testing positive for antibody against the vaccine antigen target, such as the S protein, and negative for other antigens (e.g., N) suggests that they have produced vaccine-induced antibody and that they were never infected with SARS-CoV-2.
    - Testing positive for antibodies other than the vaccine-induced antibody, such as the N protein, indicates resolving or past SARS-CoV-2 infection that could have occurred before or after vaccination.
    - Antibody testing is currently not recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination.

Current vaccines distributed in the United States induce antibodies to S protein. Thus, the presence of antibodies to N protein indicates previous infection regardless of a person's vaccination status, while presence of antibodies to S protein indicates either previous infection or vaccination. The presence of antibodies to S protein and absence of antibodies to N protein in the same specimen indicates vaccination

in a person never infected or could signal prior infection in a person whose antibodies to N protein have waned. Since vaccines induce antibodies to specific viral protein targets, post-vaccination antibody test results will be negative in persons without a history of previous infection if the test used does not detect antibodies induced by the vaccine.

Interpretation of anti-S and anti-N antibody results based on vaccination status

Vaccination status	Anti-S antibody	Anti-N antibody	Interpretation*
Vaccinated	+	+	Vaccinated and previously infected
Vaccinated	+	–	Vaccinated and not previously infected
Unvaccinated	+	+	Not vaccinated and previously infected
Unvaccinated	–	–	Not previously vaccinated or infected

If vaccination status unknown

Anti-S antibody	Anti-N antibody	Interpretation*
+	+	Previously infected, may or may not have been vaccinated
+	–	Vaccinated with no previous infection
–	–	Not previously vaccinated or infected

*Potential false positive or false negative results, failure to develop detectable antibodies after vaccination or infection, and waning of antibodies with time after infection or vaccination should be considered when interpreting antibody test results.

- Antibody tests can be used in seroprevalence studies to estimate the cumulative incidence of infection (or vaccination) in a community. Results from many seroprevalence studies can be found at CDC and NIH
- A negative antibody test does not preclude previous infection. A proportion of persons who are infected with SARS-CoV-2 might not develop measurable antibodies, thereby limiting the sensitivity of any antibody test to detect previous infection in these individuals. In addition, measurable antibodies also might wane over time, and the extent to which seroreversion occurs could vary according to the antibody test used.

Additional considerations for use of antibody tests

- Persons recovering from a COVID-19 compatible or confirmed illness should follow CDC guidance on when to resume normal activities, including work, regardless of the presence of antibodies.
- An antibody test should not be used to determine the need for quarantine following close contact with someone who has COVID-19.
- Everyone, including those who have previously tested antibody positive, should follow current recommendations to prevent SARS-CoV-2 infection.
- Persons who have previously tested positive for antibodies to SARS-CoV-2 but who currently have COVID-19 symptoms or a NAAT or antigen test indicating a new SARS-CoV-2 infection (re-infection) should be considered contagious and should follow existing isolation guidelines.
- Antibody testing is not currently recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person.

All eligible people should be vaccinated, including unvaccinated people who have previously been infected and have detectable antibodies.

Previous Updates

Updates from Previous Content

As of September 21, 2021

- Removed recommendation that persons in low-risk situations, with a positive antibody test within 3 months prior to a SARS-CoV-2 exposure or, tested immediately after an exposure do not need to quarantine. Guidance for interpretation of antibody test results added in the form of a table.

As of March 17, 2021

- Updated information on available serologic tests.
- Updated information on relationship between presence of anti-SARS-CoV-2 antibodies and immunity from subsequent infection.
- Guidance on interpretation of SARS-CoV-2 serologic tests performed on persons previously vaccinated for SARS-CoV-2.
- Guidance for quarantine of seropositive persons who have had recent exposure to someone with suspected or confirmed COVID-19.

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