Interim Guidelines for COVID-19 Antibody Testing

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Updated Mar. 17, 2021 Print

Updates as of March 17, 2021

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- 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.

Who this is for:

Healthcare providers considering serologic testing of persons with history of possible coronavirus disease 2019 (COVID-19) or public health officials and other researchers conducting investigations involving serologic tests.

Key Points

Serologic methods have public health and clinical utility for monitoring and responding to the COVID-19 pandemic, and caring for patients, respectively.

- Serologic testing does not replace virologic testing and should not be used to establish the presence or absence of acute SARS-CoV-2 infection.
- Serologic tests can vary in their individual performance characteristics; tests that have received Emergency Use Authorization (EUA) should be used for public health and clinical purposes.
- Serologic tests yielding qualitative or semi-quantitative results have been issued EUAs; there currently is no recognized public health or clinical indication for preferential use of semi-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 COVID-19 following COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person. Since vaccines induce antibodies to specific viral protein targets, post-vaccination serologic test results will be negative in persons without history of previous natural infection if the test used does not detect antibodies induced by the vaccine.

- Unvaccinated persons who have tested antibody positive within 3 months before or immediately following an exposure to someone with suspected or confirmed COVID-19 and who have remained asymptomatic since the current COVID-19 exposure do not need to quarantine, provided there is limited or no contact with persons at high risk for severe COVID-19 illness, including older adults and persons with certain medical conditions.

Background

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initiates a humoral immune response that produces antibodies against specific viral antigens such as the nucleocapsid (N) protein and spike (S) protein, which include specific anti-S protein antibodies that target the spike's S1 protein subunit and receptor binding domains (RBD). Serologic tests can detect the presence of these antibodies in serum within days to weeks following acute infection. However, serologic testing should not be used to diagnose acute SARS-CoV-2 infection. Serologic 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 individuals and populations at higher risk of infection. 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. However, it is not known to what extent emerging viral variants may impact immunity from subsequent infection.

Development of Antibodies and Immunity

Natural infection

Nearly all immunocompetent persons develop an adaptive immune response following SARS-CoV-2 infection, including B and T cell-mediated immunity (1-3) due to antiviral humoral and cellular immune responses, respectively. Our understanding of the immune response to SARS-CoV-2 is incomplete but 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 within 1-3 weeks after infection (4, 5). IgM and IgG antibodies can arise nearly simultaneously (4); however, IgM (and IgA) antibodies decay more rapidly than IgG (4, 6). The clinical significance of IgA in SARS-CoV-2 is not yet established.

How long anti-SARS-CoV-2 antibodies persist after infection remains unknown, although IgG antibodies, including IgG against the S and N proteins, persist for at least several months in most persons (7). Seroreversion has been reported among persons with mild disease (8). 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 (8, 9). The observed persistence of antibodies can vary by assay (10), and some studies have found that approximately 5-10% do not develop detectable IgG antibodies following infection (11, 12). Although neutralizing antibodies may not be detected among patients with mild or asymptomatic disease (13), the humoral immune response appears to remain intact even with loss of specific antibodies over time (14). SARS-CoV-2 neutralizing antibodies that inhibit viral replication *in vitro* mainly target the RBD (2, 3). A need exists for standardized assays that can correlate antibody titers with neutralization (15).

SARS-CoV-2 reinfection has been documented (16, 17); however, studies indicate that persons with anti-SARS-CoV-2 antibodies are less likely to develop subsequent infection than persons without such antibodies. Outbreak investigations from a fishing vessel and a summer camp in the United States found that persons with pre-existing SARS-CoV-2 antibody were protected from subsequent infection (18, 19). 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 (20). In a British prospective cohort study of persons with and without SARS-CoV-2 antibody, the adjusted incident rate ratio for subsequent infection was 0.11 among persons followed for a median of 200 days after a positive antibody test, compared to those who tested negative for anti-SARS-CoV-2 antibody (21). Another British cohort study found an 83% reduction in SARS-CoV-2 infection incidence over a five-month period among persons who had tested antibody positive for SARS-CoV-2 or had prior infection documented by revers transcription polymerase chain reaction (RT-PCR) (22). 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 antibody compared to persons without (23), and another study of military recruits found that seropositive individuals had an 82% reduction in incidence of SARS-CoV-2 infection over a 6-week period (24). Additionally, antibody development following SARS-CoV-2 in

humans infection correlates with a marked decrease in viral load in the respiratory tract, although a clinical correlation with viral load in the respiratory tract has not been definitively established (5). 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 (25). 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 (26).

Taken together, the above findings in humans and non-human primates suggest SARS-CoV-2 infection and development of antibody can result in some level of protection against SARS-CoV-2 reinfection. The durability of this immunity has yet to be determined. While life-long immunity has not been observed with endemic seasonal coronaviruses (27), studies of persons infected with the novel SARS-CoV-1 and Middle East Respiratory Syndrome (MERS-CoV) coronaviruses demonstrated measurable antibody for 18 – 24 months following infection (28, 29), and neutralizing antibody was present for 34 months in a small study of MERS-infected patients (30). It is not known to what extent persons re-infected with SARS-CoV-2 might transmit infection 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 humans, 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. This interaction between 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 are in late stage development aim to elicit neutralizing antibodies against the S protein or the RBD (31). Data from two phase III mRNA vaccine efficacy trials demonstrated up to 95% efficacy following a two-dose vaccination series (32, 33). It is unknown whether natural infection confers a similar degree of immunity compared to vaccination.

Natural SARS-CoV-2 infection results in antibody development against viral proteins including the N and S proteins, including the RBD of the S protein. Vaccine induced antibody development has implications for serologic testing. Before vaccine introduction, a SARS-CoV-2 serologic test that detects any of the N, S or RBD antibodies could be considered to indicate previous exposure to SARS-CoV-2. With the introduction of vaccine, vaccinated persons may test positive by serologic tests for the vaccine antigenic target (S and S subunits, including RBD) but not against other non-target proteins. Thus, history of vaccination and/or prior SARS-CoV-2 infection must be considered when interpreting serologic test results. Further, many persons infected with SARS-CoV-2 will be asymptomatic and never tested by viral detection tests, further complicating the interpretation of subsequent serologic testing. Testing for antibodies that indicate natural infection could be a useful public health tool as vaccination programs are implemented, provided the serologic tests are adequately validated to specifically detect antibodies to specific proteins (or antigens). Although an antibody test may employ a specific antigen(s), antibodies developed in response to different proteins may cross-react (i.e., the antigen(s) may detect antibodies it is not intended to detect), and therefore, may not provide sufficient information on the presence of antigen specific antibodies. For currently FDA authorized tests, it has not been established whether the antigen(s) employed by the test specifically detects only antibodies against that antigen and not others. Furthermore, none of the currently authorized tests have been specifically authorized to assess individuals who have received a vaccine. However, the EUA indications for currently authorized tests do not preclude the use of these tests on individuals who have received a SARS-CoV-2 vaccine. Vaccination may cause false-positive results for tests that utilize the S antigen or subunits like RBD, but not for tests that use the N antigen.

Considerations for public health and clinical practice

Accumulating evidence suggests that the presence of antibodies following natural infection may produce some level of protection from re-infection: 1) reduced incidence of infection among persons with SARS-CoV-2 antibodies followed for 3 months or longer; 2) data demonstrating that vaccination can reduce the incidence of illness (32, 33); 3) findings from outbreak investigations that pre-existing detectable antibody correlates with reduced incidence of infection (18, 19, 24, 34); 4) viral neutralization demonstrated with serum from persons following infection (2, 3); 5) decreased disease severity associated with administration of monoclonal antibody ; and 6) challenge experiments with primates demonstrating prevention of re-infection (25). While it remains uncertain to what degree and for how long individuals with antibodies are protected against re-infection with SARS-CoV-2, or what concentration of antibodies may be needed to provide such protection, cohort studies indicate 80 – 90% reduction in incidence for at least 6 months among antibody positive persons (21-23). Longitudinal patient follow-up studies are ongoing to measure antibody levels before and after vaccination or natural infection to identify an association between responses below a certain threshold and vaccine failure or re-infection. 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 natural infection, although not fully understood, likely contributes to protection from subsequent exposure to SARS-CoV-2 (35). It is also not known whether and to what extent viral evolution and the emergence of new viral variants may impact immunity from reinfection.

Current Status of Antibody Testing in the United States

Antigenic targets

While S protein is essential for virus entry 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 serologic tests. The protein target determines cross-reactivity and specificity because N is more conserved across coronaviruses than S, and within S, 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 towards functional aspects like ability to neutralize virus (3). Differential reactivity of S and N specific antibodies might be utilized to help differentiate previous infection from vaccination in serologic studies, particularly for vaccines that produce antibodies only against S protein.

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 live 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 determined. Both IgM and IgG may be detected around the same time after infection. While IgM is most useful for determining recent infection as it usually becomes undetectable weeks to months following infection, IgG may remain detectable for longer periods. IgA is important for mucosal immunity and can be detected in mucous secretions like saliva in addition to blood, though its significance in this disease is still to be determined. Depending on their complexity, some binding antibody tests can be performed rapidly (in less 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 generally are lateral flow devices that detect IgG and 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 may require trained laboratorians and specialized instruments. Based on the reagents, 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 virus *in vitro*. These tests monitor inhibition of viral growth in cell culture when incubated with serum or plasma. Three types of neutralization tests are conducted:
  - **Virus neutralization tests (VNT),** such as the plaque-reduction neutralization test (PRNT) and microneutralization, use a SARS-CoV-2 virus from a clinical isolate or recombinant SARS-CoV-2 virus expressing reporter proteins. This testing may take up to 5 days to complete. There are currently no EUA authorized 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 authorized pVNTs.
  - **Competitive neutralization tests** (cVNT) have also been developed and one has been authorized by the FDA. These are binding antibody tests designed to qualitatively detect potentially neutralizing antibodies, often those that prevent interaction of RBD with the ACE-2 receptor. The test mimics the interaction of RBD with ACE-2 in an ELISA format (similar to 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 live virus.

Performance of serological tests

FDA requires commercially marketed serologic tests to receive Emergency Use Authorization (EUA) . There are policies in place for certain other tests to be used without FDA authorization. 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 independently evaluate the performance of serology tests using a well-characterized set of clinical specimens (serum and plasma) collected before and during the current COVID-19 outbreak. Independently evaluated test performance and the status of tests (EUA authorized should not be used) are listed on an FDA website . All currently authorized tests are qualitative (providing a result that is positive, negative, or indeterminate) or semi-quantitative rather than quantitative (providing a measured and scaled assessment of antibody levels). The World Health Organization has recently developed international standards for SARS-CoV-2 serology that can serve as the foundation for the calibration of tests that quantify antibodies. Both laboratory and point of care serologic assays have received EUA from the FDA. Serologic testing technologies include single-use, low-throughput lateral flow tests where the presence of antibody is demonstrated by a color change on a paper strip and laboratory-based immunoassays that allow for processing of many samples 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

Natural acute infection from SARS-CoV-2 is determined best by diagnostic testing using a nucleic acid amplification test [NAAT] or antigen test. Resolving or previous infection is best determined by serologic testing that indicates the presence of antibody. Accumulating evidence suggests that natural infection with SARS-CoV-2 with subsequent development of antibodies may confer some level of immunity for at least 3 months. However, the robustness and durability of immunity following natural infection remain unknown, as does how it compares to vaccine-induced immunity. These recommendations will be updated as new information becomes available.

Choice of serologic test and testing strategy

- Tests issued EUA by the Food and Drug Administration (FDA) are recommended for clinical and public health purposes. As of January 20, 2021, 65 serologic tests for SARS-CoV-2 have been issued an EUA by the FDA. EUA-authorized tests include both qualitative and semi-quantitative tests. The list of SARS-CoV-2 serologic tests granted EUA by the FDA can be found on FDA's website .
- Serologic tests with very high sensitivity and specificity are preferred since they are more likely to exhibit high expected predictive values when administered at least 3 weeks following onset of illness.
- Additional considerations when selecting a serologic assay 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 may 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; therefore, detection of IgM may suggest relatively recent infection.
  - Persistence of detectable antibodies may 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, 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 serologic testing and interpretation of results

- Serologic 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 COVID-19 illness who test positive by direct viral detection methods for SARS-CoV-2 (e.g., polymerase chain reaction 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 with a previous negative antibody test (i.e., seroconversion) and who did not receive a positive viral test may 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 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.
- SARS-CoV-2 antibodies, particularly IgG antibodies, may persist for months and possibly years. Therefore, when serologic tests are used to support diagnosis of recent COVID-19 illness, a single positive antibody test result may reflect previous SARS-CoV-2 infection rather than the most recent illness.

- Serologic testing can be used for clinical, occupational health, and public health purposes, such as serologic surveys, to help differentiate natural infection from vaccination by utilizing tests that measure antibodies against different protein targets. None of the currently authorized tests have been authorized to assess individuals that have received a vaccine. However, the EUA indications for currently authorized tests do not preclude the use of these tests on individuals who have received a SARS-CoV-2 vaccine. Whether the test has been validated to specifically detect antibodies against the antigen(s) employed by the test and whether the antigen(s) 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 serologic tests may be interpreted in the following way:
    - In a person never vaccinated:
        - testing positive for antibody against either N, S, or RBD indicates prior natural infection
    - In a vaccinated person:
        - testing positive for antibody against the vaccine antigen target, such as the S protein, and negative for other antigens suggests that they have produced vaccine-induced antibody and that they were never infected with SARS-CoV-2
        - testing positive for any antibody other than the vaccine-induced antibody, such as the N protein, indicates resolving or resolved SARS-CoV-2 infection that could have occurred before or after vaccination.

The first vaccines distributed in the United States induce antibodies to S protein. Thus, presence of antibodies to N protein indicates previous natural infection regardless of vaccination status, while presence of antibodies to S protein indicates either previous natural infection or vaccination. Presence of antibodies to S protein and absence of antibodies to N protein in the same specimen indicates vaccination in a person never naturally infected or could signal prior natural infection in a person whose antibodies to N protein have waned. Since vaccines induce antibodies to specific viral protein targets, post-vaccination serologic test results will be negative in persons without history of previous natural infection if the test used does not detect antibodies induced by the vaccine.

- Serologic 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 serologic test does not preclude previous infection. A proportion of persons who are infected with SARS-CoV-2 may not develop measurable antibodies, therefore limiting the sensitivity of any antibody test to detect previous infection in these individuals. In addition, measurable antibodies also may wane over time and the extent to which seroreversion occurs may vary according to the antibody test used.

Additional considerations for serologic test results

- Unvaccinated persons who are asymptomatic and who test positive for SARS-CoV-2 antibody without recent history of COVID-19 or a compatible illness have a low likelihood of active infection and do not need to isolate.

- Persons recovering from a COVID-19 compatible or confirmed illness should follow previous guidance on when to resume normal activities, including work, regardless of the presence of antibodies.

- Unvaccinated persons who have tested antibody positive within 3 months before or immediately following an exposure to someone with suspected or confirmed COVID-19 and who have remained asymptomatic since the current COVID-19 exposure do not need to quarantine in low risk situations. Low risk situations include settings where contact with persons at high risk of COVID-19 severe illness, including older adults and persons with certain medical conditions, is not anticipated for at least 10 days following exposure. Contacts to COVID-19 should still monitor themselves for symptoms of COVID-19 during the 14 days after exposure and if symptoms of COVID-19, develop they should isolate and seek testing. Recommendations for vaccinated persons with an exposure to someone with suspected or confirmed COVID-19 are posted elsewhere

are posted elsewhere.

- All persons, including unvaccinated persons who have previously tested antibody positive should continue to follow all other current recommendations to prevent SARS-C0V-2 infection (e.g., social distancing, use of masks).
- Persons who have previously tested positive for antibody for SARS-CoV-2 but who currently have evidence of 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 COVID-19 following COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person.

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Last Updated Mar. 17, 2021