Centers for Disease Control and Prevention

Find pages with...

All these words:

Results must contain all of these words

This exact word or phrase:

Results must contain this full phrase

Any of these words:

Results must match at least one of these words

None of these words:

Results cannot contain any of these words

Language:

Any

Find pages in the language you select

Advanced Search

Coronavirus Disease 2019 (COVID-19)

Interim Guidelines for COVID-19 Antib

Interim Guidelines for COVID-19 Antibody Testing in Clinical and Publi

Data that will inform serologic testing guidance is rapidly evolving. Recommendatio
to determine protective immunity and infectiousness among persons recently infect
updated as new information becomes available.

Summary

Serologic methods have been developed and will have important public health and clir
to the COVID-19 pandemic.

- Serologic assays for SARS-CoV-2 now have Emergency Use Authorization (EUA) by
Administration (FDA), which has independently reviewed their performance.
- Currently, there is no identified advantage of assays whether they test for IgG, IgM
- It is important to minimize false positive test results by choosing an assay with hig
populations and individuals with an elevated likelihood of previous exposure to SA
orthogonal testing algorithm (i.e., employing two independent tests in sequence w
result) can be used when the expected positive predictive value of a single test is l
- Antibodies most commonly become detectable 1-3 weeks after symptom onset, a
that infectiousness likely is greatly decreased and that some degree of immunity f
developed. However, additional data are needed before modifying public health r
serologic test results, including decisions on discontinuing physical distancing anc
equipment.

Background

Serologic assays for SARS-CoV-2, now broadly available, can play an important role in u
epidemiology in the general population and identifying groups at higher risk for infecti
methods such as nucleic acid amplification or antigen detection tests that can detect a
tests help determine whether the individual being tested was ever infected—even if th
symptoms. Serologic tests detect waning or past SARS-CoV-2 virus infection indirectly, l
immune response to the virus. Therefore, serology assays do not typically replace direc
primary tool for diagnosing an active SARS-CoV-2 infection, but they do have several im
and responding to the COVID-19 pandemic.

Although serologic tests should not be used at this time to determine if an individual is
determine the proportion of a population previously infected with SARS-CoV-2 and pro
populations that may be immune and potentially protected. Thus, demographic and ge
results can help determine which communities may have experienced a higher infectio

higher rates of herd immunity. In some instances, serologic test results may assist with infected with SARS-CoV-2 and determining who may qualify to donate blood that can b convalescent plasma as a possible treatment for those who are seriously ill from CC

Development of Antibodies and Immunity

Nearly all immune competent individuals will develop an immune response following S infections with other pathogens, SARS-CoV-2 infection elicits development of IgM and I useful for assessing antibody response because little is known about IgA response in th

Antibodies in some persons can be detected within the first week of illness onset. SARS unusual because IgM and IgG antibodies arise nearly simultaneously in serum within 2 Thus, detection of IgM without IgG is uncommon. How long IgM and IgG antibodies rer is not known.

In addition, development of neutralizing antibodies can also be assessed. Neutralizing in vitro, and as with many infectious diseases, their presence correlates with immunity temporarily.

Recurrence of COVID-19 illness appears to be very uncommon, suggesting that the pre least short-term immunity to infection with SARS-CoV-2. Consistent with this observatic in primates and subsequent development of antibodies resulted in protection from rei rechallenged. Additionally, antibody development in humans correlates with a marked respiratory tract. Taken together, these observations suggest that the presence of antil infectiousness and offer some level of protection from reinfection. However, definitive uncertain whether individuals with antibodies (neutralizing or total) are protected agai and if so, what concentration of antibodies is needed to confer protection.

Current Status of Antibody Testing in the Ur

Antigenic targets

The two major antigenic targets of SARS-CoV-2 virus against which antibodies are dete nucleocapsid phosphoprotein (N). While S protein is essential for virus entry and is pr protein is the most abundantly expressed immunodominant protein that interacts with — full-length (S1+S2) or partial (S1 domain or receptor binding domain [RBD]) — are us determines cross-reactivity and specificity because N is more conserved across corona more conserved than S1 or full-length S.

Types of Antibody Testing

Different types of assays can be used to determine different aspects of immune respor
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 lower biosafety level laboratories (e.g., BSL-2). With specific reagents, individual ar IgA, can be determined. In general, IgM is one of the first types of antibodies prod useful for determining recent infection, while IgG generally develops after IgM and months or years. IgA is important for mucosal immunity and can be detected in m addition to blood, though its significance in this disease is still to be determined. D assays, these tests can be performed rapidly (less than 30 minutes) in a field setti laboratory.

  Tests that detect binding antibodies fall into two broad categories.

  - Point-of-care (POC) tests generally are lateral flow devices that detect IgG or serum, plasma, whole blood, and/or saliva. An advantage of some point-of-c they can be performed on blood samples obtained by fingerstick rather thar
  - Laboratory tests use ELISA (Enzyme-Linked Immunosorbent Assay) or CIA (c methods for antibody detection, which for some assays may require trained instruments. Based on the reagents, IgG, IgM, and IgA can be detected separ antibody.
- Neutralizing antibody detection: FDA has not yet authorized the use of neutraliz Neutralization tests determine the functional ability of antibodies to prevent infec involves incubating serum or plasma with live virus followed by infection and incu either BSL-3 or BSL-2 laboratories, depending on what form of the SARS-CoV-2 vir

  Two types of neutralization tests are conducted.

  - Virus neutralization tests (VNT), such as the plaque-reduction neutralizatior microneutralization, use a SARS-CoV-2 virus from a clinical isolate or recomb reporter proteins. This testing requires BSL-3 laboratories and may take up t
  - Pseudovirus neutralization tests (pVNT) use recombinant pseudoviruses (li that incorporate the S protein of SARS-CoV-2. This testing can be performed the VSV strain used.

FDA-authorized serologic tests

FDA now requires commercially marketed serologic tests to receive Emergency Use Au

not commercially marketed do not require FDA authorization but developers may volu
Multiple agencies — including FDA, the National Cancer Institute/National Institutes of
Biomedical Advanced Research and Development Authority (BARDA) — are collaborati
the medical community to evaluate several serology tests using a well-characterized se
plasma) collected before and during the current COVID-19 outbreak. A list of all tests a
EUA is maintained on an FDA website . All currently authorized tests are qualitative (
negative, or indeterminate) rather than quantitative (providing a quantitative assessme

Both laboratory and rapid serologic assays have received EUA. Serologic testing techno
throughput lateral flow tests where the presence of antibody is demonstrated by a colo
laboratory-based immunoassays that allow for processing of many samples at the sam

The EUA letter of authorization includes the settings in which the test is authorized, bas
appropriate settings for use during the public health emergency.

Optimizing Testing Outcomes

Test performance

The utility of tests depends on the sensitivity and specificity of the assays; these perfor
determined by using a defined set of negative and positive samples. In addition, the pr
considered because these values affect the overall outcome of testing. Positive predict
individuals with positive test results are truly antibody positive. Negative predictive va
individuals with negative test results are truly antibody negative. Positive and negative
by the percentage of truly antibody positive individuals in the tested population (preva
sensitivity and specificity of the test. For example:

- In a high-prevalence setting, the positive predictive value increases — meaning it i
positive are truly antibody positive – than if the test is performed in a population v
used in a population where prevalence is low, the positive predictive value drops l
positive results, since the pre-test probability is low.
- Likewise, negative predictive value is also affected by prevalence. In a high-prevale
predictive value declines whereas in a low-prevalence setting, it increases.

In most of the country, including areas that have been heavily impacted, the prevalenc
expected to be low, ranging from <5% to 25%, so that testing at this point might result
results and fewer false-negative results.

In some settings, such as COVID-19 outbreaks in food processing plants and congregat infection in the population may be significantly higher. In such settings, serologic testin outbreaks might result in relatively fewer false positive results and more false-negative

Testing strategies

In the current pandemic, maximizing specificity and thus positive predictive value in a s most instances, since the overall prevalence of antibodies in most populations is likely where the prevalence is 5%, a test with 90% sensitivity and 95% specificity will yield a p other words, less than half of those testing positive will truly have antibodies. Alternati with an antibody prevalence exceeding 52% will yield a positive predictive greater than in 20 people testing positive will have a false positive test result.

Three strategies can be used to improve positive predictive value:

- Choosing a test with a very high specificity, perhaps 99.5% or greater, will yield a h populations tested with prevalence ≥5%.
- Another strategy is to focus testing on persons with a high pre-test probability of i such as persons with a history of COVID-19-like illness.
- A third approach is to employ an orthogonal testing algorithm in which persons w with a second test. Effective orthogonal algorithms are generally based on testing each with unique design characteristics (e.g., antigens or formats).

Algorithms can be designed to maximize overall specificity while retaining maximum se example above with a population prevalence of 5%, a positive predictive value of 95% c positive are tested with a second different orthogonal assay that also has 90% sensitivi performance of orthogonal testing algorithms has not been systematically evaluated b line calculator from the FDA. See Table 1 for the potential improvement benefits of

Limitations of Serologic Tests

At present, the immunologic correlates of immunity from SARS-CoV-2 infection are not from BARDA, CDC, FDA, NIH, the Office of the Assistant Secretary for Health (OASH), De White House Office of Science and Technology Policy (OSTP) are working with member community to determine whether positive serologic tests are indicative of protective in work includes assessing the level of antibodies required for protection from reinfectior and the factors associated with development of a protective antibody response. The ki longevity of antibodies, the ability of antibodies to protect from repeat infection, the pr

antibody, and the correlation of binding antibody titers to neutralization ability are yet challenge studies demonstrate protection in the short run, demonstration of long-term future study. Hence, pending additional data, the presence of antibodies cannot be equ from SARS-CoV-2 infection.

Some tests may exhibit cross-reactivity with other coronaviruses, such as those that ca result in false-positive test results. Some persons may not develop detectable antibodi others, it is possible that antibody levels could wane over time to undetectable levels. I present early in infection. Thus, serologic test results do not indicate with certainty the previous infection with SARS-CoV-2.

Recommendations for Use of Serologic Test

Information that might impact serologic recommendations is rapidly evolving, particula serologic tests indicate protective immunity or decreased transmissibility among those recommendations will be updated as new information becomes available.

Choice of test and testing strategy

- Serologic assays that have Emergency Use Authorization (EUA) are preferred for p their test performance data have been reviewed by FDA.
- Serologic test results should be interpreted in the context of the expected predict
- Positive predictive value should be optimized, particularly if results are returned t
  - Assure a high positive predictive value (e.g., 95%) by choosing tests with suffi persons or populations with a high pre-test probability of having antibodies (symptoms compatible with COVID-19 or who are exposed to areas or institut
  - If a high positive predictive value cannot be assured with a single test, use ar Table 1 for examples of using one or two tests in populations with various pr antibodies.
- Currently, there is no substantive performance advantage of assays whether they antibody. Thus, immunoglobulin class should not determine the assay chosen in r of IgM antibodies may indicate a more recent infection, but the dynamics of the Ig defined at present. Over time, it may be important to characterize and evaluate th samples that are IgM negative and IgG positive to ensure that assays remain fit fo the pandemic progresses and more individuals are expected to have lower IgM le
- Serologic testing should not be used to determine immune status in individuals u duration of immunity is established.

- Serologic testing can be offered as a method to support diagnosis of acute COVID late.* For persons who present 9-14 days after illness onset, serologic testing can recommended direct detection methods such as polymerase chain reaction. This sensitivity of nucleic acid detection is decreasing and serologic testing is increasin
- Serologic testing should be offered as a method to help establish a diagnosis whe complications of COVID-19 illness, such as multisystem inflammatory syndrome ir

Recommendations for persons who test positive fc antibodies

- Although the presence of anti-SARS-CoV-2 antibodies when detected using a testi predictive value for the context of use likely indicates at least some degree of imm duration of immunity is established, it cannot be assumed that individuals with tr are protected from future infection.
- Asymptomatic persons who test positive by serologic testing and who are without compatible illness have a low likelihood of active infection and should follow gene infection with SARS-CoV-2 and otherwise continue with normal activities, including
- Persons who have had a COVID-19-compatible or confirmed illness should follow resumption of normal activities, including work.
- There should be no change in clinical practice or use of personal protective equip and first responders who test positive for SARS-CoV-2 antibody.

Additional considerations on the use of serologic t

- Serologic test results should not be used to make decisions about grouping perso congregate settings, such as schools, dormitories, or correctional facilities.
- Serologic test results should not be used to make decisions about returning persc
- Until more information is available about the dynamics of IgA detection in serum, recommended.

* Detection of specific antibody in serum, plasma, or whole blood that indicates new or presumptive laboratory evidence of COVID-19 illness according to the Council of State (CSTE) interim case definition for COVID-19 .

Additional Resources

American Medical Association. Serological Testing for SARS-CoV-2 Antibodies.

Infectious Diseases Society of America. IDSA COVID19 Antibody Testing Primer. [

Association of Public Health Laboratories and Council of State and Territorial Epidem
Considerations: Serologic Testing for COVID-19. Version 1-May 7, 2020.

Table 1: Predictive value positive using one test or two orth
background prevalence in the population tested.

Prevalence	PPV for one test (SE=90%, SP=95%)	PPV for two orthogo (SE=90%, SP=95%)
2%	26.9%	86.9%
5%	48.6%	94.5%
10%	66.7%	97.3%
30%	88.5%	99.3%

PPV = positive predictive value

SE = sensitivity

SP = specificity