

Factors to Consider When Offering Community-Based Laboratory Testing for COVID-19

Last Updated: May 22, 2020

Key Points:

- Three categories of tests are available for COVID-19: 1) molecular based (RT-PCR) 2) antigen tests 3) serology (antibody) tests. The first two are combined and called diagnostic tests in this document.
- Regardless of which type of test is used, the results are point-in-time, meaning they are relevant for the date of collection of the specimen only.
- PCR tests identify the presence of viral RNA, and antigen detection tests detect the presence of the nucleocapsid protein antigen in respiratory samples.
 - A positive result indicates current infection (i.e., the person currently has COVID-19). The person should self-isolate for at least 10 days and close contacts self-quarantine for at least 14 days from date of last exposure, as specified in other COVID-19 guidance
 - A positive PCR or antigen test does not necessarily mean viable virus is present (i.e., that the person is infectious or is able to spread the virus to others); viral RNA and proteins can persist in the respiratory tract
 - A negative result means the virus or antigen was not detected, either because the person is not currently infected, the virus is no longer present in the upper respiratory tract, an inadequate specimen was collected (PCR), or the amount of virus antigen or RNA is below the level that is detectable by the test used.
- Antibody tests identify the body's immune response to exposure to SARS-CoV-2.
 - A positive result indicates that the person has been exposed to the virus at some point in the past.
 - A negative result could indicate that the person has not been exposed, that antibodies had not yet developed at the time of specimen collection, antibody levels are too low for the test to detect, or the immune system has not mounted a response to the exposure (e.g., because of immunosuppression).
 - A positive test does not diagnose acute SARS-CoV-2 infection or determine if person is infectious.
 - A false positive result is possible if the test cross-reacts with commonly circulating coronaviruses.
 - At this point in time, it is not known if a positive serologic result means a person is protected against reinfection or the strength and duration of any protection that may exist.
 - A negative result does not preclude infection with SARS-CoV-2. If infection is suspected, follow-up with a molecular or antigen test.
- Diagnostic tests for infection in exposed contacts should be conducted 5-7 days following exposure or at the time of symptom onset. Symptomatic contacts should be prioritized for testing.
- Those who provide test results to persons who have been tested should understand what each test means and determine what public health recommendations need to be made in light of the result.

- The primary means of interrupting the spread of SARS-CoV-19 are social distancing, hand hygiene, proper cleaning and disinfection, and use of PPE in healthcare settings.
- Those with symptoms suggestive of COVID-19 or who test positive for the virus by PCR or antigen detection should self-isolate for at least 10 days and their close contacts should self-quarantine for at least 14 days from the date of last exposure.

Introduction

Up to this point in the COVID-19 response, CDC and VDH have encouraged testing of people with compatible symptoms, especially those at high risk for severe disease (e.g., ≥ 65 years of age, having an underlying health condition) or at high risk for exposure or transmission (e.g., healthcare workers, first responders, residents of long-term care facilities). The current VDH testing priorities can be seen [here](#). Diagnostic testing to confirm infection, coupled with isolation of those who are infected and quarantine of close contacts, is vitally important in controlling the spread of COVID-19 in communities. A close contact is defined a) being within 6 feet of a person with lab-confirmed COVID-19 for at least 15 minutes or b) having direct contact with infectious secretions or excretions of the person with confirmed COVID-19 (e.g., being coughed on, kissing, sharing utensils).

Consideration of testing asymptomatic individuals has been increasing. Examples include screening employees of a business or persons seeking services at a homeless shelter, testing all asymptomatic close contacts, or conducting testing of various populations in the community. Such information could be useful in various ways; however, the results of such screening need to be interpreted with caution. This document summarizes some key traits of viral and antibody tests and provides information that can be applied during discussions about more widespread testing in communities.

Background on the different types of tests

Helpful resources are listed at the end of this document. The two that were used the most in developing this document were an article in the *Journal of the American Medical Association (JAMA)* on interpreting diagnostic test results and a publication presented by the Association of Public Health Laboratories and the Council of State and Territorial Epidemiologists (APHL/CSTE) on serologic testing. Summary notes from each of those publications are provided as Attachments 1 and 2. Since the APHL/CSTE document was published, FDA has issued an Emergency Use Authorization (EUA) for an antigen test for COVID-19. Antigen tests are included with PCR as a diagnostic test in this discussion.

Diagnostic tests include the detection of viral RNA by PCR or detection of viral protein through an antigen test. They are useful in identifying persons currently infected with SARS-CoV-2. The public health response to diagnostic tests has been defined (isolation of person tested and quarantine of contacts). Positive results of these tests are considered to be diagnostic, especially when symptom and exposure information are consistent with the result. A positive PCR or antigen test does not necessarily mean the person is infectious, especially if the test was conducted after the person’s period of isolation. Viral RNA has persisted in some cases when the virus has not been viable. A negative PCR could be because the virus is no longer detectable in the respiratory sample or the person was not infected at the time of testing, though the virus was responsible for the illness. Consideration of the timing of the test and clinical symptoms is needed to evaluate the significance of the results at times. Consider re-testing and notify [LHD](#) if suspicion of COVID-19 still exists, despite negative COVID-19 test. For antigen testing, a

negative result is considered presumptive and should be confirmed by a molecular test if needed for patient management.

The value of **antibody tests** is less clear from a public health management perspective. Antibody tests detect current or prior viral infection. Antibodies develop 1-2 weeks after symptom onset, so an antibody test may not detect acute infection and should not be used as the sole basis for diagnosis.

Antibody tests - Possible Uses: These tests could be useful to determine how widespread infection has been in different populations, identify people with antibodies who can donate plasma, for serosurveys in populations to determine true infection rates, to learn more about the antibody response to SARS-CoV-2 and its relationship with symptom history, and vaccine development applications. **They should not be used to make staffing/return to work decisions, decisions about the need for PPE, or the need to discontinue social distancing.**

Antibody tests – Unknowns: The performance of the various antibody tests is variable and interpretation of results is challenging because the immune response to SARS-CoV-2 infection is not well understood. Unknowns include: are antibodies protective, for how long, how complete is the protection, if any (i.e., do they make you less likely to get sick overall or make you have a milder case of illness), how much antibody is needed to provide protection, and which type of antibody needs to be present to provide protection? It is best to use tests that are FDA-authorized, have documented and high sensitivity and specificity, and the least cross-reactivity of antibodies to other common coronaviruses, which may yield false positive results.

Antibody Tests – Interpretation of Results: A positive result indicates past and/or present infection; however, it could be because of cross-reactivity with another, more common coronavirus and therefore, be a false positive. At this time, a positive test is not considered to be an indication that the person is immune. A negative test result does not rule out SARS-CoV-2 infection. It might mean the person has not been exposed to the virus, or the test might have been performed before antibodies develop (1-2 weeks after symptom onset, which could be 2-3 weeks after infection, given the incubation period), no immune response was mounted because of a weakened immune system, or the test might not be sensitive enough to detect low antibody levels (false negative). **Neither a positive nor a negative result can determine whether the person being tested is infectious at the time of the test.** A diagnostic test is needed to rule in or rule out current infection.

Some highlights about the different types of tests are summarized in the table below.

	Diagnostic Test (RT-PCR or antigen)	Antibody Test
Offered by (in Virginia)	Public health (PCR) and private labs (PCR and antigen)	Private labs
Detects	Presence of viral RNA or viral protein antigen	Presence of antibodies
Positive means...	Infected, presumed to be contagious	Body's immune system has responded to the virus

Negative means...	Viral RNA not detectable at the time of the test; Negative antigen test results are presumptive and should be confirmed with a molecular test if symptoms warrant or if needed for patient management	Person not exposed, test done before antibodies develop, no or low level antibody response
Diagnostic?	Yes, if positive	No
Limitations	Can be positive for weeks, does not necessarily mean the virus is viable/person is infectious	Negative result does not rule out infection - It takes time for antibodies to develop; might miss new infection. Positive could indicate person has recovered; don't know how long antibodies will last or if their presence means the person is less susceptible to infection; could be result of cross-reaction with common coronaviruses. Neither result indicates infectiousness
Use as Sole Basis of Diagnosis?	Yes, for public health surveillance	No
For Clinical Diagnosis, also Need to Factor In...	Exposure and symptom history, timing of specimen collection	Exposure and symptom history, timing of specimen collection
Usefulness at Community Level	Count number of confirmed cases	Count number of people who have been infected; learn about the immune response over time
Point in Time Only?	Yes	Yes
What to Do with Positives?	Isolate patient, quarantine contacts	Follow up to determine clinical presentation and potentially recommend molecular testing

Published Recommendations for Testing Asymptomatic Persons

Little has been documented in the scientific references regarding recommended procedures for testing asymptomatic persons in community settings. The Infectious Diseases Society of America (IDSA) has published recommendations for testing certain asymptomatic patients *in the hospital setting* using molecular tests (see Resources list for diagnosis guidelines), including the recommendation to test those who are asymptomatic who have had direct contact with a lab-confirmed case, who work or reside in a congregate setting experiencing an outbreak, who are being hospitalized in areas with a high prevalence of COVID-19, who are being hospitalized who are immunocompromised, before immunosuppressive procedures, those undergoing major time-sensitive surgeries, those undergoing time-sensitive aerosol-generating procedures when PPE supply is limited, and testing unexposed asymptomatic persons if the test result will dictate eligibility for surgery or inform the administration of immunosuppressive therapy.

IDSA does not recommend testing asymptomatic persons who are hospitalized in a low prevalence area (<2%); this does not apply to immunocompromised, those undergoing time-sensitive major surgery or

aerosol-generating procedures. All IDSA testing recommendations refer to the use of a molecular test and are conditioned upon the availability of testing resources.

In determining when to test an exposed close contact, the IDSA states that 5-7 days following exposure may be reasonable because of the average incubation period of five days. The testing of symptomatic contacts should be prioritized. A negative molecular test can be accepted with no need for retesting if there is low clinical suspicion of infection, but IDSA recommends that the test should be repeated if clinical suspicion is higher (based on number, severity, and timing of symptoms). The repeat test should be conducted 24-48 hours after the initial test.

Advising Your Community

The answers are not always clear to the questions that are arising in discussions about screening asymptomatic segments of the population. Those interested in conducting screening need to understand what test they are using, what the results mean, and how the results can be used. To determine what advice to give, first gather the following information:

- Who is being tested?
- What test is being used?
- What results does that test provide?
- What is the goal of testing?
- What is the plan for handling persons with positive results?
- What is the plan for handling persons with negative results?

The public health recommendations and interpretations would be as follows:

- Review the above information about the test being used and what the results do and do not mean. Refer to the White House/HHS table on interpreting test results for further guidance (see Resources list).
- Continue to prioritize molecular testing of symptomatic persons who meet the [VDH guidelines for testing](#).
- A person with a **positive molecular (PCR) test or positive antigen test result** should stay home and self-isolate for at least 10 days (if using the symptom-based strategy for determining when to discontinue isolation) and close contacts of that person should be identified and quarantined until at least 14 days after last exposure to the person with the positive result. (www.vdh.virginia.gov/content/uploads/sites/182/2020/04/Home-IsolationQuarantine-Release-Graphic_FINAL.pdf)
- A person with a **positive or negative serology test** should be tested with a molecular test if symptoms of COVID-19 are present and the person either meets VDH guidelines for testing or their infectious status needs to be known to make public health or medical decisions. Neither a negative nor a positive serology test will tell you whether a person is infectious at the time of the test.
- Any of these test results are valid for that day only. These tests are point-in-time tests and a specimen collected on another day could yield different results. That is, the viral RNA could become detectable the day after a negative swab. The body could have built antibodies that were not detectable on the day of the test.

Some of the IDSA's hospital-based recommendations might be applied to public health. That is, public health could consider the testing of asymptomatic persons who meet the following criteria:

- Have had close contact with a lab-confirmed case without proper use of PPE,
- Work or reside in a congregate setting experiencing an outbreak and had an exposure without proper use of PPE, or
- Result will impact isolation, quarantine, or PPE decisions.

Diagnostic tests for infection in exposed contacts should be conducted 5-7 days following exposure or at the time of symptom onset. Symptomatic contacts should be prioritized for testing. A negative molecular test can be accepted if there is low clinical suspicion of infection, but the test should be repeated if clinical suspicion is higher (based on number, severity, and timing of symptoms). The repeat test should be conducted 24-48 hours after the initial test.

In general, workplaces should screen workers for symptoms upon arrival at work and send any with fever or symptoms of COVID-19 back home to self-isolate according to CDC and VDH guidance, have liberal sick leave policies in place and ensure workers know to stay home when sick, encourage use of cloth face coverings in the workplace and maintenance of at least 6 feet of space between workers to prevent the spread of the virus, and follow cleaning and disinfection recommendations (www.cdc.gov/coronavirus/2019-ncov/community/guidance-business-response.html). Persons with prolonged contact with a person suspected or confirmed to have COVID-19 should self-quarantine according to CDC and VDH guidance. The same screening and disease prevention measures also apply to other settings within the community.

Resources:

APHL/CSTE: Public Health Considerations: Serologic Testing for COVID-19 (5/7/2020) (See Attachment 2)
www.aphl.org/programs/preparedness/Crisis-Management/Documents/Serologic-Testing-for-COVID-19.pdf

CDC: Evaluating and Testing Persons for COVID-19
www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html

FDA: Important Information on the Use of Serological (Antibody) Tests for COVID-19 - Letter to Health Care Providers (4/17/2020)
www.fda.gov/medical-devices/letters-health-care-providers/important-information-use-serological-antibody-tests-covid-19-letter-health-care-providers

IDSA:
COVID-19 Antibody Testing Primer (5/5/20)
www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-covid-19-antibody-testing-primer.pdf

Guidelines on the Diagnosis of COVID-19 (5/6/20)
www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

JAMA Article: (See Attachment 1 below for summary and figure)

Interpreting Diagnostic Tests for SARS-CoV-2 by Sethuraman, Jeremiah, and Ryo (5/6/2020)
jamanetwork.com/journals/jama/fullarticle/2765837?guestAccessKey=c26c8c00-a470-4777-8abef2857a184887&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=050620

Journal of Clinical Microbiology:

The Role of Antibody Testing for SARS-CoV-2: Is There One? By Theel, Slev, Wheeler, et al.
jcm.asm.org/content/early/2020/04/27/JCM.00797-20

Medrxiv Article:

Estimating the Prevalence of COVID-19 in the United States: Three Complementary Approaches by Lu, Nguyen, Link, and Santillana (4/18/2020)
www.medrxiv.org/content/10.1101/2020.04.18.20070821v1.full.pdf

VDH Testing Guidance:

www.vdh.virginia.gov/coronavirus/covid-19-testing/

White House/HHS Guidance on Interpreting COVID-19 Test Results Table (May 2020):

www.whitehouse.gov/wp-content/uploads/2020/05/Testing-Guidance.pdf

WHO. “Immunity passports” in the context of COVID-19. Scientific Brief – April 24, 2020

www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19

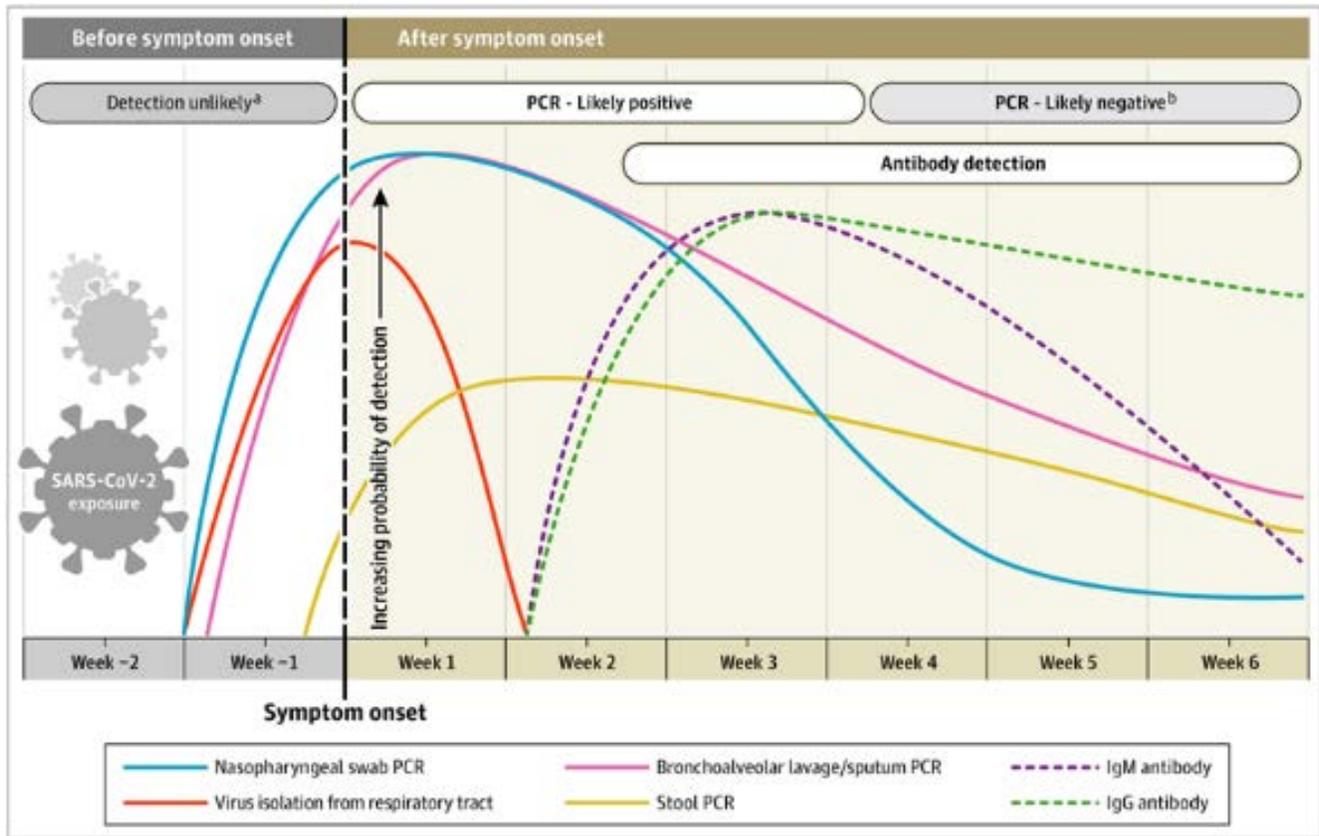
Attachment 1: Notes and Figure from JAMA Article - Interpreting Diagnostic Tests for SARS-CoV-2 by Sethuraman, Jeremiah, and Ryo (5/6/2020)

1. Reverse transcriptase-polymerase chain reaction (RT-PCR)
 - Detects viral RNA
 - In most people with symptomatic COVID-19, viral RNA in the nasopharyngeal (NP) swab is detectable as early as day 1 of symptom onset and peaks in the first week of onset. Positivity declines by week 3, but lasts longer in severely ill individuals.
 - A positive test means viral RNA has been detected, but does not necessarily mean viable virus is present (i.e., that person is infectious)
 - RNA has been detected more than six weeks after the first positive test and after two consecutive negative tests taken 24 hours apart (few cases). It is not known if this is because of testing error, reinfection, or reactivation
 - Infectivity declines after the first week of symptoms, indicated by the inability to culture the virus at that point (based on small study)
 - Sputum and stool may remain positive after NP specimen is negative
 - False negatives could be because of timing of collection compared to illness onset or poor sampling technique, especially with NP swabs
 - False positives are rare (specificity is 100%), but could be because of contamination of reagents

2. IgG and IgM Enzyme-Linked Immunosorbent Assay (ELISA, also referred to as serologic or antibody tests) (Source: JAMA) [Note from DCLS: antibody tests can also be a lateral flow device.]
 - Detects antibodies to SARS-CoV-2, indicating the host's immune response to infection
 - Can be helpful in diagnosing an individual who seeks care more than two weeks after onset or measuring the extent of infection in a community
 - Earliest marker is total antibodies. They begin to increase from the second week of onset
 - IgM and IgG have been found as early as the fourth day after onset, but higher levels appear in the second and third week (see Figure)
 - IgM and IgG have been found in all patients (in a couple of studies) between the third and fourth week after onset. IgM declines and reaches lower levels by week 5 and almost disappears by week 7. IgG persists beyond week 7.
 - Sensitivity and specificity depend on the antigen used in the test. Rapid tests do not usually reveal the antigens used and usually provide only qualitative results (antibodies present or absent). The only way to know if the antibodies are neutralizing is to conduct a Plaque Reduction Neutralization Test (PRNT). Neutralizing antibodies are ones that bind to a virus in a way that blocks infection.

These data apply to symptomatic adults who are not immunocompromised

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset*



*Source: Nandini Sethuraman, Sundararaj Stanleyraj Jeremiah, Akihide Ryo. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA. Published online May 6, 2020. [doi:10.1001/jama.2020.8259](https://doi.org/10.1001/jama.2020.8259). Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

^aDetection only occurs if patients are followed up proactively from the time of exposure.

^bMore likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Attachment 2: Notes from APHL/CSTE: Public Health Considerations: Serologic Testing for COVID-19 (5/7/2020)

- Serologic testing could be useful to determine how widespread infection has been in different populations, identify people with antibodies who can donate plasma, and determine if people mount an antibody response whether or not they had symptoms.
- Should not be used to make staffing/return to work decisions, decisions about the need for PPE, or the need to discontinue social distancing.
- Detects evidence of viral infection at some time in the past. Should not be used as the sole basis for diagnosis. Antibodies develop 1-2 weeks after symptom onset, so an antibody test might not detect current infection. (Some serologic tests detect antigen, which is a marker of current infection.)
- Most serologic tests used in the United States detect IgG antibodies, indicating infection at some point in the past. Some also detect IgM, indicating recent infection, or IgA, “associated with immunity in mucosal membranes.” If more than one antibody type is detected, it is called Total Antibody, which usually means IgG and IgM. Total antibody results that do not mention particular types of antibody indicate an infection at some point in the past.
- Different tests use different antigenic targets. Which target is used affects the test’s sensitivity and specificity.
- There are over 100 serologic test manufacturers. Some tests are FDA-authorized (under EUA) and some are not FDA-authorized. As of this writing, FDA has only authorized tests that are run in a laboratory, not point-of-care rapid antibody tests.
- Test performance is variable and interpretation of results is challenging because we do not yet know the immune response to SARS-CoV-2 infection. Unknowns include: are antibodies protective, for how long, how complete is the protection, if any (i.e., do they make you less likely to get sick overall or make you have a milder case of illness), how much antibody do you need to have to be protected, and which type of antibody needs to be present to provide protection?
- It is best to use tests that have the highest sensitivity and specificity and the least cross-reactivity with other coronaviruses, such as those that cause the common cold (yielding false positive results).
- Prevalence in the community affects the predictive value of the test, both positive and negative predictive values.
 - According to the Infectious Diseases Society of America (IDSA) primer: 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.
 - This is hard to determine, however, given the lack of data on true prevalence of infection in the community. The resource listed below from Medrix concludes that the prevalence is 10-100 times what the case counts indicate.

- Interpretation of Serology Test Results:
 - Negative does not rule out SARS-CoV-2 infection
 - The test might have been performed before antibodies develop (1-2 weeks after symptom onset, which could be 2-3 weeks after infection, given the incubation period)
 - It is possible to test negative and still be infectious
 - The test might not be sensitive enough to detect low antibody levels (false negative)
 - Need a molecular test to rule out current infection
 - Positive indicates past and/or present infection
 - Could be due to cross-reactivity with another coronavirus (false positive)
 - Does not mean person is immune
 - Does not mean person is not shedding virus
 - Does not mean person is not infectious
 - Need a molecular test to rule in current infection