



Supplement F: Laboratory Guidance

Appendix F7

Fact Sheet for Clinicians: Interpreting SARS-CoV Test Results from CDC and Other Public Health Laboratories

Key Messages

- A positive RT-PCR test result for SARS-CoV should be considered presumptive until confirmatory testing by a second reference laboratory is performed.
- A negative test result for SARS-CoV may not rule out SARS-CoV disease and should not affect patient management or infection control decisions.

Definitions

SARS	Severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus; a newly described coronavirus that is genetically and antigenically distinct from other human coronaviruses
Laboratory-confirmed SARS-CoV infection	<ul style="list-style-type: none"> • Detection of any of the following by a validated test, with confirmation in a reference laboratory: <ul style="list-style-type: none"> ○ Serum antibodies to SARS-CoV in a single serum specimen, <i>or</i> ○ A four-fold or greater increase in SARS-CoV antibody titer between acute- and convalescent-phase serum specimens tested in parallel, <i>or</i> ○ Negative SARS-CoV antibody test result on acute-phase serum and positive SARS-CoV antibody test result on convalescent-phase serum tested in parallel; or • Isolation in cell culture of SARS-CoV from a clinical specimen, with confirmation using a test validated by CDC; or • Detection of SARS-CoV RNA by RT-PCR validated by CDC, with confirmation in a reference laboratory, from: <ul style="list-style-type: none"> ○ Two clinical specimens from different sources, <i>or</i> ○ Two clinical specimens collected from the same source on two different days

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Confirmed case of SARS-CoV disease	A person with clinically compatible illness and laboratory-confirmed SARS-CoV infection
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The Centers for Disease Control and Prevention (CDC) and other institutions have been working to develop strategies to detect and control the spread of severe acute respiratory syndrome (SARS). The cause of SARS has been determined to be infection with a previously unrecognized human coronavirus, SARS-associated coronavirus (SARS-CoV). Information on SARS and SARS-CoV is provided on CDC's SARS website: www.cdc.gov/sars/. All information and guidelines, including those on SARS-CoV laboratory testing, may change as we continue to learn more about this disease. Please check CDC's SARS website regularly for the most current information.

Previous experience with SARS-CoV disease demonstrates that the best guide to diagnosis is exposure to a person with SARS-CoV disease, a setting where SARS-CoV transmission is occurring, or persons who are part of a cluster of pneumonia without a known cause. Information in diagnosing SARS-CoV disease is provided in *Clinical Guidance on the Identification and Evaluation of Possible SARS-CoV Disease among Persons Presenting with Community-Acquired Illness* (www.cdc.gov/ncidod/sars/clinicalguidance.htm). Persons without a potential risk of exposure should usually not be tested for SARS-CoV. Clinicians should seek guidance from the state or local health department regarding current guidelines for SARS-CoV testing.

Clinicians providing care for patients with possible SARS-CoV disease may find the following information useful when interpreting SARS-CoV test results.

What tests for SARS-CoV are available?

CDC has developed and validated an enzyme immunoassay (EIA) for detection of serum antibody (www.cdc.gov/ncidod/sars/lab/eia/) to SARS-CoV and a reverse transcription-polymerase chain reaction (RT-PCR) assay (www.cdc.gov/ncidod/sars/lab/rtpcr/) for detection of SARS-CoV RNA. The EIA has been distributed to most state public health laboratories, and the RT-PCR has been distributed to most laboratories in the Laboratory Response Network (LRN). Both the EIA and the RT-PCR tests are sensitive and highly specific for SARS-CoV. The ability to diagnose SARS-CoV infection in a patient is often limited, however, by either the low concentration of virus in most clinical specimens (RT-PCR assays) or the time it takes a person to mount a measurable antibody response to SARS-CoV (serologic assays). The likelihood of detecting infection is increased if multiple specimens (e.g., stool, serum, respiratory tract specimens) are collected at several times during the course of illness.

CDC considers detection of SARS-CoV antibody to be the most reliable indicator of infection. Since previous infection is still rare in most populations, seroconversion is not needed to diagnose infection. Therefore, the presence of SARS-CoV antibody in someone without a previous history of SARS is indicative of recent infection. A negative serologic test can rule out SARS-CoV infection if the serum specimen is collected >28 days after onset of illness. Some persons do not mount an antibody response (test positive) until more than 28 days after onset of illness. Patients with a negative antibody test result whose specimens were obtained 28 days before illness onset or before should have another serum specimen collected >28 days after onset of symptoms.

RT-PCR for SARS-CoV RNA is a very sensitive and specific assay when performed appropriately. This test can detect SARS-CoV RNA in serum, stool, upper and lower respiratory specimens, various tissues, and occasionally urine specimens. Testing of multiple specimen types at several times during the course of illness should increase the likelihood of detecting infection.

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Other tests for detection of SARS-CoV include immunofluorescence assay (IFA) for SARS-CoV antibody, SARS-CoV isolation studies, electron microscopic studies, and immunohistologic or in situ hybridization studies on tissue specimens. The IFA for SARS-CoV antibody gives results essentially identical to those for the EIA for SARS antibody. Cell culture, electron microscopy, and histologic studies are less frequently used and less sensitive than RT-PCR. Cell culture for SARS-CoV should be done only in a BSL-3 laboratory using BSL-3 procedures (see Appendix F5).

What does it mean if a specimen tests positive for SARS-CoV?

Laboratory test results should always be considered with clinical observations and epidemiologic data in making a final diagnosis. A positive RT-PCR result should be confirmed by testing a second specimen and confirming the result at a qualified second laboratory to ensure that the result is not an artifact of laboratory contamination. A positive serologic result is less likely to result from a laboratory artifact but should also be subjected to confirmatory testing. If the results are confirmed, then a positive RT-PCR or serologic test result indicates that the patient has been recently infected with SARS-CoV (unless the patient has a previous history of SARS-CoV disease). Guidelines for managing patients with SARS-CoV disease are provided in Supplement C and Supplement I.

How is a SARS-CoV test confirmed?

Positive antibody and RT-PCR test results should be confirmed by repeat testing of the original specimen AND by testing of the same specimen in an independent laboratory using a validated assay.

What is difference between a laboratory-confirmed clinical specimen and laboratory-confirmed SARS-CoV disease?

This distinction is made for PCR test results because of concerns about false-positive results. For serology, virus isolation, and histopathologic studies, if a specimen is confirmed positive, the patient is also considered to be confirmed positive. For PCR, a second specimen is required to be confirmed positive to decrease the chance of misclassifying a patient due to a false-positive result. In all instances, laboratory results must be considered in the context of clinical and epidemiologic information on the patient.

What does it mean if a patient with an illness suggestive of SARS has a negative SARS-CoV test result?

A negative antibody result on a serum specimen collected >28 days after onset of illness is sufficient to eliminate SARS-CoV as the cause of illness. A negative antibody result on serum specimens collected ≤28 days after onset of illness or a negative RT-PCR test does not rule out SARS-CoV infection. Clinical specimens do not always have sufficient virus to be detected by RT-PCR. An antibody response may not be detected in some patients until >28 days after onset of illness.

What does it mean if test results are positive for other respiratory diseases?

A positive test result for another respiratory pathogen does not rule out SARS-CoV disease. SARS patients can be co-infected with SARS-CoV and other respiratory pathogens. Thus, detection of another respiratory pathogen does not eliminate the possibility of SARS-CoV disease. In some circumstances (e.g., another pathogen is detected in multiple patients in a cluster of cases and can fully explain the severity of illness), detection of another respiratory pathogen may make SARS-CoV disease less likely. Factors that may be considered in assigning alternate diagnoses include the strength of the epidemiologic exposure criteria for SARS-CoV disease, the specificity of the diagnostic test, and the compatibility of the clinical presentation and course of illness with the alternative diagnosis.

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Does a negative SARS-CoV test result affect patient management?

As noted above, the interpretation of negative SARS-CoV test results varies depending on the type of specimen, the timing of specimen collection, and the test that was performed. With the exception of a >28-day negative serologic test result, a negative SARS-CoV test result should not affect patient isolation or management decisions. The clinical features of the illness and the type and risk of exposure are the keys to making decisions on patient management and isolation.

Has the identification of SARS-CoV as the etiologic agent changed the recommendations for medical treatment of patients with SARS?

No. The discovery that SARS-CoV is the cause of SARS has not changed treatment recommendations. Research on antiviral treatment for SARS-CoV disease is currently under way.

Should a person who may have been exposed to a location with transmission of SARS-CoV or who had contact with a SARS patient be tested even if not ill?

Persons who have potentially been exposed to SARS patients and are well should be tested only as part of research studies. The exposed person may contact their state health department or CDC about participating in studies of persons exposed to SARS-CoV.

For more information, visit www.cdc.gov/ncidod/sars or call the CDC public response hotline at (888) 246-2675 (English), (888) 246-2857 (Español), or (866) 874-2646 (TTY)