ISTM CLINICIAN GUIDE FOR SARS-CoV-2 COVID-19 TESTING

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As international travel begins to increase, travel clinicians will be called upon to expand their knowledge and practices of SARS-CoV-2 covid-19 testing.

The purpose of this article is to review the different methods of SARS-CoV-2 covid-19 testing, discuss the advantages and disadvantages of various testing methods and provide recent resources for a clinician's tool kit.

Currently there are three common types of detection assays relevant for SARS-CoV-2 covid-19 diagnostic testing: molecular, antigen and antibody.

1. **Molecular** tests detects the presence of viral RNA. They are also known as viral tests or nucleic acid amplification tests (NAAT), and the best known is Reverse Transcription Polymerase Chain Reaction (RT-PCR). This can detect early infection and help with diagnosis, quarantine and case tracking.

2. **Antigen** tests detect the presence of a specific viral protein/antigen from the SARS-CoV-2 virus, typically part of a surface protein. This can detect early infection and help with diagnosis, quarantine and case tracking.

3. **Antibody** tests detect the presence of antibodies against SARS-CoV-2 (IgM and/or IgG). Predominately used to establish immunity after recovery from infection.

Molecular Testing

Among the molecular tests, PCR is the most sensitive and specific of Covid-19 testing and thus considered the gold standard.

There are various ways to collect PCR tests. The preferred method in most countries is a nasopharyngeal swab as it gives the highest viral yield thus helping to achieve more accurate results. Slightly less sensitive is combining bilateral deep nasal and oropharyngeal sample using the same swab for all three. The other types of specimen samples include oropharyngeal, nasal (anterior nares,

mid turbinate), saliva or mouth rinse. The timing of the PCR test can affect the results. A PCR test is recommended 5 – 7 days after exposure. Studies show 30% or more of COVID 19 cases could be asymptomatic, and approximately 44% of secondary cases could infect others during the pre-symptomatic stage. (D.Oran and E.Topol suggest asymptomatic infection rate could be as high as 40-45%.) Once a person has been infected by the SARS-CoV-2 virus it is estimated that 2-3 days before the onset of symptoms there is a high level of viral shedding in the upper respiratory tract. SARS-CoV-2 virus is infectious before and after symptom onset.

TYPES OF PCR SPECIMENS	**PROS**	**CONS**
Nasopharyngeal swab	Early diagnosis, before symptoms develop	Uncomfortable, higher risk for health care providers. Proper training needed. Not ideal for repeat testing or children
Oral or oropharynx / Nasal	More tolerable testing/ more acceptance to have test done More available test kits	Less sensitive than NP swab
Mouth Rinse/Gargle & Swish	Non-invasive Easier to obtain specimen Procedure is observed rather than administered	Less sensitive than NP swab. Easier for children and youth. Not all labs offer this test.

TEST RESULTS	
NEGATIVE	Likely not infected
POSITIVE	Have an active infection (confirms presence of viral RNA, not necessarily a viable virus)
False – negative	Up to 30% PCR samples due to: specimen sample, timing of sample in course of disease, lab handling, kit quality
False – positive	Rare, usually due to contamination

Point of Care Tests (POC)

Nucleic Acid Amplification Tests may be performed at POC, meaning that diagnostic testing can be done at time and place of patient care. Mobile test machines are small, portable and are advantageous for use in remote, outbreak and crisis situations. Typically, they process fewer tests in a specific timeframe.

Relevance for Travel Medicine

Molecular testing (frequently specified to be PCR) has become a requirement for entry into many countries. Negative results are required anywhere from 48 hours to 7 days prior to entry. Occasionally, another molecular test is required on arrival at certain airports. This requirement is sometimes challenging in countries where there are delayed times in testing or specimen processing, and it would be difficult to have the molecular test results in time for trip departure. Certain countries require a 7 to 14- day isolation period upon arrival.

In addition to the negative SARS-CoV-2 molecular test some countries require an accompanying medical letter. An updated link to see which countries are requiring this can be found here: https://www.iatatravelcentre.com/world.php.

Also, of note, the International Society of Travel Medicine, Global Travel Clinical Directory includes ISTM member sites where testing is available

https://www.istm.org/AF_CstmClinicDirectory.asp

Antigen Testing

Antigen detection tests are rapid immunoassays that detect the presence of SARS-CoV-2 proteins produced by replicating virus in respiratory secretions. They have been developed as laboratory-based tests as well as rapid diagnostic tests (RTDs) which can be used at point of care (POC). The tests are often easier to administer and results may return more rapidly than PCR testing. Collection methods include nasal swabs, throat swabs, and mouth swish and spit but nasopharyngeal swabs can be used as well.

Antigen tests appear to perform well in patients with high viral loads which can appear 1-3 days before symptoms appear and within the first 5-7 days after symptoms appear. False negatives are more common in early stages of infection.
Patients who present more than 7 days after onset of symptoms are more likely to have decreasing viral loads and this increases the likelihood of false negative results.

Advantages

- Less expensive
- Quicker results, usually under 1 hour
- Point of care tests results can be 15- 30 minutes
- Decrease in delays of covid-19 diagnosis

Limitations

- Sensitivity is variable and not as high as RT-PCR testing although specificity has been consistently reported as high (>97%).
- Higher chance of false negatives, particularly in earlier stages of infection before peak viral load may have been reached; therefore a negative result does not necessarily rule out infection and may need PCR to confirm.

According to the World Health Organization (WHO) there are approximately 100 companies currently developing or manufacturing rapid tests for SARS-CoV-2 antigen detection. In the future, rapid antigen testing may have a role in the practice of travel medicine.

Antibody Testing

The Covid-19/SARS-CoV-2 antibody tests detect the presence of antibodies, which are proteins made in response to the SARS-CoV-2 infection. The antibodies are detected in the blood of people who were previously infected with SARS-CoV-2, regardless of symptoms. These tests detect resolving or past SARS-CoV-2 virus

infection indirectly by measuring the person's humoral immune response to the virus.

- IgM antibodies, which happen early in an infection
- IgG antibodies, which are more likely to show up later

In SARS-CoV-2 infections, IgM and IgG antibodies can arise nearly simultaneously in serum within 2 to 3 weeks after illness onset. Thus, detection of IgM without IgG is uncommon. How long IgM and IgG antibodies remain detectable following infection is not known. It is also important to note that some persons do not develop detectable IgG or IgM antibodies following infection. Thus, the absence of detectable IgM or IgG antibodies does not necessarily rule out that they could have previously been infected. Recurrence of COVID-19 illness appears to be very uncommon, suggesting that the presence of antibodies could indicate at least short-term immunity to infection with SARS-CoV-2.

Types of Antibody Testing

1. **Binding antibody detection**: These tests use purified proteins of SARS-CoV-2, not live virus. Depending on the complexity of assays, these 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** - detect IgG and IgM, or total antibody in serum, plasma, whole blood, and/or saliva. An advantage of some point-of-care tests using whole blood is that they can be performed on blood samples obtained by finger stick rather than venepuncture.
    - **Laboratory tests -** use ELISA (enzyme-linked immunosorbent assay) or CIA (chemiluminescent immunoassay) methods for antibody detection, which for some assays may require trained laboratorians and specialized instruments. Based on the reagents, IgG, IgM, and IgA can be detected separately or combined as total antibody.
2. **Neutralizing antibody detection** - Neutralization tests determine the practical ability of antibodies to prevent infection of virus in vitro. The tests involve incubating serum or plasma with live virus followed by infection and incubation of cells.

Advantages

- These tests can help determine the proportion of a population previously infected with SARS-CoV-2 and provide information about populations that may be immune and potentially temporarily protected.
- In some instances, serologic test results may assist with identifying persons potentially infected with SARS-CoV-2 and determining who may qualify to donate blood that can be used to produce convalescent plasma as possible treatment for those who are seriously ill from SARS-CoV-2.

Limitations

- Do not replace direct detection methods in diagnosing active SARS-CoV-2 infection. Because antibody tests do not detect active viral shedding, they cannot detect if an individual is infectious.
- Some tests may exhibit cross-reactivity with other coronaviruses, such as those that cause the common cold. This could result in false-positive test results. Some persons may not develop detectable antibodies after coronavirus infection. In others, it is possible that antibody levels could wane over time to undetectable levels. IgM and IgG antibodies may take 1 to 3 weeks to develop after infection. Thus, serologic test results do not indicate with certainty the presence or absence of current or previous infection with SARS-CoV-2.
- The reliability of antibody COVID-19 tests is uncertain due to the limited evidence base.
- Serology tests can also fail to detect COVID-19 if testing is performed in the acute phase of the infection prior to the development of detectable antibodies.

Relevance for Travel Medicine

Should travel medicine clinics become places that offer testing prior to travel? (Wilson and Chen 2020). Will travel medicine providers and clinics be called on to provide such documentation such as an "immunity certificate" similar to the yellow fever vaccination certificate (Chen et al 2020)? Should the certificate require an expiry date for validity? A potential "immunity certificate" requires a global standard. For this idea to be enforced, more research is needed to assure the threshold of antibody titres necessary for protection and the durability of immunity. Antibody tests need to comply with international quality standards, be

resistant to fraud including documentation, and have an exemption method available in certain circumstances. Many questions are yet to be answered.

Covid19 Testing Considerations for The Travel Health Provider/Travel Clinic

As more countries require COVID-19 testing before and/or after travel it is important for clinicians and clinics to consider the following prior to offering Covid 19 screening tests:

1. What Covid19 PCR tests are available to your practice?
2. Will you collect samples at your clinic or refer out?
3. What is the lab cost to the patient? Can they use health insurance?
4. How quickly does the lab produce Covid19 results? A negative Covid19 PCR test is often required within 72 hours prior to departure by certain countries or airlines.
5. Can you accommodate the 24-48 hour result return needed for travelers?
6. How will you get the results and a formal letter certifying the results (if required) to the travel patient? Printed or electronic?
7. Does the lab result say "PCR" on the print out? If not it could be rejected at customs.
8. What happens to travel plans when the travel patient tests positive for Covid19?
9. Are you able to provide follow-up counseling and management for those testing positive?
10. What happens to the Covid19 results when the flight is cancelled or delayed departure?

RESOURCES

https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html

https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html

https://www.travax.com/library/coronaviruses/events/coronavirus-disease-2019

https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2

https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html

https://www.fda.gov/media/136525/download

https://www.publichealthontario.ca/-/media/documents/ncov/evidence-brief/2020/08/eb-covid-19-pcr-testing-alternative-collection-testing.pdf?la=en

https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html

https://www.tga.gov.au/covid-19-testing-australia-information-health-professionals

https://www.ecdc.europa.eu/en/covid-19/latest-evidence/diagnostic-testing

https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics

https://www.travax.com/library/covid-19-fit-to-travel-certificate

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013652/full

https://academic.oup.com/jtm/article/27/5/taaa108/5863926?searchresult=1

https://academic.oup.com/jtm/article/27/5/taaa085/5847845

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https://academic.oup.com/jid/article/222/5/715/5862418

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https://www.gov.uk/government/publications/coronavirus-covid-19-antibody-tests/coronavirus-covid-19-antibody-tests

https://www.cdc.gov/sars-cov-2(covid-19)factsheet:guidance-proposeduseof point-of-care(poc)testingplatformsforsars-cov-2(covid-19)

https://www.nps.org.au/australian-prescriber/articles/testing-for-covid-19

Kovoor JG, Tivey DR, Williamson P, et al. Screening and Testing for COVID -19 Before Surgery. ANZ journal of surgery. 2020.

Carpenter CR, Mudd PA, West CP, Wilber E, Wilber ST, Zehtabchi S. Diagnosing COVID-19 in the Emergency Department: A Scoping Review of Clinical Examinations, Laboratory Tests, Imaging Accuracy, and Biases. Academic Emergency Medicine. 2020;27(8):653-670.

Oran DP,Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection.Annals of Internal Medicine. 2020;173:362-367

Podcast on testing:

https://www.nps.org.au/australian-prescriber/podcast/episode-92-testing-for-covid19