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COVID-19 Testing

This month's newsletter focuses on testing for COVID-19 infection, and summarizes information related to available test types, collection techniques, and appropriate testing populations. Data and guidance in these topics are emerging rapidly as new technologies develop and testing capacities expand.

Molecular Testing

SARS-CoV-2 tests are broadly classified in one of two categories: molecular tests and antibody tests. Molecular tests are based on polymerase chain reaction (PCR) technology. The Chinese developed the first PCR test shortly after discovery of the SARS-CoV-2 virus. The Food and Drug Administration (FDA) provided Emergency Use Authorization for PCR tests in the United States in February 2020. Published guidance related to testing for COVID-19 infection through April is predominantly related to molecular tests.

PCR-based tests identify the presence of viral nucleic acid (dead or alive) by amplifying RNA in a swab from the respiratory tract (usually from either from the nasopharynx (NP) or oropharynx (OP)).

NP vs OP Swabs:

Limited data exist to support preferential use of NP swabs or OP swabs. Pre-print, non-peer reviewed data suggests NP swabs have a higher sensitivity than OP swabs in patients with active COVID-19 infection.[1] However, false negatives remain a problem with both sample types, and lack of a gold standard makes interpretation difficult.[2] The Centers for Disease Control and Prevention (CDC) initially recommended NP swabs as the primary sample for PCR-based COVID-19 tests. On April 2, the CDC revised their guidance to allow OP swabs as an acceptable alternative.[3] However, NP specimen remain the preferred choice for swab-based SARS-CoV-2 testing per CDC.

The rate of false negatives identified in recent studies may reflect poor sampling quality. In general, all PCR-based tests have a high level of sensitivity and specificity when testing a known amount of virus, but testing accuracy decreases when sample quality is poor.

Technique and Training

Proper technique for NP and OP swabs should elicit a tearing and gag reflex, respectively. The procedure is difficult for both patients and clinicians, and the resulting variability in swabbing technique translates directly to variability in testing performance.[4] In other words, if no viral RNA is collected on the swab due to poor sampling, a PCR-based platform will result negative regardless of the presence of true infection.

Dedicated teams that perform upper respiratory tract sampling can improve the quality of sample collection for COVID-19 testing. Trained personnel reduce inter-operator variability and also reduce the likelihood of poor sampling technique. For this reason, we recommend implementing a dedicated 'sampling team' if local personnel resources allow. At a minimum, educational material related to NP or OP sampling should be distributed to health care workers and made easily available. The *New England Journal of Medicine* produced a video that demonstrates proper nasopharyngeal swabbing technique that may be used.[5]

Utility of Re-Testing:

The utility of re-testing patients after a negative result is unknown. Re-testing may be appropriate in cases of a clinical syndrome that is *highly* suspicious for COVID-19 infection without a reasonable alternative diagnosis, or in cases where the sample quality is in question. However, wide-spread re-testing leads to distrust of test results, even when the results represent the true absence of disease. Re-testing should not be performed routinely after a negative result or in cases without a consistent clinical syndrome.

Testing Asymptomatic Persons

PCR-based tests for COVID-19 are unable to reliably identify SARS-COV-2 when testing pre-symptomatic or asymptomatic patients. Thus, as a general rule, testing for COVID-19 disease should be done when a patient presents with symptoms consistent with infection. If testing is done in the absence of symptoms, a positive PCR test could mean either a) dead viral RNA is present following recovery b) colonization without infection or c) the patient is in the pre-symptomatic stage of infection.[6] ***We recommend against routinely screening asymptomatic patients because this information is not actionable.***

Testing asymptomatic persons routinely may lead to a false sense of security, as these persons may develop symptoms a few hours or days later.

At present, there is insufficient evidence to recommend asymptomatic screening in special populations (i.e. immunosuppressed) but this may change as data from ongoing studies becomes available.

Point-of-Care Tests

The FDA also recently authorized multiple point-of-care (POC) PCR tests for COVID-19. Routine PCR tests typically have a turn-around time between 24-72 hours depending on the equipment available, and dozens of samples may be run simultaneously. In contrast, POC tests automate several steps to return results within minutes to an hour.[7] However, POC testing is limited in capacity; available equipment typically runs only a few samples simultaneously. Thus, POC testing should be limited to clinical scenarios in which an early result is actionable. Examples include settings like nursing homes or settings where a negative test may preserve inpatient COVID-19 ward bed utilization or personal protective equipment (PPE). As capacity for POC testing expands, rapid results will also impact antibiotic stewardship. Early experience indicates that over 50% of hospitalized patients are initiated on empiric IV antibiotic therapy[8]. Early COVID-19 results may discourage inappropriate antibiotic use.

Saliva sample testing is the newest innovation in PCR-based testing. Saliva sample tests are currently only available Rutgers Clinical Laboratory after the FDA provided emergency use authorization on April 13.[9] A saliva sampling technique reduces the invasive nature of NP or OP swabbing and may help with scaling testing efforts as it reduces the reliance on testing materials (i.e. swabs) that have been in short supply.

Antibody Tests

The next phase of testing for the COVID-19 pandemic will include serologic antibody tests. Antibody tests identify the presence of immunoglobulins (IgM and IgG) in a sample. IgM is a large antibody produced early after response to an antigen (i.e. virus), and IgG is the delayed antibody response that typically confers immunity to a pathogen.

The FDA provided regulatory relief for COVID-19 serologic test development in March 2020.[10] While the CDC serologic test is still under development,[11] various private and public institutions are working to create accurate antibody tests. How these tests will perform

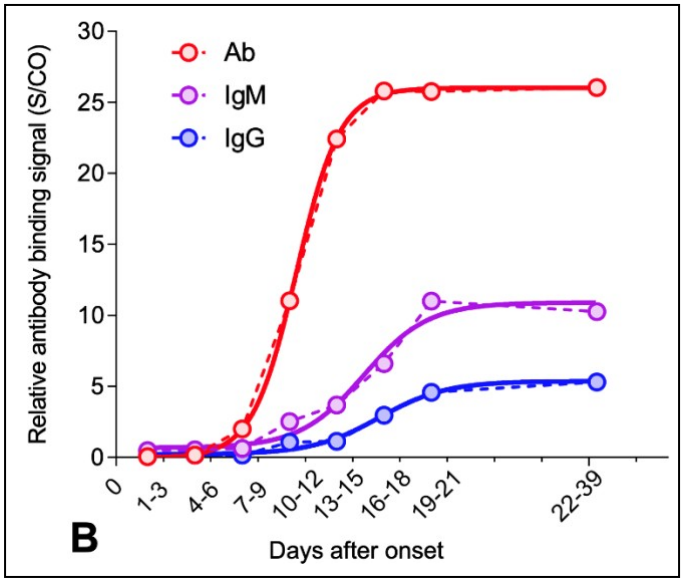

Fig 1. Days to antibody response for SARS-CoV-2[12]

remains unknown. For example, the role of cross-reacting antibody from prior infection with other human coronaviruses is an unresolved issue and further data is needed to understand the accuracy of identifying prior infection or long-lasting immune response.

No antibody tests can identify acute infections because immunoglobulins appear days into the course of disease.[12] Instead, antibody tests aim to answer two important epidemiologic questions: a) how many people have been exposed and b) who is immune?

Earlier this month, the National Institute of Health (NIH) began enrolling 10,000 healthy individuals for antibody testing to determine the estimated prevalence of COVID-19 in the population.[13] Prevalence of disease and subsequent immunity will have significant implications in identifying herd immunity and relaxing policies related to the widespread stay-at-home orders. In addition, personnel in essential jobs (or eventually non-essential) could be issue return-to-work 'passports' if a reliable antibody test is developed to identify immunity. However, until we know the validated characteristics of serologic testing and details of the long-term immune response, the full role of antibody testing is unknown.

Finally, antibody tests will be useful in identifying appropriate donors for convalescent plasma therapy, which transfuses immunoglobulins from a donor with a known immune response to a patient with an active COVID-19 infection. Convalescent plasma therapy is under study in numerous clinical trials.

Conclusion

A few key principles are important:
1) PCR testing identifies COVID-19 infection in patients *with* symptoms consistent with active infection.
2) False negative tests are more likely to be due to poor sample collection or testing asymptomatic or presymptomatic persons, rather than test performance. Repeat testing should be performed only if clinically indicated.
2) POC tests provide immediately actionable information to improve clinical care and limit resource waste.
3) Personnel who obtain NP or OP swabs should have training for sampling and use of PPE.
4) The role of antibody tests is currently unknown as we still do not have reliable data on their sensitivity and specificity.

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