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DUKE INFECTION CONTROL OUTREACH NETWORK

Isolation and Quarantine using the "10+1" Rule: Does the CDC's Math Add Up?

This newsletter will focus on the CDC recommendations for duration of isolation following diagnosis with COVID-19 released July 17, 2020, with a particular focus on guidance for discontinuing isolation in hospitalized patients. The full set of recommendations for "discontinuing transmission-based precautions" can be found at https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html.

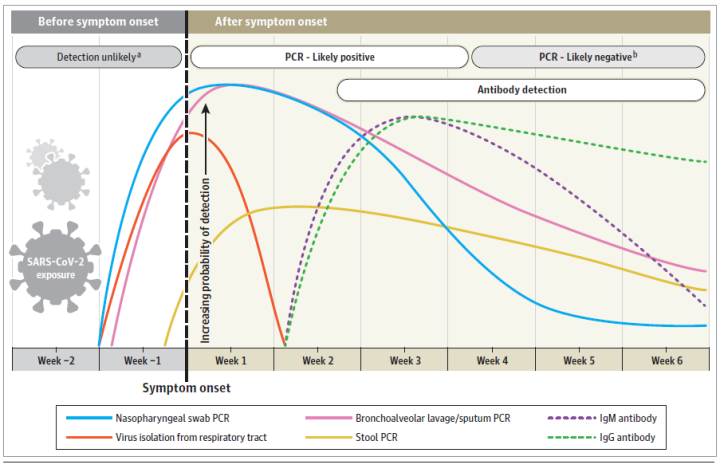
The content of this newsletter represents a summary of current information as of July 30, 2020, and is subject to change.

Before beginning the discussion, it's important to understand the difference between three types of tests for COVID-19: PCR, antibody tests, and viral culture.

1. Reverse transcriptase-PCR (RT-PCR) is the most common test currently used for diagnosis of COVID-19. The test is designed to detect the presence of specific parts of the SARS-CoV-2 virus. It does not distinguish between live virus or dead virus; it simply notes whether viral parts are present or not.
2. Antibody tests detect whether the immune system has responded to the virus. These tests typically identify either IgM (part of the body's acute response to infection) or IgG antibodies (part of the body's long term memory of the infection).
3. Viral cultures are performed in specialized laboratories in which the specimen is added to cells to identify a "cytopathic" effect (i.e., can the virus kill the cells).

A figure published by Sethuraman et al in JAMA[1] well summarizes the dynamics of results of these tests related to time and symptom onset (Figure; note that the **blue** line represents nasopharyngeal PCR test results and the **red** line represents viral culture results).

Figure. Test result dynamics related to time of diagnosis of COVID-19[1]



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.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Evaluate the Data - How long can someone with COVID-19 transmit infection to someone else?

Transmission can occur before symptoms begin. In fact, the highest amount of viral shedding (which corresponds with the highest period of infectiousness) is in the 24 hours prior to symptom onset and the first 24-48 hours after symptoms onset.[1] Patients with severe illness in the ICU can shed living virus (and are thus contagious) in respiratory specimens for a week and half or occasionally even longer.[2] For most with mild-moderate illness, however, the infectious period is less than 8 days after symptom onset.[1] Several research publications support this statement:

- 9 patients underwent extensive sampling of sputum, blood, and stool over several weeks after diagnosis of COVID-19. While PCR tests remained positive for several weeks, no virus could be detected with viral cultures after day 8.[3]
- In a similar study of 12 patients, detectable virus could not be detected after 9 days.[4]
- CDC reviewed data from 14 patients and could not detect viable virus after 9 days.[5]
- Bullard et al evaluated 90 specimens from patients with COVID-19 and noted that no

samples obtained after day 7 since symptom onset had viable virus.[6]

- Though still in pre-print, Cevik et al. developed a living systematic review and meta-analysis of 79 studies on SARS-CoV-2.[7] The median duration of PCR positivity was 17 days in the upper respiratory tract, 15 days in the lower respiratory tract, 17 days in stool, and 17 days in serum. The maximum durations encountered were 83, 59, 41, and 60 days, respectively. Despite the long durations of viral shedding observed, no studies cultured live virus after 9 days, despite high viral loads.
- However, van Kampen and colleagues evaluated 129 patients, the vast majority of whom were severely ill in ICU (and requiring mechanical ventilation) or immunocompromised.[2] In their cohort analysis, longer duration of viral culture positivity was observed. One patient had culture isolated on day 20; even among this group, the likelihood of viable virus detection was <5% after 15 days.
- To date, studies have not demonstrated transmission of COVID-19 from contact with urine, stool, or blood.

How long can someone with COVID-19 have a positive PCR test? As noted above, PCR tests often remain positive for 2 to 3 weeks after symptom onset,[1,8] but some people can continue to have intermittent positive PCR tests for several months.[7] In other words, a positive PCR test does not confirm that the person remains infectious to others. This conclusion was confirmed in a large study conducted by the Korean CDC; more than 700 close contacts of individuals with prolonged (and recurrent) positive PCR tests were evaluated. None of these close contacts contracted COVID-19 from the study patient.[9] This phenomenon of ongoing shedding of viral particles (which can lead to positive PCR tests) but no longer being contagious is commonly seen in viral infections.

What is the current guidance for return to work following COVID-19 infection? The CDC recommends one of two strategies for safely returning to work:[10]

1. The symptom/time-based strategy (or the "10+1" strategy) – a person with COVID-19 must remain in isolation for a minimum of 10 days after onset of symptoms, at least 1 day since resolution of fever in the absence of fever-reducing medications, and improvement in symptoms. Of note, loss of sense of smell or taste is not included in the list of symptoms that must be resolved. For severely ill patients in the intensive care unit or severely immunocompromised patients, the time is extended to 20 days (the "20+1" strategy).
    a. While the CDC leads the designation of "severely immunocompromised" to treating clinicians, they provide several examples, including chemotherapy for cancer, untreated HIV infection with CD4 T lymphocyte count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days.
2. The test-based strategy – a person with COVID-19 must remain in isolation until he or she has had two consecutive negative PCR tests taken at least 24 hours apart. However, this strategy is now discouraged in light of evidence summarized above re: prolonged positive tests and need for resource conservation.
3. For asymptomatic persons or those who present with only symptoms of anosmia or dysgeusia, isolation precautions can be discontinued 10 days for non-immunocompromised patients and 20 days for severely immunocompromised patients *after the date of their first positive RT-PCR test for SARS-CoV-2.*

Is there a "test of cure" for COVID-19? No. All currently available testing strategies have limitations. At this point, no specific test is available to definitively confirm that someone with COVID-19 is no longer infectious. As noted above, PCR tests remain positive for weeks even though the person is no longer infectious. Viral cultures are used in research studies but are not feasible for routine use. In fact, even positive viral cultures are not absolutely indicative of infectiousness. Currently, antibody tests are not sufficiently accurate to demonstrate that a person is no longer infectious.

Should I repeat testing for COVID-19 when patients with documented prior COVID-19 present with compatible signs or symptoms after a certain time has elapsed? Currently there have been no documented cases of SARS-CoV-2 reinfection within a 6-month window.[5] Markers for immunity have not been defined at this time.[5] As such, the optimal timeframe to consider re-testing for COVID-19 after having a documented infection is not known. Repeat testing prior to 90 days after a positive test, however, is not recommended based on the cases of prolonged shedding.

Take Home Points:

1. Current testing strategies for COVID-19 are limited. No "test of cure" exists.
2. For the majority of patients, the 10+1 approach for removing isolation ensures a sufficient amount of time has passed to ensure that patients are no longer infectious to others.
3. For severely ill patients in the ICU and severely immunocompromised patients, the 20+1 approach is recommended.
4. Repeat testing for COVID-19 prior to 90 days after a positive test is unlikely to be helpful and a positive test in this setting should be interpreted as non-infectious viral shedding based on available data.
5. We agree with the CDC's current recommendations for removal of isolation. In other words, the CDC's math adds up!
6. Regardless of what strategy is used to guide "return to work" policies, everyone must continue to practice the three basic prevention strategies for COVID-19: social distancing, universal use of face masks, and frequent hand washing.

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