State of the Pandemic Commentary

The perplexing problem of persistently PCR-positive personnel

David K. Henderson MD1, David J. Weber MD, MPH2, Hilary Babcock MD, MPH3, Mary K. Hayden MD4, Anurag Malani MD5, Sharon B. Wright MD, MPH6, A. Rekha Murthy MD7, Judith Guzman-Cottrill DO8, Sarah Haessler MD9, Clare Rock MD, MS10, Trevor Van Schooneveld MD11, Latania Logan MD, MSPH4 and Corey Forde MD, DM12 for the SHEA Board of Trustees

1National Institutes of Health, Bethesda, MD, 2University of North Carolina at Chapel Hill, Chapel Hill, NC, 3Washington University School of Medicine, St. Louis, MO, 4Rush University Medical Center, Chicago, IL, 5St. Joseph Mercy Health System, Ann Arbor, MI, 6Beth Israel Deaconess Medical Center, Boston, MA, 7Cedars-Sinai Health System, Los Angeles, CA, 8Oregon Health and Science University, Portland, OR, 9Baystate Health, Springfield, MA, 10Johns Hopkins University School of Medicine, Baltimore, MD, 11University of Nebraska Medical Center, Omaha, NE and 12Queen Elizabeth Hospital, Barbados

Early in the coronavirus disease 2019 (COVID-19) pandemic, the Centers for Disease Control and Prevention (CDC) published return-to-work criteria for healthcare personnel who had recovered from severe acute respiratory coronavirus virus 2 (SARS-CoV-2) infection. These criteria were most recently updated on April 3, 2020. The CDC has endorsed 2 different approaches to allow staff to return to work: a symptom or time-based strategy and a test-based strategy. Many institutions initially adopted the test-based strategy, in part because CDC initially recommended it as the preferred option (but no longer does so) and, in part, because it seemed the more definitive or conservative of the 2 CDC options.

As a result of using the test-based strategy, many institutions now have significant numbers of staff whose nasopharyngeal swabs remain RT-PCR positive for COVID-19, despite the fact that they have recovered from their episodes of illnesses and have been asymptomatic for weeks or, in some instances, months. These staff effectively remain in limbo; they feel well but have persistently asymptomatic for weeks or, in some instances, months. These staff have recovered from their episodes of illnesses and have been consistently PCR positive for COVID-19, despite the fact that they no longer culture positive for HCP who suffered severe disease (eg, with hospitalization, who recovered from the disease and who remain persistently positive by PCR, no longer harbor cultivable virus 10 days after symptom onset. Notably, these studies have assessed relatively healthy populations who developed COVID-19 infection but were not severely ill. We do not yet know whether the 10-day cutoff is appropriate for immunocompromised healthcare personnel (HCP) who develop COVID-19, but it clearly does not apply for HCP who suffered severe disease (eg, with hospitalization and/or prolonged intubation). Such individuals will have to be managed on a case-by-case basis until more data become available.

In the Canadian study cited above, the authors retrospectively evaluated 90 previously identified positive samples by both PCR and viral culture in Vero-cells. They compared both the number of days from onset of symptoms to the day the test was performed as well as the cycle thresholds of PCR positivity to recovery of viable virus in tissue culture. In no instance were the investigators able to recover virus if >8 days had elapsed from the onset of symptoms, despite the persistence of positive PCR tests. In addition, if the cycle threshold for the sample was >24, they could not recover virus in tissue culture.

Relying on a cycle threshold limit as a return-to-work criterion has some limitations. Cycle thresholds are not directly comparable from site to site or even from test to test. In addition to the number of copies of RNA in a given sample, cycle thresholds depend on a variety of factors, including the specific gene target(s) and the number of gene targets chosen for the assay, the platform used, variability in reagents used from site to site, and more. Optimally, to use the cycle threshold, an institution would validate the procedure in its own laboratory, demonstrating, as the study from Manitoba did, that samples above a certain cycle threshold did not contain cultivable virus. The challenge in doing such a validation is that you need a Biosafety Level 3 laboratory to do the tissue culture work, and many, if not most centers will not have access to those resources. Additionally, if any aspects of the PCR assay change, revalidation is appropriate. Another challenge in
using cycle thresholds is that not all diagnostic nucleic acid amplification assays use RT-PCR, so cycle thresholds are not available, and some rapid instruments use PCR but do not yield cycle threshold values. Finally, regarding the standardization of testing, if the clinical laboratory community developed universal standards for SARS-CoV-2 similar to the World Health Organization’s standards for hepatitis B and C, a multicenter study of all currently manufactured SARS-CoV-2 nucleic acid amplification tests could be designed to correlate the cycle threshold values on each platform for patients who have positive and negative viral cultures. Clinical laboratories could then calibrate their assays using the universal standard, thus allowing laboratories to estimate virus viability from the cycle threshold with some certainty. To assure proficiency and reliability, the College of American Pathologists could develop proficiency panels for labs for quality assurance. This standardization scenario represents a desired future state; for the time being, we will have to rely on other strategies.

Conversely, relying on time from symptom development as a return-to-work criterion is also fraught with a few challenges. The onset of COVID-19 may be insidious and may be difficult for an individual provider to pin down. Recall bias may affect the provider’s ability to be precise about the onset of symptoms. As asymptomatic provider surveillance testing expands, protocols will have to be developed to manage asymptotically infected individuals.

So how do we approach these issues, balancing the safety of patients and staff with the need to avoid having staff unnecessarily sidelined staff who could be contributing to an important pandemic response when we need them the most? Given the data cited here, the test-based strategy appears likely to delay HCP return to work longer than is necessary for the protection of patients and coworkers around them, especially at a time when most facilities are recommending universal masking of HCP. For HCP who had relatively mildly symptomatic cases (ie, managed as an outpatient), a symptom-based strategy as recommended by the CDC appears appropriate based on the same data. For asymptomatic cases, questions remain about relative transmission risk and possibly about timing of infection related to testing. The CDC strategy of returning those HCP to work 10 days after their positive test seems reasonable. Staff who developed more severe symptoms by the CDC appears appropriate based on the same data. For asymptomatic provider surveillance testing expands, protocols will have to be developed to manage asymptotically infected individuals.

Thus, based on these data, one approach to managing recovered HCP who work primarily with patient populations at high risk of complications would be to use the “time from symptom development” strategy plus “sustained improvement in respiratory symptoms” and add a safety factor (eg, adding an additional week or 2) to the time from symptom onset, or perhaps adding 2 weeks from test positivity for asymptomatic staff detected as positive. Institutions can decide how much of a cushion is appropriate, based on local factors, patient populations, etc. In addition, the use of source-control masking should be required for such individuals.

The dynamic nature of the pandemic necessitates that the healthcare epidemiology community continue to closely monitor the data as it emerges and to adjust policies and procedures, both to maximize patient and staff safety, while preserving the labor force that is essential to our ultimate success.

Acknowledgments.

Financial support. No financial support was provided relevant to this article.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

*After this manuscript was submitted and accepted, the Centers for Disease Control and Prevention modified their recommended “return to work” criteria to state that a test-based strategy is no longer recommended and to advocate strategies basically consistent with the suggestions outlined in this paper (See https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html).

References


