Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Should qualitative RT-PCR be used to determine release from isolation of COVID-19 patients?

Dear Editor,

COVID-19 patients can continue to shed viral RNA well beyond clinical recovery.[1-4] Problematically, while qualitative RT-PCR, the most commonly used diagnostic test for COVID-19, identifies SARS-CoV-2 virus genome, it fails to distinguish between viable infectious virus and noninfectious viral particles. Persistently positive RT-PCR following clinical recovery does not necessarily indicate infectiousness, yet such testing is still being used as a surrogate marker of infectivity.

Healthcare providers and public health officials are asked to provide guidance for the discontinuation of isolation precautions in persons with suspected or confirmed COVID-19. For symptomatic persons with COVID-19, the current guidance from the United States Centers for Disease Control and Prevention suggests either a symptom-based or a test-based strategy. The symptom-based strategy—in which isolation can be discontinued after 3 days have passed since clinical recovery and 10 days since symptoms first appeared—can be used in non-immunocompromised patients and leads to most cases being released within two weeks.[5] However, the test-based strategy—in which isolation can be discontinued when two consecutive samples of respiratory specimens, collected ≥24 h apart, are negative by RT-PCR—is being used "out of an abundance of caution" for recovered persons for whom there is low tolerance for infectious risk, and this is presenting a dilemma.[6]

In fact, in the absence of legal guidance to the contrary, the administrators of some healthcare and congregate living facilities are requiring the test-based strategy as a condition for an employee to return to the workplace, for a patient to be transferred to another healthcare facility, or for isolation to be discontinued in the recovered patient.[7] Consequently, many ostensibly well COVID-19 patients, including mothers of newborns, have been in prolonged isolation for six or more weeks beyond recovery.[7] Such persons also include healthcare providers who may pose a risk of transmitting infection to patients who are at high risk for complications and to other healthcare workers. Another high-stakes scenario is congregate living facilities (e.g., correctional/detention facilities, homeless shelters, retirement communities, ships) where there might be increased risk of transmission, morbidity and mortality. Not surprisingly, this results in undue hardship for affected persons and their families, as well as for employers.

The concern in relying solely on non-test-based criteria is that they may not prevent all instances of secondary transmission—including in immunocompromised patients.[5] By contrast, a *qualitative* PCR test-based strategy may unnecessarily prolong the need for isolation. This is suggested by an emerging understanding of the clinical, microbiological, and serological aspects of the natural history of COVID-19, as well as by the results of a recent epidemiological study. At around 18 days after onset of illness, 50% of patients are still positive by RT-PCR of nasopharyngeal swab, 5% may still be positive by day 33, and some cases have been reported to be positive more than eight weeks after illness onset.[3, 6] Yet the median time from illness onset to clinical recovery for mild cases is only 14–15 days. Using total antibody enzyme-linked immunosorbent assays (ELISAs) that detect antibodies to the receptor-binding domain of the spike protein, the median seroconversion time of 173 patients with SARS-CoV-2 infection was 11 days after illness onset, and by day 14 almost 90% of patients had seroconverted, and by day 39 all had detectable antibodies.[8]

The detection of SARS-CoV-2 using cell culture may not have utility in clinical practice given its low sensitivity and long turnaround time. However, it is a useful proxy for infectious virus shedding that can serve to evaluate other potential surrogate markers such as viral RNA load (using quantitative RT-PCR) and serology testing (using serum neutralization antibody titers). The longest time from symptom onset to isolating SARS-CoV-2 has been 18 days, and the lowest viral RNA load at the time that SARS-CoV-2 could no longer be isolated has ranged from ≥33–35 cycle threshold (<6.51 Log10 RNA copies/mL).[1, 5]

Perhaps the most persuasive data, published to date, of the lack of association between post-recovery viral RNA shedding and infectiousness are from the contact investigations that the Korea Centers for Disease Control and Prevention carried out on 285 COVID-19 patients who had met symptom-based and test-based criteria for release from isolation.[2] Of these, 107 (37.5%) were re-tested because of symptom onset, and 170 (59.6%) were re-tested for screening purposes—fregardless of symptoms. Of the 284 persons who were checked for symptoms, 126 (44.7%) were symptomatic. Contact tracing of these 285 "re-positive" cases identified 790 contacts. After a minimum 14-day monitoring of these contacts, 27 of the contacts were found to be positive, of which 24 were previously confirmed, and the remaining 3 were newly-confirmed cases with a history of an exposure to another confirmed case in their family or religious community. The virus could not be isolated from cell culture in two of these cases, and was not possible in the remaining one because the PCR result was indeterminate. Furthermore, neutralizing antibody production, suggestive of acquired protective immunity, was detected in the first serum sample of all "re-positive" cases.

For those with prolonged shedding of viral RNA, requiring conversion of qualitative RT-PCR for release from isolation has poten-

Abbreviations: COVID-19, coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; mL, milliliter; RNA, ribonucleic acid; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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tial economic, physical, psychological, and social detriments. For many, there is a loss of income which disproportionately affects the poorest and most vulnerable whose employment often does not include sick leave. Psychosocially, a prolonged period of physical isolation can lead to loss of connection and perceived social isolation ("loneliness") which is associated with suicidal behavior and psychotic disorders among persons with severe mental illness, and is linked to depression in those without a preexisting psychiatric disorder.[9] Furthermore, social isolation has been associated with higher mortality in general ("all-cause mortality"), including cancer and cardiovascular disease.[10] In COVID-19 patients with prolonged isolation, these issues are even more compounded by their reduced access to medical care. Further research into more accurate test-based criteria for determining release from isolation is much needed—potentially ones using *quantitative* RT-PCR and/or *quantitative* immunoassays, with cut-off values that have been validated to correlate with lack of infectivity.

Authors' contributions

CMPV conceived the manuscript; all authors performed literature search; KK wrote the first draft of the manuscript; CMPV revised it; all authors reviewed it.

Declaration of Competing Interest

None

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References

1. Liu WD, Chang SY, Wang JT, Tsai MJ, Hung CC, Hsu CL, et al. Prolonged virus shedding even after seroconversion in a patient with COVID-19. *J Infect [Internet]* 2020 https://doi.org/. doi:10.1016/j.jinf.2020.03.063.
2. Korea Centers for Disease Control and Prevention Division of Risk Assessment and International Cooperation. Findings from investigation and analysis of re-positive cases. 2020. Available from: https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030.
3. National Centre for Infectious Diseases; Chapter of Infectious Disease Physicians of the Academy of Medicine of Singapore. Period of Infectivity to Inform Strategies for De-isolation for COVID-19 Patients. 2020. Available from: https://www.ams.edu.sg/view-pdf.aspx?file=media%5c5556_fi_331.pdf&ofile=Period+of+Infectivity+Position+Statement+(final)+23-5-20+(logos).pdf.
4. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. *Clin Infect Dis [Internet]* 2020 ciaa638. https://doi.org/. doi:10.1093/cid/ciaa638.
5. Centers of Disease Control and Prevention National Center for Immunization and Respiratory Diseases Division of Viral Diseases. Symptom-Based Strategy to Discontinue Isolation for Persons with COVID-19: decision Memo. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html.
6. Woodruff A, Walsh K, Knight D. COVID-19 Follow up Testing. *J Infect [Internet]* 2020 S0163-4453(20)30289-9. Available from: https://doi.org/. doi:10.1016/j.jinf.2020.05.012.
7. Branswell H. Positive Covid-19 tests kept a mom and baby apart for 55 days. Experts see it as a bigger testing problem. *STAT [Internet]* 2020. Available from: https://www.statnews.com/2020/06/08/viral-shedding-covid19-pcr-montreal-baby/?fbclid=IwAR18Gmu3pnl42lO48d9mvSRRsiL98ZE0NERjg7rd61GdxKAEYqAdLZprXbI.
8. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis [Internet]* 2020 Mar 28 cia344. Available from: https://doi.org/. doi:10.1093/cid/ciaa344.
9. Wang J, Lloyd-Evans B, Giacco D, Forsyth R, Nebo C, Mann F, et al. Social isolation in mental health: a conceptual and methodological review. *Soc Psychiatry Psychiatr Epidemiol [Internet]* 2017;**52**(12):1451–61 Available from: https://doi.org/. doi:10.1007/s00127-017-1446-1.
10. Alcaraz KI, Eddens KS, Blase JL, Diver WR, Patel AV, Teras LR, et al. Social Isolation and Mortality in US Black and White Men and Women. *Am J Epidemiol [Internet]* 2019;**188**(1):102–9 https://doi.org/. doi:10.1093/aje/kwy231.

Karl Krupp
Department of Health Promotion Sciences, Mel & Enid Zuckerman College of Public Health, University of Arizona, 1295N. Martin Ave.; Drachman Hall A206X; PO Box 245209, Tucson, AZ 85724, USA

Purnima Madhivanan
Department of Health Promotion Sciences, Mel & Enid Zuckerman College of Public Health, University of Arizona, 1295N. Martin Ave.; Drachman Hall A206X; PO Box 245209, Tucson, AZ 85724, USA
Division of Infectious Diseases, College of Medicine, University of Arizona, Tucson, Arizona, USA

Carlos M. Perez-Velez*
Division of Infectious Diseases, College of Medicine, University of Arizona, Tucson, Arizona, USA
Pima County Health Department, 3950 South Country Club Road, Suite 100, Tucson, Arizona 84714, USA

*Corresponding author at: Pima County Health Department, 3950 South Country Club Road, Suite 100; Tucson Arizona 85714, USA.
E-mail addresses: KKrupp@arizona.edu (K. Krupp), PMadhivanan@arizona.edu (P. Madhivanan), CMPerezVelez@gmail.com (C.M. Perez-Velez)