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April 8, 2020

Kelvin Droegemeier, Ph.D.
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1650 Pennsylvania Avenue
Washington, DC 20504

Dear Dr. Droegemeier:

Attached please find a rapid expert consultation in response to your request concerning 1) the duration of viral shedding by stage of infection, clinical signs and symptoms and patient attributes; 2) the levels and duration of antibody response; and related resistance to illness; and 3) optimal duration of isolation of cases.

Members of the National Academies' Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats who were instrumental in preparing this response include Peter Daszak, EcoHealth Alliance; Diane E. Griffin, Johns Hopkins Bloomberg School of Public Health; Kent E. Kester, Sanofi Pasteur; and Mark S. Smolinski, Ending Pandemics.

This document stresses what is known and what are the most salient questions yet to be answered to guide critical decisions related to duration of isolation of infected patients, potential effectiveness of vaccine and when we can be confident that previously infected patients are resistant to re-infection.

My colleagues and I hope this input is helpful to you as you continue to guide the nation's response in this ongoing public health crisis.

Respectfully,

Harvey V. Fineberg, M.D., Ph.D.
Chair
Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

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April 8, 2020

This rapid expert consultation responds to your request concerning 1) the duration of viral shedding by stage of infection, clinical signs and symptoms and patient attributes; 2) the levels and duration of antibody response and related resistance to illness; and 3) optimal duration of isolation of cases.

Our intent is to answer three questions in response to each issue:

- What is the relevant scientific evidence and state of current scientific knowledge?
- Who is doing the best work in the area and what new results can we anticipate?
- Gaps in knowledge: What investigations should be initiated or extended to provide a more complete answer?

Shedding of infectious virus from the respiratory tract tends to be highest early in disease. This is followed by a prolonged period of viral RNA shedding, but the extent to which this represents infectious virus is uncertain (1). In addition, the role of shedding from the gastrointestinal tract in transmission is unclear. Antibody responses begin to appear over a period of days to weeks after infection. Studies of SARS and MERS survivors suggest that antibody responses for SARS-CoV-1 and MERS-CoV are not durable (2-4). Further investigation is needed to understand the duration of protective immunity for SARS-CoV-2. The groups referenced in this rapid expert consultation are continuing to produce work in these areas. We anticipate that additional studies based on cases coming out of the United States and Europe will provide further information on these critical topics.

1) Duration of viral shedding by stage of infection, clinical signs and symptoms, patient attributes

Viral shedding has been assessed and detected by culture, but most often by RT-PCR for viral RNA (5). RNA can be detected from infectious virus or from remnants of virus that is no longer infectious. In a patient recovering from illness who was previously PCR positive, at least two sequential negative tests for viral RNA is a reasonable indicator of when infectious virus is no longer being shed. Most studies have analyzed respiratory secretions (throat and/or nasopharyngeal samples), but stool samples are also often positive for RNA later in the course of the infection while other sites (e.g. blood, urine, tears, vaginal secretions) are usually negative. These data are likely to be important for the understanding of routes and periods of transmission.

It is not uncommon for viral shedding in respiratory secretions to occur 2-3 days prior to first symptoms (6-8). Higher amounts of virus and viral RNA are seen early in infection independent of severity of symptoms with sputum and nasopharyngeal samples more likely to be positive than throat swab samples (5, 6, 9-11). More severe clinical disease is associated with longer

persistence of viral RNA shedding and may represent a significant occupational transmission risk for health care workers (12, 13). Viral RNA shedding for up to a week after resolution of symptoms is common and in one case has been documented to continue for as long as 49 days although this viral RNA may not represent infectious virus (5, 14-16). No differences in these parameters have been detected based on age or sex.

In addition, gastrointestinal symptoms may be common and viral RNA is frequently detected in stool. Viral RNA persists in stool after symptoms have subsided for longer than in samples from the respiratory tract, but a role in transmission is unclear (17-20)[1]. In a recent report infectious virus was readily isolated from respiratory samples, but not from stool samples (5).

Gaps in knowledge:

- Effect of various treatments on length of shedding
- Epidemiologic evidence of transmission while RT-PCR+ after recovery
- Significance of viral RNA shedding after resolution of symptoms
- Importance of shedding from non-respiratory sites
- Innovative assays to determine if the virus is infectious

2) Levels and duration of antibody response and related resistance to illness

Time of antibody detection after infection is dependent on the sensitivity of the assay and the viral protein used as antigen. IgM can be detected by enzyme immunoassay to nucleoprotein 3-6 (median 5) days after onset of symptoms and has been used to complement RT-PCR for diagnosis of CoVID-19 (21, 22). IgG to the same protein is detected 10-18 (median 14) days after onset of symptoms (21). Anti-nucleoprotein antibody did not correlate with virus clearance (15) and a higher antibody titer was independently associated with more severe disease (21). Antibody to the receptor-binding domain of the spike protein was detected a median of 11 days after onset of symptoms, but the timing of seroconversion did not correlate with clinical course (5, 22).

The duration of the antibody response and acquired immunity to reinfection will be critical to understanding 1) how effective vaccination is likely to be; 2) how durable immunity is; 3) whether it is possible to achieve herd immunity against COVID-19; 4) how safe it is for people who are positive in a serology test to return to work. One key uncertainty arises from the fact that we are early in the outbreak and survivors from the first weeks of infection in China are, at most, only 3 months since recovery. Some lessons may be gleaned from evidence about the duration of antibody responses to SARS-CoV and MERS-CoV, which are related viruses. Studies of patients who recovered from the SARS outbreak in 2003 show a steady decrease in amounts of antiviral binding IgG over time with 12% negative at 2 years and 50% at 3 years (3, 4).

[1] During the SARS epidemic in Hong Kong in 2003, virus was spread in an apartment complex (Amoy Gardens) due to aerosolized waste flushed from toilets that found its way into the air of other apartments through poorly designed bathroom floor drains.

Similarly, health care workers with mild to moderate MERS-CoV infection had no detectable antiviral binding IgG 18 months after recovery (2). The response to SARS-CoV-2 virus is likely to be similar to this closely related virus. Longitudinal data from the large numbers of recovered cases in China from earlier in the outbreak may give us insight into the temporal dynamics of antibody titers to this virus.

Gaps in knowledge:

- Evaluation of whether the presence of antibodies confers protection from illness due to re-infection, and if so, what levels of antibodies are needed.
- A better understanding of the role of specific antibodies will inform possible therapy with immune plasma and development of monoclonal antibodies for potential treatment, as well as vaccine design.
- Following antibody titers in cohorts of patients with mild, moderate, severe and critical COVID-19 disease will be revealing. This would best be done in multiple geographies, with diverse age classes, ethnic background etc.
- Evidence of waning antibody titer can be anticipated after 2 years, but any indication of earlier significant drop in titers per age class or other grouping would be very important to identify because it might affect vaccine efficacy, the ability of these people to be re-infected and potential for disease attenuation with an anamnestic response.

3) Optimal duration of isolation of cases

Because many patients continue to be RT-PCR positive for viral RNA in both respiratory secretions and stool, this is a difficult question that will best be informed by observational studies of transmission from discharged patients with known status for viral RNA by RT-PCR. Waiting for all tests to be repeatedly negative is the most conservative approach, but may result in prolonged unnecessary isolation. Assessment of humoral and cellular immune response may also be informative. Current CDC recommendations are that patients are no longer infectious after seven days of illness and three days without symptoms.

Gaps in knowledge:

- Duration of shedding of infectious virus by recovered patients and the relationship to detection of viral RNA
- Knowledge of immune mechanisms responsible for virus clearance that might predict recovery and help determine when patients are no longer infectious
- Immune correlates of protection
- Duration of protective immunity

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REFERENCES

1. Joynt GM, and Wu WK. Understanding COVID-19: what does viral RNA load really mean? *Lancet Infect Dis.* 2020.
2. Alshukairi AN, Khalid I, Ahmed WA, Dada AM, Bayumi DT, Malic LS, et al. Antibody Response and Disease Severity in Healthcare Worker MERS Survivors. *Emerging infectious diseases.* 2016;22(6).
3. Liu W, Fontanet A, Zhang PH, Zhan L, Xin ZT, Baril L, et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *The Journal of infectious diseases.* 2006;193(6):792-5.
4. Wu LP, Wang NC, Chang YH, Tian XY, Na DY, Zhang LY, et al. Duration of antibody responses after severe acute respiratory syndrome. *Emerging infectious diseases.* 2007;13(10):1562-4.
5. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature.* 2020.
6. He X. Temporal dynamics in viral shedding and transmissibility of COVID-19. *medRxiv.* 2020.
7. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. *MMWR Morbidity and mortality weekly report.* 2020;69(13):377-81.
8. Li C, Ji F, Wang L, Wang L, Hao J, Dai M, et al. Asymptomatic and Human-to-Human Transmission of SARS-CoV-2 in a 2-Family Cluster, Xuzhou, China. *Emerging infectious diseases.* 2020;26(7).
9. Yu F, Yan L, Wang N, Yang S, Wang L, Tang Y, et al. Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. *Clinical infectious diseases.* 2020.
10. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *The New England journal of medicine.* 2020;382(12):1177-9.
11. Cereda D et al. The early phase of the COVID-19 outbreak in Lombardy, Italy. *MedRxiv.* 2020.
12. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis.* 2020.
13. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis.* 2020.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-62.
15. Tan W. Viral kinetics and antibody responses in patients with COVID-19. *medRxiv.* 2020.
16. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA.* 2020.

17. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect.* 2020;9(1):386-9.
18. Lo IL, Lio CF, Cheong HH, Lei CI, Cheong TH, Zhong X, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. *Int J Biol Sci.* 2020;16(10):1698-707.
19. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl).* 2020.
20. Xu Y. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nature medicine.* 2020.
21. Guo L, Ren L, Yang S, Xiao M, Chang, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clinical infectious diseases.* 2020.
22. 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. *Clinical infectious diseases.* 2020.

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APPENDIX

Authors and Reviewers of this Rapid Expert Consultation

This rapid expert consultation was prepared by staff of the National Academies of Sciences, Engineering, and Medicine, and members of the National Academies' Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats: Peter Daszak, EcoHealth Alliance; Diane E. Griffin, Johns Hopkins Bloomberg School of Public Health; Kent E. Kester, Sanofi Pasteur; and Mark S. Smolinski, Ending Pandemics.

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