VIEWPOINT

Translating Science on COVID-19 to Improve Clinical Care and Support the Public Health Response

Carlos del Rio, MD
Division of Infectious Diseases, Department of Internal Medicine, Emory University School of Medicine, Atlanta, Georgia.

Preeti Malani, MD, MSJ
Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor; and Associate Editor, *JAMA*.

Now in its fifth month, the coronavirus disease 2019 (COVID-19) pandemic continues to advance with nearly 5 million documented infections worldwide and with the US having the largest number of infections and deaths globally. The speed of the scientific response to the epidemic has been unprecedented. On January 7, Chinese investigators identified a novel coronavirus as the cause of an unusual cluster of pneumonia cases, and 5 days later the virus genetic sequence was published. By February 21, the first treatment trial had been initiated and March 18 marked the start of the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine trial in humans. The time from the initial viral sequencing to the first in human injection of a candidate vaccine was a record 65 days.

By April 29, the National Institute of Allergy and Infectious Disease reported that preliminary results of a randomized clinical trial of remdesivir (NCT04280705) suggested that this drug, compared with placebo, shortened the time to recovery from 15 to 11 days and was associated with a nonsignificant, small, but clinically relevant survival benefit.[1] Based on these findings, on May 1 the US Food and Drug Administration (FDA) granted emergency use authorization (EUA) for remdesivir for the treatment of adults and children with suspected or laboratory-confirmed COVID-19 and severe disease. At present, more 1300 intervention COVID-19 studies are registered in ClinicalTrials.gov ranging from monoclonal antibodies to novel antivirals like favipiravir and drugs previously approved for other indications like lopinavir-ritonavir and hydroxychloroquine.

This Viewpoint updates previous guidance for clinicians[2] and summarizes the current status of potential therapies, advances in vaccine development, and the potential role of convalescent antibodies as treatment and for the evaluation of immunity. The concept of herd immunity and what relaxing of social distancing recommendations might mean for a possible second wave of infections also are explored.

Treatment and Chemoprevention

Guidelines for the medical management of COVID-19 have been issued by the National Institutes of Health (NIH) as well as the Infectious Diseases Society of America.[3,4] Currently only remdesivir has received EUA, but several strategies are being used or studied through either clinical trials, expanded access, or single patient emergency investigational new drug application.[5]

Other drugs under investigation include lopinavir-ritonavir and hydroxychloroquine with and without azithromycin, although a recent observation study of the latter found no clinical benefit associated with hydroxchloroquine.[6] However, hydroxychloroquine is now being studied both as a therapeutic option for patients with mild disease to prevent hospitalization and as chemoprevention in high-risk health care workers. Other pharmacologic approaches being studied include IL-6 and IL-1 inhibitors and monoclonal antibodies. Promising nonpharmacologic strategies under investigation include the use of convalescent plasma collected from recovered patients. Published results to date have consisted of a handful of descriptive studies with small numbers of patients. Given the suggestion of modest benefits, multiple, large clinical trials using convalescent plasma have begun.

Vaccine Development

The development and deployment of an effective SARS-CoV-2 vaccine remains the number one priority. In general, it is difficult to make fully protective vaccines against respiratory viral infections, so the goal of such a vaccine needs to be considered in terms of protecting against severe infection, not preventing all infection. At this time, more than 100 vaccine candidates are in development and 8 have entered clinical trials in humans. In the US, an mRNA vaccine developed by Moderna through funding from Biomedical Advanced Research and Development Authority (BARDA) has completed phase 1 trials and shown to be safe and immunogenic (NCT04283461). However, developing a vaccine during a pandemic brings additional challenges. For example, the Zika epidemic ended before a vaccine was available; thus, efficacy trials were not completed. For this reason, some have considered a controlled human infection challenge to test vaccine efficacy; however, this approach carries substantial risk and ethical challenges.

Nevertheless, the Moderna mRNA vaccine is expected to enter a phase 3 study in the summer. Assuming this trial and others are successful and that an effective vaccine or vaccines are developed, quickly producing hundreds of millions if not billions of doses will be the next challenge, likely requiring the construction of new manufacturing facilities. Thus, even if the early candidate vaccines prove immunogenic and safe, it is unlikely that a vaccine will be widely available in less than 24 months.

Antibody Testing

In the absence of an effective vaccine, some governments have considered documentation of immunity as a path out of restrictive social measures and the use of "immunity licenses or passports."[7] In theory, individuals who have already been infected and can demonstrate the presence of antibodies could return to daily life without restrictions. However, such an approach has numerous logistical and ethical challenges.[7] On April 24, the World Health Organization issued guidance about such an approach stating that presently there is no evidence that individuals who have recovered from COVID-19 and have

Corresponding Author: Carlos del Rio, MD, Emory University School of Medicine, 49 Jesse Hill Jr Dr, FOB Room 201, Atlanta, GA 30303 (cdelrio@emory.edu).

antibodies are protected from subsequent infection.[8] However, it would it be extremely unusual if individuals who recover from COVID-19 do not develop protective antibodies for some time.

The current landscape of antibody tests in the US is varied and remains clinically unverified with no peer-reviewed parallel evaluations of available antibody assays. The Foundation for Innovative New Diagnostics is conducting independent evaluations of SARS-CoV-2 molecular tests and immunoassays that will ultimately be informative. But until then, antibody tests should not be used as a sole diagnostic test. Use of serology for public health surveillance has begun with results suggesting variations in seroprevalence depending on geographic location. For example, a recent study in New York City suggested that approximately 20% of the population had been infected with SARS-CoV-2, whereas another study in Santa Clara, California, demonstrated a lower prevalence of between 2.5% and 4.2%.

Herd Immunity

The term *herd immunity* is often used when considering vaccine preventable infections. Vaccines protect in 2 ways. First, they induce an active immune response in the individual receiving the vaccine to directly protect against exposure to the pathogen. Second, vaccines indirectly prevent transmission of the pathogen to susceptible individuals because the potential for transmission is decreased with the higher the level of vaccine coverage in a population. Thus, both individual and population-based vaccination benefits society by helping to protect the broader community (ie, persons who are susceptible but cannot be vaccinated such as those who have medical contraindications). However, herd immunity does not mean inducing active indirect immunity in the population rather reducing the probability of being exposed to the pathogen.

As the term suggests, herd immunity considers protection from a particular disease at the population level. The more people who are immune, the fewer people a virus can infect. Estimates suggested that 60% or more of the population would need to be immune to reach herd immunity for COVID-19, approximately 200 million individuals in the US.[9] Even at the current pace of new COVID-19 infections in the US. with more than 25 000 confirmed cases a day, it would be well into 2021 before the herd immunity threshold would be reached. If current daily death rates continue, more than half a million US residents would have died from COVID-19 by then. Thus, a strategy relying on herd immunity in absence of a vaccine carries an enormous potential human toll.

Second Wave

As states and countries throughout the world begin to relax social distancing restrictions and begin reengaging with day-to-day life, there are growing concerns that a second and more deadly wave of COVID-19 cases could occur. The concerns regarding a second wave of infection is based on data from the 1918 Spanish influenza pandemic. In some regards, the public health landscape of the US is less like a single nation and more like 50 separate countries, much like the European Union, and decisions to relax restrictions are being made by governors without a coordinated national strategy. The criteria proposed by the White House including a downward trajectory of documented cases within a 14-day period in the setting of a robust testing program has not been met by most states. The burden of the pandemic in the US is not equally distributed but rather it is disproportionately affecting minority communities with infection rates that are 3-fold higher and death rates that are 6-fold higher among predominantly black counties than among predominantly white counties.[10] Therefore, adequate testing capacity must be available in all communities along with resources to safely isolate those who become ill.

Conclusions

Despite enormous progress in understanding COVID-19, there is little evidence that a solution, therapeutic or preventive, is close to being achieved. During the next phase of the pandemic, robust containment strategies will be vital to enter "the new normal" but even then, it may be too risky for some populations such as nursing home residents and other vulnerable groups. Even with adequate testing and contact tracing, it is important to recognize that cases of COVID-19 infection and some outbreaks continue to occur. Improved understanding of which individuals do poorly when infected and whether early interventions can prevent severe disease and death are essential research questions. For the foreseeable future, fundamental public health measures such as physical distancing, wearing a mask in public, frequent handwashing, and staying at home when symptoms occur, will remain the best tools to prevent COVID-19.

ARTICLE INFORMATION

Published Online: May 22, 2020. doi:10.1001/jama.2020.9252

Conflict of Interest Disclosures: Dr del Rio reported receiving grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases. No other disclosures were reported.

REFERENCES

1. National Institute of Infectious Diseases. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. Published April 29, 2020. Accessed May 10, 2020. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

2. Omer SB, Malani P, Del Rio C. The COVID-19 pandemic in the US: a clinical update. *JAMA*. Published online April 6, 2020. doi:10.1001/jama.2020.5788

3. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated May 12, 2020. Accessed May 21, 2020. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/

4. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Published April 11, 2020. Accessed May 11, 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management

5. Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. Published April 29, 2020. Accessed May 12, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19

6. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. Published online May 11, 2020. doi:10.1001/jama.2020.8630

7. Persad G, Emanuel EJ. The ethics of COVID-19 immunity-based licenses ("Immunity Passports"). *JAMA*. Published online May 6, 2020. doi:10.1001/jama.2020.8102

8. World Health Organization. "Immunity Passports" in the Context of COVID-19. Published April 24, 2020. Accessed May 11, 2020. https://www.who.int/publications-detail/immunity-passports-in-the-context-of-covid-19

9. Walensky RP, Del Rio C. From mitigation to containment of the COVID-19 pandemic: putting the SARS-CoV-2 genie back in the bottle. *JAMA*. Published online April 17, 2020. doi:10.1001/jama.2020.6572

10. Yancy CW. COVID-19 and African Americans. *JAMA*. Published online April 15, 2020. doi:10.1001/jama.2020.6548