VIEWPOINT

The COVID-19 Pandemic in the US
A Clinical Update

Saad B. Omer, MBBS, PhD

Yale Institute for Global Health, Department of Internal Medicine (Infectious Diseases), Yale School of Medicine, New Haven, Connecticut; and Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, Connecticut.

Preeti Malani, MD, MSJ

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

Carlos del Rio, MD

Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia; and Hubert Department of Global Health, Rollins School of Public Health of Emory University, Atlanta, Georgia.

Since the first US case of coronavirus disease 2019 (COVID-19) infection as identified in Washington State on January 20, 2020, more than 235 000 cases have been identified across the US in just over 2 months. Given the challenges in expanding testing capacity and the restrictive case definition of persons under investigation, the true number of cases is likely much higher.

By March 17, the outbreak had expanded from several isolated clusters in Washington, New York, and California to all 50 states and the District of Columbia. As of April 2, there have been more than 5000 COVID-19–associated deaths in the US. With a global total now of more than 1 million cases, the US is now the country with the largest number of reported cases, comprising about one-fifth of all reported infections.

With community transmission firmly established, the US epidemic enters the exponential growth phase in which the number of new cases is proportional to the existing number of cases. This phase continues until either enough susceptible individuals become immune as a result of infection, stringent public health measures are followed, or both.

Case Fatality

A yet unanswered question that adds to uncertainty around the outbreak involves the case-fatality rate (CFR), defined as the percentage of deaths among all cases. Presently, global mortality is reported at 4.7% but this varies widely by location from a high of 10.8% in Italy to a low of 0.7% in Germany. Several factors influence the CFR including a reliable estimate of the total number of cases. Among the first 140 904 cases in the US, 1.7% died; however, given the uncertainty in the denominator, this is not a reliable CFR estimate. For example, the crude CFR in Wuhan, China, was reported to be 5.8% on February 1, whereas more methodologically robust estimates using novel methods to estimate the actual number of cases reported the CFR as 1.4%.[1]

In the coming weeks, surge capacity at US hospitals will influence the CFR. However, to have reliable estimates, better approximations of the overall population (denominator) are essential, and methods such as serosurveys using statistical sampling generalizable to the populations of interest will inform these estimates.

New Clinical and Epidemiological Insights

Is PCR Always Positive? What Is the Meaning of a Negative PCR? Several types of tests are being used to identify severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] These can be classified into 2 general categories: molecular diagnosis/polymerase chain reaction (PCR)–based testing and serological testing. In clinical settings, PCR-based testing remains the primary method of identifying SARS-CoV-2. Given the lack of a reference standard for diagnosing COVID-19, the sensitivity and speci-

ficity of diagnostic testing are unknown. In addition, inadequate sample collection may reduce test sensitivity. In a study of 5 patients, individuals with chest computed tomography findings compatible with COVID-19, and a negative reverse transcriptase (RT)–PCR result for SARS-CoV-2, tested positive on subsequent testing, suggesting that certain patients (eg, with compatible radiological findings) might require repeat testing with specimens collected from multiple sites in the respiratory tract.[3]

It is likely that lower respiratory samples (eg, minibronchial alveolar lavage) are more sensitive than a nasopharyngeal swab. Thus, it is important to emphasize that, depending on the clinical presentation, a negative RT-PCR result does not exclude COVID-19. Multiple serological tests are in various stages of development. With wider availability of serological testing, it will be possible to determine whether patients have a false-negative PCR result.

Can Patients Become Reinfected? Reports from China and Japan have indicated that some patients with COVID-19 who were discharged from the hospital after a negative RT-PCR result were readmitted and subsequently tested positive on RT-PCR. It is unclear from the available information if these were true reinfections or the tests were falsely negative at the time of initial discharge. However, while other coronaviruses demonstrate evidence of reinfection, this usually does not happen for many months or years. Therefore, it is unlikely that these were true cases of reinfection. Some reassuring evidence comes from a challenge study among rhesus macaques.[4] After initial challenge and clearance of SARS-CoV-2, the animals were rechallenged with the virus but were not infected. While the evidence on reinfection is evolving, current data and experience from previous viruses without substantial seasonal mutation do not support this hypothesis.

How Long Does Immunity Last? Presently, there is no validated immune correlate of protection for SARS-CoV-2, ie, antibody level or another immunological marker associated with protection from infection or disease. However, in a study that included 82 confirmed and 58 probable cases of COVID-19 from China, the median duration of IgM detection was 5 days (interquartile range, 3-6), while IgG was detected at a median of 14 days (interquartile range, 10-18) after symptom onset.[5] Because the outbreak is only a few months old, there are no data on long-term immune response. Data from SARS-CoV-1 indicate that titers of IgG and neutralizing antibodies peaked at 4 months after infection, with a subsequent decline through at least 3 years after infection.

Should Everyone Wear a Mask in Public? Current guidelines from the Centers for Disease Control and Prevention (CDC) do not recommend routine use of medical masks among healthy individuals and suggest limiting mask use to health care workers and those caring for

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

patients with COVID-19. However, this guidance is likely to be modified. Regardless, any change in policy should prioritize the availability of masks for health care workers. Priority should also be given to others with risk of exposure such as first responders and incarcerated individuals. Due to the current scarcity of masks, many in the community have begun sewing masks for themselves and for health care workers. A fitted N95 respirator is the preferred type of medical mask for health care workers; however, supplies in the US are very limited. Medical masks are also recommended for symptomatic individuals to prevent them from transmitting the virus.

The rationale supporting the recommendations comes from studies finding limited to no efficacy of masks in protecting healthy individuals from influenza infection and also for the need to preserve supplies. However, evidence from influenza studies might not be relevant for COVID-19. For example, in a systematic review, masks, particularly combined with other measures such as handwashing, were found to be effective in preventing SARS-CoV-1 infection.[6] Moreover, with the increasing evidence of presymptomatic transmission of SARS-CoV-2, there might be value in the use of masks among individuals at risk of transmission.[7]

How Does SARS-CoV-2 Spread? Current evidence suggests that SARS-CoV-2 is primarily transmitted through droplets (particles 5-10 μm in size). Person-to-person transmission occurs when an individual with the infection emits droplets containing virus particles while coughing, sneezing, and talking. These droplets land on the respiratory mucosa or conjunctiva of another person, usually within a distance of 6 ft (1.8 m) but perhaps farther.[8] The droplets can also settle on stationary or movable objects and can be transferred to another person when they come in contact with these fomites. Survival of the virus on innate surfaces has been an important topic of discussion. While there are few data, the available evidence suggests that the virus can remain infectious on inanimate surfaces at room temperature for up to 9 days. This time is shorter at temperatures greater than 30° C. The good news is that cleaning and disinfection are effective in decreasing contamination of surfaces, emphasizing the importance of high-touch areas.[9]

Transmission through aerosols, particles smaller than 5 μm, can also occur under specific circumstances such as endotracheal intubation, bronchoscopy, suctioning, turning the patient to the prone position, or disconnecting the patient from the ventilator. Cardiopulmonary resuscitation is another important aerosol-generating procedure.

In a recent study of environmental sampling of rooms of patients with COVID-19, many commonly used items as well as air samples had evidence of viral contamination.[10] In the context of the heterogeneity in evidence and possibility of aerosolization of the virus during certain medical procedures, public health agencies (including the CDC) recommend airborne precautions in situations involving patients with COVID-19.

When Can Social Distancing Measures Be Lifted? With the exponential increase in US COVID-19 cases and deaths, several jurisdictions have implemented social-distancing measures. Modeling and empirical studies suggest that social-distancing measures can help reduce the overall number of infections and help spread out cases over a longer period of time, thus allowing health systems to better manage the surge of additional patients. However, long-term social distancing can have detrimental effects on physical and mental health outcomes as well as the economy.

A few changes may allow for easing restrictions: First, an aggressive program of testing to identify asymptomatic and mild cases combined with proactive contact tracing and early isolation as well as quarantine of contacts. Second, there must be a focus on reducing home-based transmission. In Wuhan, particularly after the initial phase, most transmissions occurred within households. While the CDC has published guidelines for preventing household transmission, it did not place enough emphasis on the importance of having the infected person always wear a mask. Third, even a treatment that only shortens an intensive care unit stay by 20% to 30% can have a substantial benefit on health system capacity.

When Will a Vaccine Be Available? The ultimate strategy for controlling this pandemic will depend on a safe and efficacious vaccine against SARS-CoV-2. However, only 3 vaccine candidates are currently in phase 1 human trials: a messenger RNA vaccine and 2 adenovirus vector-based vaccines. The estimated timeline for availability of an initial vaccine is between early and mid-2021.

Conclusions

As the COVID-19 outbreak expands in the US, overall understanding of this disease has increased, with more information available now than even a few weeks ago. However, more evidence is needed, particularly for public health and clinical interventions to successfully prevent and treat infections. Even during a pandemic, obtaining rigorous, reliable data is not a distraction, rather it is essential for accurately measuring the extent and severity of COVID-19 and assessing the effectiveness of the response.

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