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Undergraduate

COVID-19: Insights from UC Berkeley's Infectious Disease Experts

By Sharon Binoy, Ananya Krishnapura, Esther Lim, Elettra Preosti, Melanie Russo, Michael Xiong, Katheryn Zhou, Matthew Colbert, and Rosa Lee

COVID-19, the disease caused by the novel coronavirus, SARS-CoV-2, has spread rapidly across our planet and changed our lives in unimaginable ways. In this interview in April 2020, we sought out information from experts in emerging diseases, public health, and epidemiology here at UC Berkeley.

INTRODUCTIONS



SANDRA MCCOY¹

Sandra McCoy, PhD, MPH, is an Associate Professor in the Division of Epidemiology and Biostatistics at the UC Berkeley School of Public Health. She is on the editorial board of the journal *mHealth*. Her research focuses on utilizing technology and behavioral science to advance healthcare access and treatment adherence across different countries, cultures, and populations. Dr. McCoy has led projects in Tanzania and the United States to combat HIV infections and improve reproductive health.

ARTHUR REINGOLD²

Arthur L. Reingold, MD, is the Division Head of Epidemiology and Biostatistics at the UC Berkeley School of Public Health. He has studied the spread and prevention of infectious diseases for over 40 years. He worked at the Centers for Disease Control (CDC) for eight years, serving as the Assistant Chief of the Respiratory & Special Pathogens Epidemiology Branch from 1981-85 and as the CDC Liaison Officer of the Office of the Director from 1985-87. His current research interests include vaccination and vaccine-preventable diseases, outbreak detection and response, and the emergence of infections in the United States and developing countries.



JULIA SCHALETZKY³

Julia Schaletzky, PhD, is the Executive Director of the Henry Wheeler Center for Emerging and Neglected Diseases (CEND). She is also the co-founder of the COVID Catalyst Fund, which aims to provide rapid funding to accelerate COVID-19 research within the Bay Area Virus Network. Before joining CEND, Dr. Schaletzky worked at the biotechnology company Cytokinetics, where she focused on developing first-in-class medicines against heart failure and neurodegenerative disorders. Dr. Schaletzky's current research focuses on treating neglected and emerging diseases, establishing effective collaboration between academia and industry, and translating basic science into new companies and ultimately cures.

JOHN SWARTZBERG⁴

John Swartzberg, MD, FACP, is an infectious disease specialist and Clinical Professor Emeritus at the UC Berkeley School of Public Health. Before becoming a faculty member, Dr. Swartzberg had 30 years of clinical experience working in internal medicine. He is currently the hospital epidemiologist and Chair of the Infection Control Committee at the Alta Bates Medical Center, a chair of UC Berkeley School of Public Health's Health and Wellness Publication editorial board, and a past director of the UC Berkeley–UCSF Joint Medical Program.



BSJ: How does SARS-CoV-2 spread?

REINGOLD: This is a virus that is spread from and to the mucous membranes of the respiratory tract. That can also potentially include the eyes and the nose, in addition to the mouth. So, we basically worry about the virus making it from secretions in my mouth, my nose, or possibly my eye into your nose, mouth, or eye.

SCHALETZKY: It spreads through surfaces and droplets, and it is also aerosolized, meaning it floats in the air for a little bit. So, if you are in a room with a lot of people and shared air, like an airplane, it can stay in the air for a while. Also, initially we thought that when you cough, you only make droplets fall within a six-foot radius around you. However, the virus can be detected from even 23 feet away because it is aerosolized and can waft in the air, although at lower concentrations. So, spread is not just caused by droplets. However, one particle is not going to infect you; you have to reach a certain critical mass of particles in order to get an infection.

BSJ: How does its rate of spread compare to the seasonal influenza or other diseases?

SWARTZBERG: We use this term called R_0 , which is the reproductive number. The R_0 for SARS-CoV-2 was around 3 in March. This means one person, on average, is going to infect three people. That compares to an R_0 for seasonal influenza from this year of about 1.8, and we see how many people got influenza. But, the R_0 is an elusive number. By late April, it was below 1.0. It does not take an R_0 that is very high to get an awful lot of people infected. The most infectious, contagious disease that we deal with currently is measles, and the R_0 for that is around 15. These R_0 values show you how much less contagious SARS-CoV-2 is than measles, but how much more contagious it is than seasonal influenza.

McCoy: An issue that helps determine mitigation and control measures is the level of transmission that occurs before symptoms develop or from people who never develop symptoms. For influenza, people become contagious about one day before they develop symptoms. This means that infected individuals are going through their daily lives and could be unknowingly transmitting to others. For the 2003 SARS coronavirus, people were not able to transmit to others until after they had symptoms. This meant that a combination approach of case finding, isolation, contact tracing, and quarantine was enough to interrupt the 2003 SARS epidemic. However, some people infected with SARS-CoV-2 have peak viral shedding before they develop symptoms, and potentially up to 25% of all people infected never develop symptoms at all. This means that we have to take much more aggressive control strategies.

BSJ: How many people do you estimate have actually been infected as compared to the number of documented cases [as of April 18, 2020]?

SWARTZBERG: We know that this virus did not enter the United States until sometime in early January. We also know that if you have a positive antibody test, you have been infected sometime in

the last three and a half months. So, initially, I would have told you we have 10 times more cases than are reported. However, a study came out of Stanford recently, surveying a few thousand people in Santa Clara County. There are a lot of valid criticisms in terms of how well their antibody tests work, whether they used the best representative sample, and so on. But, putting those criticisms aside, what they found was that the number of people who had antibodies was 80 to 85 times greater than the number of cases reported. So, if their data is accurate, it means we have between 50 and 85 times more cases than we thought we had. This paper tells us that there are a lot more cases out there than we know about. How many more is still a question, but I think a conservative number is 10.

BSJ: With over 900,000 confirmed cases and 50,000 deaths⁵ [as of April 26, 2020], how effective have the U.S.' attempts been to "flatten the curve"?

SWARTZBERG: You cannot speak of the United States in the aggregate because, like any pandemic, it flares up in a community, dies down, and then flares up in another community. You have to look at specific communities to answer your question. If we look at the San Francisco Bay Area, there is no question that the number of cases we had in March and April is far fewer than were predicted. We never got a spike or a peak; we got a hill. We never exceeded the medical resources in the Bay Area that we needed. Clearly, something that we did here worked. New York was not successful in flattening the curve; they have had an incredible spike in cases. What is the difference? One hypothesis that I think is really tenable (but, is not sufficient in itself) is that the Bay Area was the first large metropolitan area in the United States to shelter-in-place. New York followed between five to seven days after California or almost 10 to 12 days after the Bay Area. Although five to seven days does not sound like a lot, in the rate of spread of this virus, it is a lifetime.

BSJ: What are the current preventative measures against COVID-19, and what are some long-term projections?

REINGOLD: Ways to prevent spread include various social distancing measures such as covering your mouth when you cough and sneeze, staying home when you are sick, washing your hands, and wearing a mask. Once a virus like this starts to spread, the sooner you introduce prevention and control measures, the more likely they are to be effective.

McCoy: Right now we are implementing a very aggressive and intensive community-based approach. However, our goal is to eventually transition to a case-based approach where we can ease social distancing policies and rely on intensive case identification, isolation, contact tracing, and quarantine. One proposal is a series of phases spanning 12 to 18 months where we repeatedly tighten and then loosen physical distancing directives according to the level of virus transmission in the community. We would have smaller and smaller epidemic curves as we gradually dampen the epidemic. But until we have a safe and effective vaccine or therapeutic, we cannot go back to life as we previously knew it.

SCHALETZKY: For the pandemic to stop spreading, we need people

to either get it and become immune, or we need to have a vaccine or a therapy. It is also important to remember that the regulating step in this is really hospital capacity. We do all of this social distancing because we do not have the hospital capacity to deal with a scenario where everybody gets infected at the same time. Even if everyone got better in two weeks, it would not be possible. For that reason, we want to flatten the curve. It increases the survival of patients. But, although quarantine is a good method, we cannot do this forever. If we were all on lockdown and nobody was interacting with each other, we could in theory eradicate the virus, but that is impractical. So ultimately, people need to build immunity by either getting the virus and getting optimal care so the survival rate is maximized, or we get a vaccine out really fast. It is a balancing act.

BSJ: Currently, how accurate are the diagnostic tests for COVID-19?

REINGOLD: There are basically two types of tests people are interested in: do you have the virus now and have you had the virus in the past. The “do you have it now” tests you hear about are polymerase chain reaction (PCR) tests that detect the viral RNA. But, RNA might still be present when the virus itself is not there. So, there is a slight problem with using PCR tests because it could be that you are no longer infectious, but still have the RNA detected. Another problem is that most PCR tests currently take a day or two to get the results back. The third problem is that they are not very sensitive, so there may be a lot of false negatives. You can also do viral cultures, but they are much more expensive, difficult, and laborious, so they are not routinely done out in the real world. Thus, people are currently working really hard to do point-of-care diagnostic tests where, just like a pregnancy test or a test for group A strep pharyngitis, I take your sample and 15 minutes later, I tell you the result. That is what we need.

People are also developing and starting to use antibody tests, called serological studies, where I take some of your blood and I look for an immune response. If there is an IgM response, that means it is a recent infection. If it is an IgG response, it means that the infection occurred longer ago, and we can test for antibodies, immunity, or both.

BSJ: What does the timeline look like with respect to potential vaccines or treatments?

SWARTZBERG: There are quite a few therapeutic drugs that are being tested, but there is nothing that looks like it is going to be a panacea. There are also quite a few vaccines being developed in the United States and over 70 internationally. Two major things have to be established in vaccine trials: safety and efficacy. There is currently one vaccine in a Phase 1 trial testing for safety in a small group. If it passes the Phase 1 trial, then we have to determine whether it is efficacious, first in a small group, then in a larger group. Let us say we find one or more of these vaccines to be efficacious. We then have to expose larger groups of people to also make sure they are safe. To do this, you give a group of people the vaccine and follow them for as long as you possibly can. If it is efficacious, but not safe, it is no good. If it is safe, but not efficacious, it is no good. If we are

lucky, we can have a vaccine in 14 to 18 months. It will be the fastest we have ever developed a vaccine by years.

BSJ: Of the different types of vaccines—live attenuated or inactivated (including conjugate, subunit, toxoid, or recombinant)—which one is most suitable for combating COVID-19, and why?

SCHALETZKY: The most well-known or original way to make vaccines is to attenuate the virus so it cannot be fully infectious. But in the SARS epidemic, we saw morbidity associated with the live attenuated vaccine, possibly due to the lung-specific pathology the SARS coronavirus causes in the immune system. We do not know for sure if that will also occur for COVID-19, but that is why people are a little wary of live attenuated vaccines. The next most frequent approach is to make a recombinant vaccine where you purify an antigen [a foreign substance that elicits an immune response in the body] in some other system like yeast or plants. Johnson & Johnson is working on one and has already done work on mice. They estimate that they may be able to manufacture a vaccine by summer 2021 in the best case scenario. The mRNA vaccine is a little different. Instead of making the antigen already in a system, you inject the genetic information into you so that your own body can make the antigen. The advantages are that you can make it a lot faster because a nucleotide synthesis is in principle simpler. Moderna is developing an mRNA-based vaccine. They already dosed people weeks ago with the first dose, and so far we have not heard anything about adverse effects.

REINGOLD: We do have a live attenuated vaccine for influenza and for some other viruses, but I do not think that it is very likely for COVID-19 because you could potentially end up not attenuating it enough and causing the disease instead. The vaccine is also pretty unlikely to be a killed, inactivated whole virus vaccine; nowadays, there are much more modern approaches, such as using DNA or RNA vaccines. My guess is that the vaccine that an Oxford group is working on, which is a carrier virus that has coronavirus antigens being expressed, may work. You take a virus that you know cannot harm people and put certain genes from the virus you are trying to protect against into that backbone. These genes are for antigens that will produce the antibodies we want to protect you with.

BSJ: What are some of the challenges faced by scientists who are trying to create a COVID-19 vaccine?

SCHALETZKY: There are a few issues surrounding the mRNA vaccine. One is does it actually elicit an immune response? If your body for some reason does not make the protein very well, or the mRNA is degraded or is not taken up by your cells in the proper way, you might not actually make enough antigens. The other is if you make enough antigen, do you actually make any antibodies and are those antibodies actually protective?

One of the biggest non-scientific obstacles in our fight against COVID-19 is having too many regulations. Now we have testing capacity, yet there is so much over-regulation in the US that makes it impossible to do simple community testing of who has

SWARTZBERG: The major challenge we have with COVID-19 is that we do not know what correlates with protection. There are infectious diseases where our bodies respond to the infection by producing antibodies, but they do not correlate with protection. We do not know whether the humoral immune response and antibody production will be the major way to protect us or if it is going to be the cell-mediated immune response or some combination of the two.

REINGOLD: The \$64 question—that is an old saying—is do these tests tell you anything about your immunity? An assumption made by many people is that if you have antibodies, then you are now immune. But, it is going to take some work to figure out if the antibodies that we are measuring correlate with clinical protection or not. For example, some people are talking about using a positive antibody test as proof of immunity. We also do not know how long immunity will last. You might not still be protected after some time.

BSJ: In your opinion, when will it be safe for students and professors to return to campus?

SWARTZBERG: I do not know what is going to happen in the fall semester because other respiratory viruses, especially influenza, start circulating in our area right around late October through April. So, we are going to add on the annual influenza epidemic that occurs every year along with whatever else starts coming to us at that time. However, when we do attempt to bring people back to campus, we will need to get some of the researchers back to have some of the labs open up. But, who should those researchers be? Once we start reintroducing people back on campus, then who would be the students to be reintroduced if we are not going to let all students come back once? Where will students live? Everybody wants to be back there, so how are you going to prioritize that?

REINGOLD: There will definitely be a fall semester. I sit in on the calls with the Chancellor and Vice Chancellor three mornings a week. We are definitely planning to have school in the fall. The question is how much can be on-campus, in-person education and how much will be online. I do not know the answer to that and neither does anybody else, including the Chancellor and the Vice Chancellor. I am working with the Tang Center and the City of Berkeley on the issue of tracking who might have become infected and preventing infected people from transmitting the disease to others once we do start letting people be more out and about. All that preparation is underway. Anybody who says that he or she can predict what is going to happen three or four months from now, I think is delusional. They might get it right by chance, but I am not smart enough to know the answer to that question.

1. Sandra McCoy [Photograph]. Retrieved from <https://publichealth.berkeley.edu/people/sandra-mccoy/>
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