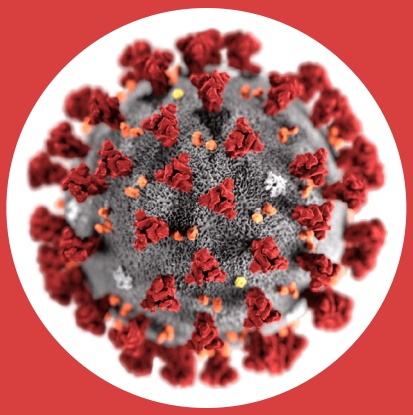

COVID-19 Year in Review: Insights from UC Berkeley's Infectious Disease Experts

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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.

BSJ: Reflecting upon the past year, what was predictable about the course of the pandemic, and what were you surprised by?

Schekman: I did not think that the pandemic would be as overwhelming as it has been, and I am shocked at the level of death and severe illness. On the other hand, it amazes me how quickly vaccines have been developed. Even so, wealthy countries have taken advantage of this speed by hoarding vaccines at the expense of developing countries, which is discouraging because we cannot return to normal until a majority of people globally are vaccinated. Fortunately, there are non-governmental agencies and projects, such as a vaccine initiative supported by the Gates Foundation, that aim to distribute vaccines in developing nations.

Schaletzky: There has been a real renaissance in biology in the last year, and people who did not previously specialize in viruses are now entering the field and bringing all kinds of new technologies into it. That is wonderful. Additionally, I was positively surprised by the speed of the science being developed. However, I was negatively surprised by the lack of deregulation. The United States administration has been ossified; we have not really been able to deal with this pandemic quickly enough. It gives me a bad feeling for future disasters.

BSJ: Since the last time we talked, which new findings on SARS-CoV-2's mechanism of infection surprised you the most? Are there any clinical mysteries that you are still curious about?

In this piece, we discuss the evolution of the COVID-19 pandemic and how it has both driven and shifted the scientific community. We met with eight infectious disease and genetics experts in late March to discuss their perspectives on global response, vaccination, and lessons learned.

BY LIANE ALBARGHOUTHI, LEXIE EWER, TIMOTHY JANG, ESTHER LIM, EMILY MATCHAM, REBECCA PARK, KAITLYN WANG, ALLISUN WILTSHIRE, AND SABRINA WU

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.

John Swartzberg, MD, FACP, is an infectious disease specialist and Clinical Professor Emeritus at the UC Berkeley School of Public Health. Before becoming a full-time faculty member, Dr. Swartzberg had 30 years of clinical experience working in infectious diseases and internal medicine.

Randy Schekman, PhD, is a professor of Cell and Developmental Biology at UC Berkeley and an investigator at the Howard Hughes Medical Institute. He launched the open access journal *eLife* in 2012 and won a Nobel Prize in Physiology or Medicine in 2013.

Stacia Wyman, PhD, MS, is a Senior Genomics Scientist at the Innovative Genomics Institute. Dr. Wyman works on computational research involving CRISPR and has recently transitioned to researching COVID-19 genomics.

Swartzberg: What surprised me the most with COVID-19 was that I anticipated it to behave very much like influenza. However, it can be much more aggressive than most cases of influenza and carries a significantly higher morbidity and mortality rate. There have also been some disconcerting developments, specifically regarding how SARS-CoV-2 attacks many other parts of the body aside from the airways. The myocarditis issue [inflammation of the heart] and neurological complications following infection, for example, were not anticipated and were difficult to predict.

Another concern we have regards what has been described as the post-COVID syndrome or long COVID. This is a condition that is probably multifactorial in cause and of which we have a very poor understanding, even though it appears to be extremely common. It defies a really good pathophysiologic mechanism because it seems to occur in everyone, from people who were very ill with COVID-19 to those who were asymptomatic. Post-COVID syndrome could be a very significant long-term tragedy for millions of people and could also be a tremendous burden on our healthcare system going forward.

Another issue that is fortunately not as common as we were initially afraid of is the multisystem inflammatory syndrome in children. It appears to be an inflammatory process triggered by the virus, but we neither know what causes it nor why certain children are more predisposed to it. We see it more commonly, for example, in African-American children than in other racial and ethnic groups, but we do not have an explanation as to why. We also do not know about the long-term sequelae from that.

These are just a few things that immediately come to my mind when I think of how confusing COVID-19 really is.

"Post-COVID syndrome could be a very significant long-term tragedy for millions of people and could also be a tremendous burden on our healthcare system going forward."

BSJ: Within this past year, how has the COVID-19 pandemic affected you and your colleagues' research focuses?

Conklin: My lab has become pretty good at pivoting and trying new things. For example, we were able to start two completely new projects. One of these, which was inspired by virologist Dr. Melanie Ott, explores the reaction of cardiac cells to SARS-CoV-2. Many researchers in the pathology community thought that COVID-19 was only a lung disease; however, we found that the tissue in cardiac cells not only gets infected, but actually produces the live virus! There have been signs of cardiac effects—specifically, increased troponin levels—among COVID-19 patients. Troponin is a cardiac-specific protein; its normal levels should be very close to zero, so chest pain and a small bump in troponin is a sign of a heart attack. COVID-19 patients have increased troponin levels, but it has been very hard to show that the virus was in the heart. Overall, the assessment is that the SARS-CoV-2 virus can circulate around your body and rarely breaks into cardiac cells. But when it does infect the heart, troponin levels go up and mortality rates increase across the board, even in relatively young people. What is really unknown is how severe the effects on the heart are and whether or not they will be long-term.

Wyman: It has had a huge impact. On March 13 of last year, Dr. Jennifer Doudna, the head of the Innovative Genomics Institute (IGI), got a slew of IGI and UC Berkeley scientists to come together for our last in-person meeting to discuss how we can pull together our resources and expertise to address the pandemic. That meeting sparked many different COVID-related projects since researchers could only return to the lab for COVID-19 work. For example, Dr. Patrick Hsu and Dr. David Savage have developed a rapid COVID-19 test that can be read with an iPhone. It has been amazing to see individuals from different areas of expertise come together to work on this one thing. This kind of scientific pivot has had a huge impact on getting everything ramped up fairly quickly, such as the vaccines, new technologies for testing, and genomics efforts.

BSJ: What are some widespread misconceptions about how mRNA vaccines work?

Schaletzky: A misconception is that the mRNA vaccine causes some kind of DNA modification of the host genome, but that is not true. We have echo chambers on social media now, where conspiracy theories can grow and be distributed so easily. I would say to people that they should follow the central tenet of the Enlightenment and just think for themselves and look at the data that has been published. The mRNA vaccines work very well, better than other modalities. In Israel, we already have a whole country more or less vaccinated with really good results.

BSJ: How do the Moderna and Pfizer COVID-19 vaccines compare to vaccines we have seen in the past? What would you say to someone who is on the fence about receiving a vaccine? How do social systems impact a person's perspective on vaccination?

Schaletzky: The only change is that the mRNA basically allows our own body to make the antigen that is needed for generating immunity. In the past, we purified the antigens outside of the body using recombinant and biotechnology methods and injected the protein that is already formed into the body. In this case, the mRNA acts as a transcript or blueprint for this protein, and your own body makes the protein for the immune reaction—and this works better than the old way of making a vaccine, it turns out. I would trust this vaccine because it is more efficacious than the subunit vaccines that are generated via the usual recombinant methods, and it works in more than 95% of the cases. We currently also have no evidence to say that it would not work against the other emerging variant strains.

McCoy: Vaccine hesitancy is a really important issue, and I think we know from behavioral science and psychology that trying to convince someone that they are wrong often just makes them more staunch in their beliefs, and it can actually backfire. It is really important to understand where their concerns come from. Concerns about side effects or contraindications for pre-existing conditions are valid concerns that we as public health professionals can ease by providing patients with information so that they can make informed decisions. The more finger-wagging that we do as scientists, the less effective we will be in achieving our public health goals, so we have to be coming from a place of understanding and wanting to find a middle ground. For one, in the U.S. there has been a history of horrifying ethical violations tied to racism against communities of color, so it is no surprise that even several generations later many communities are distrustful of the biomedical community and their products or services, such as vaccines. I think that is a really important context to consider when working with communities of color as well as any disadvantaged or vulnerable communities, as there are existing legacies that predate all of us but still influence people's willingness to engage in health services and use health

"Many researchers in the pathology community thought that COVID-19 was only a lung disease; however, we found that the tissue in cardiac cells not only gets infected, but actually produces the live virus!"

products. Certainly, we also have to acknowledge that there is a political element that is shaping people's mistrust or disbelief of science. However, it is really important to not immediately discount people who are vaccine-hesitant as being uninformed or any host of other adjectives because it is really difficult to navigate the swarm of information and misinformation that is readily available at our fingertips.

Reingold: I have a lot of experience talking to people about vaccination, including people who are not interested in vaccination. In general, people love their families and their children, and they want to do what is best for them or for themselves. It can be difficult to make a wise decision when there is an enormous amount of misinformation, rumors, and outright nonsense. I understand why it is hard for people. I understand why people are disinclined to listen to an elderly Berkeley professor. Having said all of that, it is very much my judgment, and the judgment of people who are a lot smarter than me, that the benefits of vaccination against COVID-19 far outweigh the risks. There are unfortunately some young, healthy people who get seriously ill and even die from COVID-19. No vaccine is perfectly risk-free. No medication you take is risk-free. In fact, nothing you do in life is risk-free, but these vaccines are very safe and effective. People of color might be more resistant or hesitant about vaccination because of a long history of medical mistreatment. Concerns about vaccination have always been there in every group, whatever your race, whatever your socioeconomic status, and whatever your political views. The enormous difference in concern about this pandemic and interest in this vaccine by political parties may be new, and those things influence the extent to which people worry about COVID-19 and the extent to which they are willing to change their lives. It has become highly politicized, and that is very unfortunate.

BSJ: As new SARS-CoV-2 variants are spreading throughout the world, do you notice any trends in individual responses to these variants? In what ways do the variants affect the vaccine response and the goal of achieving herd immunity?

Wyman: A virus is always accumulating mutations, and that is completely normal. Sometimes these mutations are deleterious to us but beneficial for the virus. When we had a huge surge of the virus in December and January, it gave the virus the opportunity to accumulate these deleterious mutations, and then the resulting variants were able to take over some populations. For example, Alpha (B.1.1.7) has been in the U.S. for a while now, but in Northern California, it is rare compared to Southern California. Instead, we have a California variant, which now makes up more than 50% of the cases in Northern California and constitutes a large number of cases in Oregon and is now found in most states. For these variants, there are certain mutations that have been shown to have a negative functional impact, and those mutations have been arising independently in different locations. The E484K mutation spontaneously arose with Alpha, and now it has spontaneously arisen in some other variants as well. It is really important to be aware of what is out there and monitor the spread of new variants but not be panicked before having any functional evidence. I personally feel

"No vaccine is perfectly risk-free. No medication you take is risk-free. In fact, nothing you do in life is risk-free, but these vaccines are very safe and effective."

quite optimistic about where we are heading with vaccinations and with surveillance of the variants. Right now, we have information about the variants that have been resistant to the vaccines, as well as how they react with convalescent plasma (to simulate if someone was reinfected). We need to continue to do extensive sequencing and sampling around the world, and in particular, continue monitoring and sequencing the cases of vaccine breakthrough. This will help us know what is out there and what kind of impact it is having so that vaccine manufacturers can adapt to the current situation and give us boosters or modify the vaccine.

Reingold: Our primary concern as human beings in a race with these viruses is figuring out which variants can, on average, make you sicker if you are getting infected. The second question is whether they are more readily transmitted from one person to another. The third, and in some ways the most important, is whether they pose a problem in terms of vaccine-induced immunity or even naturally acquired immunity to a different variant. That raises the question of whether people have to generate other variations of a vaccine and whether this will increase the need for booster doses. The program I run, the California Emerging Infections Program, is currently conducting surveillance across multiple Bay Area counties. We work with the state and county health departments and have received a large amount of additional funding to help answer these questions. Nationally, we are part of a network of about 10 or 15 sites, and we have all been given more money by the CDC in Atlanta to allow us to contribute to answering these questions, particularly in regards to mapping the variants and studying vaccine effectiveness against the various areas.

BSJ: In what ways has this pandemic called attention to the need for open access journals?

Bertozzi: The pandemic has done more to support preprints than it has open access journals. Overwhelmingly, new scientific advances with respect to COVID-19 have been posted on one of the preprint servers, and then moved from there into traditional publishing. However, even if they are moved into a journal, the preprints may be published by a journal that is not open access. So, the fact that the preprint is publically available means that people have access to that information—even though it may not be the final version. Nevertheless, it is usually enough to create the kind of access that open access strives to achieve. Interestingly, this devalues what people are willing to pay for the published version in a subscription-based journal. So, I think it helps to drive the whole world in the direction of open access.

Schekman: This pandemic has really changed the public perception of science because even commercial journals, which are closed access and are available only by license agreements with institutions, have realized that COVID-19 research needed to be put out there for all to see. However, these journals only made available the research that was relevant to the pandemic; they did not do so for all of the other work that was published. As soon as this pandemic is over, the door is going to close again. A trend that happened even before the pandemic—which is a good thing—is that there was a lot of pressure for people to put their publications in a public archive once they were ready to be reviewed. Overall, preprint servers have allowed more eyes on every paper. The usual closed-review approach is as follows: the paper is submitted to a journal, it is assigned to several experts, and these experts read and offer comments—usually on specific mistakes or limitations. However, if this process is only done by three or four people, there could be things that are missed, even by experts. Now, when researchers post something on the preprint servers, they can have thousands of people reading it. As a result, flaws can be pointed out more effectively.

BSJ: What are your thoughts regarding the likely return to in-person instruction by fall? What kinds of precautions do you think need to be in place for in-person instruction to begin?

Swartzberg: First and most importantly, it is going to require a cooperative student body, along with our staff and faculty, following public health rules. Second, it is going to require careful monitoring: we are going to need to have robust testing of staff, faculty, and students, as well as the alacrity to act on that testing quickly with contact tracing. Third, we are going to need to have vaccine availability. My aspiration is that all of our students, faculty, and staff will be vaccinated.

I really want to stress individual behavior. The vast, vast majority of the students on our campus behave really responsibly and do the right things. But when you have over 30,000 students, you are going to have a small percentage who do not.

In sum, we have the tools to make it safe. This virus does not cause as much disease in younger people (although it certainly can). It causes most deaths in older people. However, the major driver of transmission is primarily young people. This creates an interesting conflict—we are asking people to tell themselves that they need to protect others from getting infected because they are driving the pandemic. There is not as much in it for them to do those things, and that can be problematic.

Reingold: A key issue is going to be vaccination. There is discussion about whether vaccination will be mandatory for students to come on campus. This is a system-wide discussion across ten campuses. That could only happen if the various vaccines get full approval from the FDA. At the moment, they only have emergency authorization. If they, as planned, get full authorization in June along with increased availability of vaccines, it is quite likely that students will not be allowed to come to campus if they have not been vaccinated. There is nothing unusual about doing that. I am sure there will be resistance. I am sure there will be people who object. I am sure there will be lawsuits, but mandatory vaccination will enhance safety and the ability to be together in a classroom.

"This creates an interesting conflict—we are asking people to tell themselves that they need to protect others from getting infected because they are driving the pandemic."

BSJ: What lessons has the pandemic taught you, both in your personal and professional life? What are some important takeaways from the global response to COVID-19?

Bertozzi: There is so much we did wrong that it is difficult to point to the positive lessons learned. One specific lesson is that for each type of pathogen, the international response needs to be differentiated by the kind of transmission with which it is associated—for instance, respiratory, blood-borne, or sexually transmitted. Another major takeaway is that PPE can and needs to be stockpiled for the next pandemic. Since respiratory pathogens spread the most quickly, we need to have the appropriate PPE in massive quantities so that they can be deployed immediately. We need to invest in advancing production capacity for the tools that we know we will need the next time we have a problem, whether it is a new variant of this virus or a new pandemic. That means we must improve our ability to quickly diagnose disease and develop monoclonal antibodies that can fight or prevent infection. Ideally, we should also invest in monoclonal antibody technology, which will enable treatments to be just a squirt in the nose rather than an infusion, simplifying the treatment modality by a lot. Thirdly, not only do we need to invest in vaccine development, but we should also develop a consolidated, coordinated, preexisting understanding of how we will rapidly scale up manufacturing as soon as a vaccine is available. Further, we should have predetermined financing available. This time, we had to start looking for financing when the pandemic hit, even though we should have had an immediate infusion of money to prepare manufacturing capacity for vaccines, drugs, and diagnostics. Finally, we need to think about our public health infrastructure and how that can be rapidly activated.

Conklin: I think a pandemic is one of those events that really makes you most aware that we are one people living on one planet and that what happens in some other part of the world is going to affect you, even if it is far away. The countries that were most prepared were the ones that actually had SARS-CoV-1 outbreaks and knew how to handle this exact kind of virus with targeted public health measures. Our own public health system, in particular the CDC, was remarkable in how it dropped the ball. By suppressing testing and targetedly dismantling the public health system, their errors really had a huge effect on our country and our economy. However, I am hopeful that we can come out of this with a greater sense of urgency and responsibility towards global public health measures,

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especially for infectious disease. This is also the first time that mRNA has been used really as a therapeutic in any kind of large scale, and it is a huge addition to the biomedical armamentarium. People are now thinking of other applications for mRNA technology, like cancer immunotherapies and CRISPR systems. The power of this technology is something that can really accelerate our approach, biomedically speaking and beyond.

McCoy: We are learning just at the university level that we can pivot really fast, and that students and faculty are very resilient. The fact that we all went remote within weeks' notice is incredible. I am the program lead for the online epidemiology and biostatistics program, and one thing that has been a silver lining for us is just that people are becoming increasingly interested and respectful of remote education, which can bring education to many more vulnerable populations who might be left out of the formal university setting but can attend from other places.

This interview, which consists of multiple conversations with each expert, has been edited for brevity and clarity.

IMAGE REFERENCES

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2. *Conklin headshot*: [Photograph of Bruce Conklin]. Gladstone Institutes. https://gladstone.org/people/bruce-conklin. Reprinted with permission.
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5. *Schaletzky headshot*: [Photograph of Julia Schaletzky]. Henry Wheeler Center for Emerging and Neglected Diseases, University of California, Berkeley. http://cend.globalhealth.berkeley.edu/julia-schaletzky-phd/. Reprinted with permission.
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