# Transcript

## Quinn Barnette:

Welcome, everyone, to the Recover Research Review or R3 Seminar. My name's Quinn Barnette. I'm an epidemiologist for the RECOVER Administrative Coordinating Center, and I'll be your moderator for today's session. The goal of this seminar series is to catalyze a shared understanding of the research within the RECOVER Consortium.

I want to start by thanking everyone who submitted questions in advance and remind everyone that you can submit any questions during today's presentation using the Q&A feature in your Zoom menu. After today's panel, our speakers will answer as many questions as possible. The Q&A document will also be posted with a recording of the seminar on recovercovid.org. The document will include answers for submitted questions relevant to today's presentations.

Questions about other scientific topics will be addressed in future seminars, and answers to broader questions about RECOVER will be available in the FAQs found at recovercovid.org. As a reminder, we cannot answer questions about individual clinical care.

I'm pleased to share that our presenters today are Dr. Elizabeth Oelsner, Dr. John Kim, and our discussant will be Dr. Wendy Post. Dr. Oelsner is a general internist, respiratory epidemiologist, and associate professor of medicine at Columbia University Irving Medical Center. Her research leverages multidisciplinary and collaborative studies to investigate emerging risk factors for chronic lung diseases.

Dr. Oelsner is the principal investigator for the Collaborative Cohort of Cohorts for COVID-19 Research, or C4R, which is ascertaining SARS-CoV-2 Infection and post-COVID-19 Conditions across 14 NHLBI and NINDS-funded studies. C4R aims to provide a collaborative resource to define risk and resilience factors for COVID-19 and to study the impact of the pandemic on trajectories of health and disease.

Dr. Kim is a pulmonologist and assistant professor of medicine at the University of Virginia. He has translated his clinical interest in interstitial lung disease into a research career that integrates imaging biomarkers, multiomics and phenotype data to identify subgroups of individuals at higher risk of developing pulmonary fibrosis.

Dr. Kim has published research identifying strong associations of non-pulmonary fibrosis, genetic variants with automated imaging biomarkers of early lung inflammation in fibrosis, and potential modifiable risk factors. Dr. Kim's long-term goal is to design and implement clinical trials aimed at preventing the development of pulmonary fibrosis, and in recent years, he's extended his work into SARS-CoV-2, including antibody responsiveness to COVID-19 vaccines in associations of pre-pandemic lung-imaging abnormalities.

Finally, Dr. Post is the Lou and Nancy Grasmick Professor of Cardiology in the Department of Medicine at the Johns Hopkins University School of Medicine with a joint appointment in epidemiology at the Bloomberg School of Public Health.

Dr. Post is a cardiologist at the Ciccarone Center for the Prevention of Cardiovascular Disease where she's director of cardiovascular research for the Division of Cardiology and director of research for the Cardiovascular Fellowship Training Program. Dr. Post's research interests include prediction and prevention of coronary heart disease, heart failure and sudden cardiac death, genetics of cardiovascular disease, sex and ethnic disparities in heart disease, and cardiovascular disease in people living with HIV.

The topic of today's seminar is Vaccine Response and Time to Recovery from COVID-19 and Multi-Cohort Collaborative. Today's speakers will present findings from the Collaborative Cohort of Cohorts for COVID-19 Research, or C4R, which is analyzing data from over 50,000 US adults participating in long-term NIH-funded cohort studies.

Investigators will discuss how pre-pandemic health and lifestyle factors are associated with the level of anti-spike protein response following COVID-19 vaccination and the time to recovery after infection.

Please welcome all of our speakers. And with that, I will turn it over to our first speaker, Dr. Oelsner.

## Dr. Elizabeth Oelsner:

Thank you so much for that kind introduction. Hold on. Let me share my slide. Okay.

I'm really delighted to have this opportunity to introduce C4R. I hope that this presentation is going to provide the important context behind the scientific results that we're going to discuss later in this session, and I also really hope it inspires new research that we can do with the C4R resource.

We started planning C4R almost five years ago in March 2020, and at that time, we set as our general framework to consider the past, the present, and the future of COVID-19 research, so looking at the past, looking at pre-pandemic factors, health, lifestyle, social determinants, and how they might influence risk of SARS-CoV-2 infection in the present, the present at that time being 2020, thinking about how severe the infection might be.

We didn't know yet about variants in vaccinations, but that came soon into 2020 and 2021. And then even from the very beginning, we were asking ourselves, what is the future here? Will SARS-CoV-2 infection and COVID-19 illness lead to persistent symptoms, lead to new diagnosable conditions, broadly put, sequelae.

So now years later, we're looking still at the past, and infection and the sequelae are very much our present. We've developed a huge amount of data to better understand some of these questions, and there are still many unanswered questions and many new questions, and we hope that C4R, together with other recover studies and other resources across the world, can help us get to the answers to these current and future questions.

C4R's approach was relatively unique because we were focusing on the resources available to us in 2020. We wanted to put together pre-pandemic data with pandemic data to advance our epidemiology of COVID-19. Specifically, we proposed to harmonize measures that had already been collected by NIH-funded cohorts as part of pre-pandemic exams, and I'm going to talk more about that.

Then we wanted to do standardized data collection across all 14 pre-existing NIH cohorts starting in April 2020 and continuing through the present, and we wanted to make these data available as soon as possible to as many investigators as possible. So we developed a cloud-based platform called the C4R Analysis Commons for pooled-cohort data, and we have other options to access the data that I'll talk about at the end.

So who were our 14 pre-existing NIH-funded cohorts that we wanted to bring together as a team to help study COVID-19? There are eight cardiovascular cohorts or cohorts that were designed to look at general population health that we were able to bring together for this effort. You may or may not be familiar with these cohorts. They are, in my world, famous. For many people, the one they've heard of the most is the Framingham Heart Study, and that's one of our cohorts.

We also had four pulmonary disease-focused cohorts and two cohorts that were developed to look more at neurocognitive outcomes. This group of 14 cohorts agreed to come together as a historic collaboration in 2020 to try to do our best to answer questions on COVID-19, and we continue to work together to this day.

These cohorts had been collecting data for decades prior to the pandemic. This is a complicated figure. I'll just give you a little orientation to it. So along the top are the icons for each of those cohorts I had on the prior slide, and you won't be able to read all the details. If you want to see those, they're in our methods paper published in the American Journal of Epidemiology in 2022.

Along the vertical side, we have the timeline from 1971 when the first Framingham Offspring Cohort Exam occurred through 2025 around the corner from us now. You see that all the little boxes, those are in-person exams conducted by the cohorts over the years for their participants. All of these cohorts have been also evaluating participants during the pandemic and the post-pandemic period. Those exams are shaded in blue.

In 2020, we thought this was an incredible resource to look at this pre-pandemic health and other health-related factors with respect to how the pandemic would impact participants. What was really special about the data that had been collected prior to the pandemic is that it includes lots of different measures that are very biologically important to understanding SARS-CoV-2, and now long COVID and post-acute sequelae for SARS-CoV or PASC.

So this slide shows a tally of the number of C4R participants with specific measures collected over the period, 2010 to 2020. There are too many of these to go through. Again, they're published in our methods paper if you want to review them in detail. But what this shows is there are tens of thousands of measures for biomarkers, everything from genomics data to gut microbiome data.

We have information on sleep and actimetry. We have information on neurocognitive performance. These are exams that can take up to 90 minutes to administer, and exams like this were conducted in our C4R participants prior to the pandemic and then harmonized by C4R so that all of those studies can be put together and leveraged as a large data resource.

We have information on the heart from electrocardiograms to echocardiograms to cardiac MRI. We have imaging of the chest, both cardiac imaging and lung imaging, and those data have been harmonized for the first time, as part of C4R, using deep learning approaches so that we can really see the lung structure prior to acute infection prior to long COVID and PASC.

We also have physical function measures of a variety of types, including lung function or spirometry, and those data were actually harmonized before the C4R effort to look at other research, and we were able to build that into the C4R data.

All told, the C4R cohorts were able to enroll over 51,000 diverse participants to date, and this slide just shows some really basic sociodemographic data on those 51,000 participants. You see that we have a bit more women than men. We have two-thirds of our participants who were 65 years of age or older in 2020, so it's a more older adult resource than a young adult resource, but we still have tens of thousands in that group, too.

And then in terms of the racial and ethnic composition of our sample, we have less than 50% non-Hispanic whites and then very large numbers of Hispanic, Latino, and Black participants, and smaller numbers, but still very substantial numbers, of American Indian participants and Asian participants.

Across this group of over 51,000 participants, we were able to do standardized data collection from 2020 through the present. I won't go into too much detail here, but we have done three waves of

questionnaires. The third wave of questionnaires is ongoing, and these are getting at experiences of SARS-CoV-2 infection, SARS-CoV-2 symptoms.

We have questions on vaccination history, hospitalization history. We also have questions on mood, on finances, on attitudes and beliefs, so a very rich picture of how individuals were experiencing SARS-CoV-2 and also the pandemic period itself, disruptions to their behaviors, to their jobs, to their finances.

We also conducted two serosurveys. The second serosurvey is underway. You're going to learn more about this from Dr. Kim in the next presentation, so I won't go into too much detail, but we have gotten blood from our participants during the pandemic to look at antibodies against SARS-CoV-2.

And finally, we have been actually reviewing medical records for all COVID hospitalizations and deaths across the consortium to make sure that our outcomes are really validated so that we really know when we say that someone had a COVID-related stroke, for example, we've confirmed that in the original medical record.

With respect to the pre-pandemic data, as I mentioned, we had a lot of it, and we've been trying to harmonize as much as we reasonably can. I highlighted that we've already done harmonization of neurocognitive exams, also of brain MRI, of chest CTs. We have the spirometry harmonized. And then this is a bit of a sampler of other data that has been harmonized across the cohorts.

You see that we have tens of thousands of participants with information on lifestyle factors from smoking to cannabis to exercise, on clinical factors across a broad range of diagnosable conditions, also depression and anxiety. We have information on social and structural determinants of health, like educational attainment, household income, occupational status.

Finally, this is just a bit of a sampler of some of the biomarkers we have on hand from the pre-pandemic period. They include things like C-reactive protein, Factor VII, cystatin-C, fasting blood glucose, covering a broad range of potential health conditions and potential pathophysiologic pathways which are important to SARS-CoV-2.

We currently have 35 investigators working on C4R data across the country, leading, at last count, 47 approved C4R analyses. So there are probably even more than that at this time, but that was the latest that I prepared for this presentation. This is just a map to show that they really are all over the country, and some of them might be at a university near you.

We're coordinating the work out of Columbia University, which is where I work. We have a bunch of publications, and we're going to be highlighting two of them today. So Dr. Kim is going to talk about this Nature Communications article on Demographic and Clinical Factors Associated With SARS-CoV-2 Spike Antibody Response Among Vaccinated US Adults.

After that, I am going to talk about our publication in JAMA Network Open, looking at Epidemiologic Features of Recovery From SARS-CoV-2 Infection. We also have articles in some journals shown on the right side of the slide and many that are currently under review, and we look forward to publishing very soon.

We think that C4R has some unique advantages for long COVID and PASC research. Those include our diverse US general population-based sample. I already showed you that we have a very large group of participants who include men, women across the age range of adulthood and also from many different racial and ethnic backgrounds, also various regional backgrounds, social backgrounds.

What is quite unusual about C4R data is that our participants joined the studies before COVID-19 existed. So they did not join our study because they were particularly interested in COVID-19 or

because of their experience with COVID-19. This means that our sample is relatively free of some selection biases that occur in studies that are conditional on a certain disease. Those studies are also highly valuable, but this is one advantage of our cohort approach.

We also have rich data on social and structural determinants of health, including geocoding, which can be used to look at a lot of really important questions relating to disparities. A second major advantage is that we have this pre-pandemic, pandemic, and post-pandemic data. So, as I showed you, the cohorts have been connecting exams since 1971, in some cases, all the way through 2025, and many of them are going to keep going through the 2020s.

That means that we have quantitative imaging, biobanks, and multiomics from the pre-pandemic period, much of which we've harmonized, and we will in the future have, in the same participants, post-pandemic imaging, biobanks, and multiomics, which is a really exciting opportunity for research.

We have been collaborating throughout with RECOVER. Many investigators have leadership roles in both C4R and RECOVER, and I couldn't put all the areas of collaboration on a slide, but I wanted to highlight that our latest wave-three questionnaire was actually developed together with RECOVER so that we could really look at some of the same questions in the RECOVER observational cohort and the C4R cohort to confirm results, to validate results, to assess any differences, and to potentially pool our strengths to answer as many questions as well as possible.

Our data is currently available in a number of ways. The data is available on BioData Catalyst, which is an NIH repository that does require a data-access application, but is, by most terminology, publicly available. So the data are there for analysis. The data are also posted to the TOPMed Exchange area for TOPMed investigators who are looking at multiomics questions.

Our resource, which we tend to use within the C4R consortium, is the C4R Analysis Commons. This, again, is a cloud-based data enclave, which allows us to work very closely across different universities in a secure manner to do the work as quickly as possible and to get the harmonization done swiftly and reproducibly.

Furthermore, all of the data that was developed by the 14-cohort consortium of C4R is transferred back to each of the 14 cohorts. So each cohort that's participating gets a full harmonized copy of their own C4R datasets so that that data can be used by cohort investigators and combined with other resources from the group.

In terms of research opportunities going forward, we think there are too many to fit on a slide. I just want to highlight that we still are very interested in questions linking pre-infection and post-infection health and looking at how SARS-CoV-2 may have altered trajectories of health or disease. So we have these omics biomarkers imaging data. We have tons of characterization of SARS-CoV-2 infections and COVID-19 across our very large set of participants.

We also have some really important information on the pandemic itself to look at independent of the infection effects. What might be the secular effects, the cultural effects the pandemic might have had on health and health-related behaviors? So we welcome new proposals for research. We welcome ideas, and we feel very lucky to have been able to conduct this study with such an incredible team over the past few years. So that's my last slide. I'll stop there.

## Quinn Barnette:

All right. Thank you so much, Dr. Oelsner. I think now we'll turn to Dr. Kim.

## Dr. John Kim:

I just want to thank RECOVER for the opportunity and the invitation to share our research and our recent publication out of C4R. The title of this presentation is Anti-S1 Response to Vaccination in US Adults, The C4R Study. It may or not be relevant, but the only disclosure is that we do receive grant support from the NIH.

A background of the study is that I think we can appreciate that vaccination is a critical public health intervention that has been shown to prevent infection and attenuate illness severity. The messenger RNA vaccines, they're proven to be effective in COVID-19, but then studies were emerging that showed heterogeneity of antibody responses to the vaccines in certain populations.

We think this is important because research and data has shown that antibody levels after vaccination may correlate with the degree that an individual is protected from being infected, but also potentially being protected from how severe they become if they are infected. Prior studies had linked some comorbidities such as heart disease, lung disease, as well as other risk factors like older age, linking to a lower response to vaccinations.

What was noted is that those studies, one was that they were comprised of smaller samples. Some of them were from the pharmaceutical trials. Some of them were based just at single medical centers. And then larger data that was emerging, a lot of it was actually coming from the United Kingdom.

So we thought that it would be interesting and informative to look at it in the United States and particularly because in the United States we had two major mRNA vaccines, Pfizer and Moderna, whereas the studies from UK, they mainly looked at Pfizer and vaccines from AstraZeneca. Also, those prior studies, it was noted that there were certain, self-reported at least, race and ethnic groups that were absent from those analyses.

I think, as Dr. Oelsner highlighted, a unique aspect of C4R is that we had pre-pandemic assessments of these comorbidities as well as other risk factors, whereas a lot of these other studies had used pandemic-era or post-pandemic assessments. So we thought that it would be interesting to apply the harmonized data out of C4R to look at factors that might at least associate with antibody responses to COVID-19 vaccines.

The main objective of this study was to identify correlates of anti-S1 IgG antibody levels after COVID-19 vaccination in US adults. I'll get to why we focus on anti-S1 IgG antibody in a couple of slides. So again, these were C4RR participants who had anti-S1 antibody levels measured and who had received two doses of the mRNA COVID-19 vaccine, and this was primarily based on individuals reporting that they had gotten at least two doses of that vaccine.

We used linear regression models to examine candidate risk factors and their associations with these anti-S1 IgG levels. There was some data that was missing in terms of demographics, so we use statistical methods here to try to what we call impute and fill in that missing data.

As Dr. Oelsner alluded to in her talk about all the data that has been compiled in C4R, one of the major unique aspects is this dried blood spot or what we call, in short, DBS. Here, you can see in this figure above, participants actually received a kit where they would just do a finger stick, like a prick, and they would drop blood onto these what we call these cards.

Here on the second figure on the top, you can see there's a finger with a drop of blood, and you would drop it into this dotted circle. This is actually a real-life size of what the size of these circles are. So you would drop a blood into, I think, about five of these spots. And then all you actually needed to do

was actually take a punch hole of that spot and actually can run a lot of different lab measurements, like you would if you were to collect actual blood in a laboratory.

I should credit that these are slides from Dr. Monica Parker who is at the New York Department of Health Wadsworth Center. They actually overlooked measurements of these antibody levels from these dried blood spots collected on these cards. An advantage of this is that these cards are actually pretty durable. You can actually store them in room temperature.

They actually can last for several years, and you can still run measurements and tests from these samples. I won't go into detail, but basically they would take these spots, these punch holes, and then run these tests and be able to quantify and measure COVID-19-related antibody levels.

We were interested primarily in anti-S1 because we know that anti-S1 antibody levels are a bit more specific to vaccines. So typically, if you receive a COVID-19 vaccine, you will have an increase in these anti-S1 antibody levels, which again, we think correlates with how effective the vaccine is working, whereas anti-N1 antibody, that's a bit more specific to infection.

So this was a study, again, out of the New York Department of Health Wadsworth Center. This was led by Dr. Linda Styer. What they did was, in the beginning of the pandemic, they actually collected both blood samples as well as dried blood spots, those spots in the blood, and they correlated how good these dried blood spot levels correlated with actual whole blood levels.

Here, the boxes, the squares here indicate anti-S1 levels, and what matters is that we see a pretty straight line at almost a 45-degree angle, and this says that basically the levels of antibody from the dried blood spot correlated really strongly with those antibody levels from blood measurements. So we thought that maybe these dried blood spot measurements of antibody levels were pretty accurate.

This was the paper we published just this past year in Nature Communications, again, looking at factors that might correlate with these antibody levels. Out of that big C4R cohort, we had 6,245 participants who had valid dried blood spot measurements as well as who received two doses of the vaccine.

In the meantime, between at least the first vaccine dose and when they did the dried blood spot was about four months. The average age of this cohort was 73 years with a range of anywhere from 21 to 100. It was an older cohort, so over 70% were over the age of 65. Over half of the cohort were female, and about 76% were non-Hispanic white.

This is a plot here showing what the antibody level measurements were at the time between the first vaccine dose and when the blood spot was collected. Here overall, we can see that it seems at 60 days, which is indicated by the vertical blue line here, is when these antibody levels peaks, so about 60 days after that first vaccine dose. And then you see this gradual decrease in these antibody levels as there's more time between your first vaccine dose and when you gave the dried blood spot test.

We looked at certain risk factors that might associate with these antibody levels over time. So here in this first panel we at whether age correlated with these antibody levels after a vaccine. And again, the X-axis is the time between that first vaccine dose and the dried blood spot sample. Here, we can see that in the red line, these are people who were below the age of 65, so younger.

Participants who were below the age of 65 seem to have a much more stable antibody response. So even if you were 180 days out from your first vaccine dose, you actually had a higher anti-S1 IgG level compared to older participants, so suggesting maybe a little bit more protection than those individuals of older age.

In the next panel here, we compared males and females. In the red line are females, and there we see that, one, they seem to have a higher initial antibody response after the first vaccine dose and that, over time, this seemed to still remain at least higher levels than men.

Other risk factors we looked at was smoking status. So here we see that in those participants who at least reported a history of current smoking, these participants had lower anti-S1 levels over time, and this was sustained throughout. Whereas, people who reported to have never smoked here in the blue line or were former smokers in the green line, they had higher levels of anti-S1, again, suggesting they had a little bit better protection with the vaccine.

We know that diabetes had seemed to be a risk factor at least in COVID-19 illness and severity, and so we looked at this as a risk factor in how well you responded to the vaccine. Here, as indicated by the red line, participants who at least had a history of diabetes, again, this is pre-pandemic, people who had a history of diabetes seem to have, one, a lower response to the vaccine indicated by these lower antibody levels and that this, again, seemed to persist over time compared to those participants without a history of diabetes.

Again, a unique aspect of C4R in the study was that it's primarily based in the US, and so we were at least able to compare the two major mRNA vaccines that were used, which was BNT162b2 and mRNA-1273. So we looked at antibody levels responses to these vaccines, and here it seemed that at least those participants who reported to have gotten the Moderna vaccine, they had higher anti-S1 IgG levels and that this higher levels compared to the Pfizer vaccine seemed to persist the more days, again, between your first vaccine dose and when you gave the dried blood spot sample.

Then we also looked at infection severity related to COVID-19, and again, correlates with anti-S1 levels again in those who received the vaccine. This is a busy slide. But what I want to highlight is that, in general, what we found was that in participants who reported to have a history of COVID-19 infection prior to receiving the vaccine, they actually had higher antibody levels compared to those participants who had no infection.

So in the green line here, these were participants who, again, received two doses of the vaccine but had no history of COVID-19 infection prior to receiving the vaccine. They had lower antibody levels over time. But then again in those at least indicated by the purple line here and the blue line, those participants who had gotten COVID-19 infection and then gotten vaccinated, they seemed to have higher antibody levels and that this seemed to at least be consistent over time compared to those who did not infected.

Now, we did have a very small subgroup of participants who reported to have gotten the vaccine, then got COVID-19 infection, and then had gotten their dried blood spot sample measured. Here, we see that their levels were a little bit lower compared to those with pre-vaccine infection participants, but that this was still higher compared to those participants who had no history of infection.

In summary, we found several demographic factors, as well as comorbidities, that seem to correlate with vaccine antibody responsiveness. It's notable that these factors that we found that associate with a lower antibody response to vaccine, these are the same factors that seem to also associate with an increased risk of more severe COVID-19, such as diabetes, older age.

I didn't show it here for the sake of time, but we found other factors, like a history of COPD as well as higher body mass index, also associating with lower vaccine responsiveness. I think our findings at least seem to support ongoing efforts to augment vaccine responsiveness and strategies to improve the effectiveness, again, if we think of these antibody levels as correlates of that effectiveness.

Notably, we think that these findings may not just be specific to COVID-19 or SARS-CoV-2, but this may extend to other vaccines for other viral inflections such as influenza.

Our study does have several limitations. Most notably, we restricted our analysis to those participants who received two doses of the vaccine recipients. So we didn't really have data analyzed for those participants who received other types of vaccines in the study, and that despite overall C4R being very diverse, for this actual analysis of about 6,200 participants, we did have smaller subgroup sizes of underrepresented minority groups, which may limit the generalizability.

So just want to thank our collaborators, particularly Dr. Oelsner, who leads C4R as well as Dr. Sun and Dr. Balte, two of the many bio-statisticians that work with Dr. Oelsner, Particularly thanks to the New York Department of Health Wadsworth Center who basically measured these dried blood spot antibody levels, as well as Dr. Demmer who helped co-lead this study with Dr. Oelsner And myself and as well as University of Vermont led by Russell Tracy as well. Thank you.

## Dr. Elizabeth Oelsner:

All right. Thank you, Dr. Kim. I am going to now present on another paper we published this year on Epidemiologic Features of Recovery from SARS-CoV-2 Infection. Just for a little context to tie it back to what I started with with the introduction to C4R, Dr. Kim was presenting work emerging from our first serosurvey, the Serosurvey 1.0 done by dried blood spots.

I'm going to be presenting on results that are really drawn from our wave-one and wave-two questionnaires. I think that there are lots of questions that can spring from both of these papers in terms of what we can do with our second serosurvey and our latest set of questionnaires in terms of future directions.

I think that the people attending this call are probably very well aware of the massive burden of long COVID on the US population and globally, and that's the general motivation for this work that we started early on in our project. We were aware from the earliest months of the pandemic in 2020 that people were taking a really long time to recover from SARS-CoV-2 infection. Some people weren't seeming to recover at all. So we included that type of question very early on in our work.

This slide just shows a few national data which summarize the proportion of US adults who say that they've ever had long COVID or currently had long COVID by age and sex. So these are results based on interviews with American adults in 2022, and this shows that 6.9% or about one out of 14 American adults say that they had ever had long COVID two years ago. So that number can only go up.

At that time, 3.4% or about one in 30 people thought that they currently had long COVID, defined as having symptoms lasting three months or longer that did not predate the SARS-CoV-2 infection. So we are going to show what we did to try to understand risk factors for having delayed recovery from SARS-CoV-2 infection, which would be one way of thinking about long COVID, not the only way.

Our objective in this work was to determine the time to recovery following SARS-CoV-2 infection in our population and identify correlates of recovering or not recovering by 90 days, by three months, among community-dwelling US adults participating in C4R.

The question we used to define recovery from SARS-CoV-2 infection was very much relying on patient self-reports and was included in our very first questionnaire administered in April 2020. The question was, "Since your COVID-19 infection, would you say you are completely recovered now?" And there were two options, yes or no. If the answer was yes, we asked, "how long did it take for you to recover in days?"

So we got an estimate from those participants who'd had infections, had recovered. How long did it take to get better? If a participant said, no, they weren't fully recovered at the time of the questionnaire, we looked at the difference between the date of the questionnaire when they were not recovered and the date of their infection, and that gave us a days to non-recovery.

So we were able to estimate that. And then, of course, we never would know unless we had a subsequent questionnaire such as the wave-three questionnaire whether they eventually recovered or whether they were still experiencing COVID-related symptoms.

We took these data, and we looked at trends in the median time to recovery by variant period and by vaccination status at time of infection. So I'll try to explain slowly what we see in this figure. So along the vertical axis, this is the number of days to recovery or non-recovery. Along the horizontal axis here, we have the first wave of infections, which was associated with wild-type viruses, the second wave also associated with wild type, the third wave, which was linked to Alpha variants, the fourth also linked to Alpha variants.

Then we had the fifth wave which was linked to the Delta variants. And then the sixth wave linked to the Omicron variants. Our data was from the wave-one and wave-two questionnaires in C4R covering 2020 to 2023, so not data beyond March 2023. Each of these bars in blue shows the median time to recovery for someone who was unvaccinated at the time of infection, unvaccinated for COVID-19.

Obviously, there were no vaccines during the first and second waves at all. So there are only blue bars. If we focus on the blue bars, we see that during the first wave, early on from February to May 2020, the median time to recovery was about four weeks median. So half of people took longer.

That number fell to about three weeks in the summer of 2020. And then it stayed at around three weeks through the fourth wave, and then it trended down in the fifth and finally the sixth wave. So at the time of the sixth wave, the Omicron period, the median time to recovery was about two weeks.

If you look at the yellow bars, these are the median time to recovery for the vaccinated participants. These are people who were vaccinated prior to their infections, and you see that during the third wave when the vaccines first became available, these individuals had managed to be vaccinated before they then had an Alpha variant period infection. You see that their time to recovery was markedly lower.

There was a lower time to recovery across the subsequent waves, four to six, in the vaccinated versus the unvaccinated, although the differences are a little bit less dramatic, with the shortest time to recovery across this entire figure, people who were vaccinated prior to an Omicron variant infection.

This is a table summarizing some key numbers that are indicated by that graph. So we looked at the median days to recovery overall for that entire period I show from 2020 through spring 2023, and we said the median days to recovery was 20, and the probability of not recovering by 90 days after infection was 23%. So if you treat non-recovery by 90 days as your definition of long COVID, which many people would, the probability of having long COVID overall in our sample was 23%, almost one in four.

If we focus in on the Omicron period, which may be more relevant to our current variants, although we do not have data in this study to look at the current period, you see that the median days to recovery during the Omicron period was 14 days, two weeks, and the probability of non-recovery by 90 days was 17%, so almost one in five. Lower than the overall estimates, but still very high.

So the next question we asked was we have all these data in terms of pre-pandemic health and lifestyle, can we see which of those factors might have been associated with a greater or lesser

likelihood of recovering before three months were up? So really, the hazard ratios here are if they're less than one, that means that you were less likely to recover by 90 days. So conversely, you were more likely to qualify for a long COVID definition.

If the hazard ratios were greater than one, the reverse is true. So that means you were more likely to recover before 90 days after your infection and you were less likely to meet a long COVID definition. So we ran these models using Cox proportional hazards regression, and we adjusted the models for all of the factors that were easily harmonized across the cohorts.

There was a question about this in the chat. Harmonized means we were able to find a way to make sure that the measure was the same in each of the cohorts because each cohort might have collected the data in a slightly different way, in a slightly different unit, in a slightly different number of categories, and we had to find a way to combine those data correctly so that we had apples-to-apples data in each cohort before we pooled them.

So here in terms of the tabular results, we see that the orange rows, those are risk factors that reduced the likelihood of recovering by 90 days or essentially increased the likelihood of meeting a long COVID definition. You see that the most extreme hazard ratios were for American Indian participants who, compared to non-Hispanic white participants, were much less likely to recover by 90 days, with a hazard ratio of 0.64.

Participants with COPD, chronic obstructive pulmonary disease, were less likely to recover by 90 days compared to those who did not have COPD. Individuals with current smoking or former smoking, they're both in the orange group here. They were less likely to recover by three months. Individuals with cardiovascular disease and also women compared to men were less likely to recover by three months.

The only two rows here that are green, meaning the hazard ratio was favorable, it was showing greater likelihood of recovery by three months, that would be infection during the Omicron wave compared to infection during the first wave and being vaccinated against COVID-19 before being infected versus the unvaccinated conditions. So those were both factors that increased the likelihood of recovering before 90 days were up.

Among this group, the strongest independent association after a bunch of sensitivity analyses were really for cardiovascular disease, female sex, the Omicron wave, and vaccination before infection. All of these factors could be, or are we've shown, associated with the likelihood of having a severe infection, the likelihood of being hospitalized for COVID-19, the likelihood of needing oxygen or other intervention for COVID-19.

We also know from our data that people with a more severe, acute SARS-CoV-2 infection, those people who needed to be hospitalized, for example, are more likely to take longer to recover from their infection. So we asked the question, how much of the relationship between a factor like vaccination and time to recovery is actually explained by the fact that vaccination tends to reduce the risk of severe infection, which tends to reduce time to recovery?

This is called mediation, where there might be a relationship that's mediated. That's the orange here, where the association between the risk factor is associated with the outcome via an intermediary step that's associated with both of them. That can be differentiated from a direct effect where the risk factor is just associated with the outcome, and it's not explained by the intermediary. So the risk factor could be associated with time to recovery, but not via its association with disease severity.

We asked this question statistically in the data, and here are the main results. So this is the mediation of associations for our major risk factors by infection severity. The mediated effect is shown

in orange, and the direct effect is shown in blue. So let's focus first on Omicron and vaccination. Those were our advantageous factors that reduced time to recovery.

You see that each of them was associated with fewer days to recovery. That's the horizontal axis here, effect on mean days to recovery. Both of them had a significant amount of that reduced time to recovery that was attributable to a reduced severity of original infection. That was particularly true for vaccination. So you see that out of the 18 or so days that were cut off recovery time with vaccination, about six of them were via reducing acute infection severity, and the remainder were direct effects via some other pathway.

Omicron had a smaller proportion mediated and had a larger proportionate direct effect on reducing the time to recovery. Marching up on this figure, you see that CVD was associated with a longer time to recovery and that a small portion of that was mediated by a greater severity of acute infection in people who had CVD.

And then with female sex, you see something a little counterintuitive. Overall, women took longer to recover on average than men, and women also were less likely to have a very severe acute infection. So this is like a reverse mediation. You would expect women to take less time to recover based on their infection severity than they did.

So our conclusions, in general, are that recovery time from SARS-CoV-2 infection has trended down over the course of the period 2020 to 2023. And yet the probability of not recovering by 90 days remained very high even in that Omicron era, 17%. Vaccination and Omicron-era infections were favorably associated with recovery, which was mediated in part by lower severity of acute infection, but not entirely.

Female sex and cardiovascular disease were adversely associated with recovery, so longer recovery times and less recovery observed by 90 days in those groups. And then there were also similar associations observed for smoking and COPD. There were racial disparities observed, particularly with a slower recovery probability observed in American Indian participants compared to non-Hispanic white participants.

So some key questions emerging from this are shown here, and there are more. One, why are women more likely to experience long COVID despite a lower risk of severe infection? Two, what are the underlying mechanisms for long COVID? There are probably different phenotypes of long COVID, as we've all thought about, and how do we untangle that, leveraging data in C4R and other resources?

How are repeated exposures to SARS-CoV-2, new variants, vaccines, number of vaccines, and treatments like PAXLOVID associated with risk of long COVID? This is a moving target because obviously we continue to have more vaccines available, more variant development, and people are accruing more and more reinfections. How does that experience relate to risk of long COVID in the current time?

Does having long COVID increase the risk of developing future health problems such as cardiovascular disease, metabolic disease, lung disease? Do we parse that into different conditions or is that part of the long COVID group of conditions? And then finally, will long COVID affect US health disparities, especially since we see such differences in probability of recovery in some of our data? So that is my last slide, and I will stop there.

## Dr. Wendy Post:

Great. Thank you so much. I am Dr. Wendy Post, and I'm going to be leading the discussion. I wanted to thank Dr. Oelsner and Dr. Kim for their very interesting and informative presentations.

Dr. Oelsner, congratulations on your leadership role, bringing together 14 long-standing observational cohorts to study important factors related to the COVID pandemic, including having, importantly, pre-pandemic information that we can compare to information gathered during the pandemic.

You referred to the post-pandemic period. There was a question about that. We're hoping someday there will be a post-pandemic period, and that these cohorts will continue to collect data. But I don't think Dr. Oelsner meant to imply that we were in a post-pandemic period. It was just the study design. When we designed it, we had no idea what was going on, or when Lizzie designed it, Dr. Oelsner.

It's just a very rich dataset that allows us to answer questions in a very unique way, capitalizing on data that the NIH has invested in for decades, and it complements the data that is available through RECOVER, which is incredibly rich as well, but the data is acquired in a different fashion. So the two cohorts, C4R and rec, mega-cohorts, can answer potentially the same questions in different ways and hopefully the answers will complement each other.

So thank you for telling us about the epidemiologic features of recovery from SARS-CoV-2 infection. It's very encouraging that recovery time is trending down over the course of the pandemic. It's nice to hear some good news for a change. There's been a wealth of data demonstrating racial disparities in the incidence and severity of infection within the United States.

So it's troubling that we, again, see such disparities emerge from C4R data analyses, and I was wondering what you think might have led to greater risk of slower recovery after COVID infection in American Indians in C4R.

## Dr. Elizabeth Oelsner:

Thank you, Dr. Post, for all of your support and for this very helpful question. So I don't have what I consider a satisfactory answer to this really important question of why we saw longer recovery times in American Indian participants versus non-Hispanic white participants. It was very dramatic. We have thought about it, but as of yet, we don't have answers. We have questions that we need to follow up on.

We've been so lucky to be able to partner with American Indian communities to generate data to do the necessary work to find some real answers. I would say some ideas I've thought of that could contribute to what we saw is that, often, the American Indian participants had their first infections earlier in 2020. And what does that mean? That could mean many things.

It could mean that they had earlier variants, that they had less access to therapies, that they were treated with therapies that were later found to not be helpful or maybe even detrimental. There are questions about whether viral dose, so the amount of the virus you're exposed to when you're first exposed, could relate to the severity of your acute infection. If they had less access to masks early in the pandemic or because of other conditions were exposed to just more virus, that could contribute.

I think that's just the beginning of the list of what we are looking at here. The association was found to be independent, so not explained by the major clinical conditions that we considered in our model, anthropometry, so blood pressure, BMI, age. Our associations were controlled for all those factors, so that's not explaining what we're seeing. Something else is, and we really need to look into it.

I would say that we have compared the national data by race and ethnicity developed by CDC with the C4R data to look at the incidence of severe COVID-19, defined as COVID-19 hospitalization and death, and long COVID burden, defined in a variable way because the definitions have changed.

Our C4R findings, in terms of disparities, line up almost perfectly with the national data, which is just important to state because I think the C4R data therefore provides a really important laboratory to get the answers because we are clearly finding something that is shown in our major surveillance databases, and we have this additional biologic data and social data to interrogate these questions more deeply and hopefully get answers that help our communities.

## Dr. Wendy Post:

Thank you. I also just wanted to mention that the community that is enrolled in C4R that identifies as American Indian asked to be referred to as American Indian, so that is their preferred terminology for the people included in this study. So I just wanted the audience to know that because I know there are various terminology that can be used to describe that important part of our population.

Dr. Kim, thanks for telling us about risk factors related to anti-S1 antibody responses to vaccination based on C4R serosampling using dried blood spot tests. So dried blood spots are a fantastic way to collect data, especially during a pandemic, because participants didn't need to leave their homes for a blood draw. They could easily collect these samples at home and return the cards to the lab through the mail.

I had had limited experience with dried blood spots in my research career. I am affiliated with C4R, so I learned a lot from that affiliation. But I was wondering if you could tell me a little bit more about dried blood spots and whether you think that might be an approach that could be used clinically in the future in order to do clinical testing.

## Dr. John Kim:

Well, thank you. Dr. Post. Yeah. Truthfully, I was really surprised about the dried blood spot data, and I think one big feature of it in C4R I think Dr. Oelsner highlighted in her first presentation was we had a lot of participants send samples. So I think it reflects the ease and just very simple nature of this test.

I think what has made it an appealing test is that people can do it at their home. It doesn't require them to go to a lab to get the sample collected process. From my understanding is that these samples can last for several years and still be measured from. So I'm hopeful with more studies and research that look at how to implement this dried blood spot, that it might actually address some of the issues of inequity and access to care and monitoring.

I really think an exciting opportunity, and I'm not aware of anything right now that's looking at this, but whether to implement dried blood spot testing and measure almost in real time vaccine responsiveness, and so in people who may have decreases in this level, whether it would affect management. Again, that's 10 steps ahead, but I think this is just really just the start of it.

I think maybe 10, 12 years ago, the technology wasn't there maybe for the dried blood spot correlating with the lab measurements, but I think in recent years, it's really exciting. I should comment that a lot of those other studies in the United Kingdom that looked at the antibody levels after vaccines, they also allowed them to use dried blood spots.

So I think we have a lot of different independent studies looking at the potential utility of these dried blood spots. So I think it's exciting. I think it's just getting back to more perspective research needed.

### Dr. Wendy Post:

Thank you. So on the same theme, do you think there's any clinical utility in monitoring antibody levels? I know we didn't specifically address this in the observational study, but if you were to want to comment on what your recommendations would be about that?

### Dr. John Kim:

Yeah. I don't know. That's the simple answer. I'm not sure about the actual clinical utility of actually measuring these antibody levels and monitoring over time because I think one thing is we're not sure the strategies and things to do if let's say you do see maybe a lower level. I think also we don't have really standardization of these lab tests that measure these antibodies.

So I think there's a lot of things that need to be done before these are really implemented clinically. But I think the start is to actually at least look at this with the research so that it can maybe propel other studies and eventual potential clinical utility.

### Dr. Wendy Post:

So not quite ready for prime time, but something we need to learn a lot more about for potential utility in the future.

### Dr. John Kim:

Exactly.

### Dr. Wendy Post:

Yeah. So, Dr. Oelsner, Do you want to comment on additional research that's being done in C4R, either related to time to recovery or in general? You mentioned multiple papers that are underway and proposals. Just tell me a little bit more about what exciting research we will hear about in the future.

### Dr. Elizabeth Oelsner:

Of course. I'll do what I can. We have to keep some of these things under wraps because that's how publication works, unfortunately. But I can tell you that we have really been working on linking up those pre-pandemic factors, including the structural-imaging measures, the spirometry measures, for example, with risk of severe acute infection because that's an important issue to clarify.

It sounds maybe a bit straightforward that people who had health conditions before the pandemic were more likely to have severe infection. That's a reasonable expectation. But plenty of people in the world have maybe a lower lung function or maybe a higher sugar level than average, and are they at higher risk than average? They might not know this about themselves, so we want to really understand some of the physiology and the biology about what might increase the risk of a severe COVID-19 illness.

That might be generalizable to other causes of acute respiratory failure, for example, influenza, RSV, other things out there. So we are completing a large body of work looking at our outcome of severe COVID-19 illness. We're also doing a wave of work around psychosocial health factors and infection and the pandemic period itself, looking at issues of how psychological factors, social factors may be

associated with a greater or lower risk of severe COVID-19 or behavioral changes or vaccination behaviors as well.

And then I think that we are just scratching the surface as we are completing our latest wave of data collection with our wave-three questionnaire, which goes much more into long COVID-related symptoms, and also we're updating all of our reinfection data, our re-vaccination data so that we can get into those questions I was mentioning.

How do repeated exposures to the virus or to vaccines or to other factors maybe modify your risk of having a long COVID diagnosis or just a delay of slower-than-average recovery or a new diagnosable condition such as cardiovascular disease, hypertension, diabetes, and things like this? So that is a body of work that we are embarking upon now as we start to close our datasets.

There's certainly a ton more work to do, and we welcome new ideas in terms of making the most out of the fact that we have long-term longitudinal follow-up in so many diverse Americans where we can look at where people were before 2020 and their experiences with infection with long COVID and with other conditions that they might not themselves link to their COVID history. But maybe through analysis, we can uncover additional findings that might not be self-evident with self-report.

## Dr. Wendy Post:

Yeah. Great. Looking forward to seeing all these results come out in the literature so we can all benefit. I know we're all working very hard to do that.

You presented data that's observational, not randomized clinical trials. But using the observational data that we have acquired, what would you hypothesize would be a good way to help prevent long COVID or delay of recovery of symptoms?

## Dr. Elizabeth Oelsner:

That's obviously a critical question for everyone, very top of mind. The very clear signals in the study I presented today suggest that anything that will reduce your risk of a more severe acute infection may reduce your risk of a prolonged recovery. On that list of things that you can do to modify your risk of a more severe infection would obviously be vaccination, which vaccination has been shown in so many clinical trials to be effective.

And then I think general health measures in terms of resilience with respect to any viral exposure, so we know that means taking care of yourself, taking care of your chronic conditions, seeing your doctor, and trying to be as strong as you can if you do encounter the virus. So those are some basic, common-sense things that we can all do to try to reduce our risks.

In terms of things you can take, I don't have any answers from our data yet, but that is certainly a question that we're all asking. We will be looking forward to exploring any biology or physiology to help answer those questions and support our colleagues as they are building clinical trials for potential new interventions.

## Dr. Wendy Post:

Great. Of course, there are people who were vaccinated and did everything to take good care of their health who still developed long COVID symptoms. This is just a general recommendation of reducing risk for long COVID or persistent symptoms that come out of our data, and hopefully we'll be

seeing less virulent strains going forward, as you suggested, that hopefully, with our knowledge, will lead to fewer people with severe infections and hopefully fewer people with persistent symptoms.

So again, I thank Dr. Oelsner and Dr. Kim for really interesting presentations today, and I'm going to turn it back to Quinn to help with moderating audience Q&A.

## Quinn Barnette:

All right. Well, thanks, everyone, for such a rich discussion. We'd like to open our audience Q&A with just a few questions that we received in the Q&A chat. Just as a reminder to the audience, we'll also post a Q&A document on recovercovid.org for any questions that we can't get to today.

So the first question is perhaps relevant to both Dr. Kim and Dr. Oelsner's presentations and asks, "In your work, have you seen a difference between patients that had COVID first before they got vaccinated and their response to the vaccine? And if so, did that help or hinder their recovery?" Maybe, Dr. Kim, if you want to start?

## Dr. John Kim:

Yeah. Thank you, Quinn. At least the paper we published seems to suggest that those ... Again, the order of events, so those participants in C4R who had a history of COVID-19 infection, then followed by getting two doses of the mRNA vaccine followed by getting a dried blood spot given and their antibody levels, they seem to have significantly higher antibody levels, again, as a surrogate of increased vaccine responsiveness.

So if you had an infection, then got vaccinated, and then gave your blood sample, you seem to have a higher antibody level, again, that suggests that you had a bit maybe more protection as a surrogate. I think that way I'll pass it on to Dr. Oelsner to follow up about the recovery in that part of the question.

## Dr. Elizabeth Oelsner:

Thanks. We don't have enough data yet to answer some of the questions we really do want to answer about antibody responses to vaccination and long COVID. So watch that space. We're working on it.

We are developing data looking at also anti-nucleocapsid responses, which is an antibody response that only occurs after natural infection, and how that might differ based on sequencing of infection and vaccination and also how that may relate to long-COVID risk. So that's yet another dimension of how our serosurvey will be used to explore some of these issues.

Once we have the serosurvey 2.0, we'll have a second sample. So, in many individuals, we'll have two tests of their antibodies, and we're going to be able to look at the sequencing of different events around those antibodies. That includes the ability to look at people who might have had a long-COVID phenotype before the first blood that resolved before the second blood versus someone with long COVID at both times versus someone with long COVID that developed between the two blood spots.

So study designs like that will help us to dig deeper into some of these really interesting questions and tell us more about the immunology underlying long COVID and the different factors.

### Quinn Barnette:

Thank you. Very interesting and exciting work, it sounds like, that could be coming around the pike.

Our next question is for Dr. Kim, and it asks, "Did you have the opportunity to look at vaccine-response trajectories from patients who already indicated they had long COVID. And if not, are there any plans to look at this?"

### Dr. John Kim:

That's a great question. So the question is, basically, were we able to account for participants who reported history of long COVID in terms of antibody-level response to vaccine? At the time of the analysis and the publication, I don't think we really had that data to incorporate. So I believe, and again, I defer to Dr. Oelsner, the architect of C4R, but I believe that is potentially a future research area with more data coming in as part of C4R.

### Dr. Elizabeth Oelsner:

That's right. Our dried blood spot, the first one, was really timed with the timing of our second questionnaire, so we couldn't see what would happen in the future after those antibodies until we got the wave-three questionnaire, and that wave-three questionnaire is being finalized now. We're approaching 30,000 out of a target of 31,000 wave-three questionnaires, so we hope to have that data ready for analysis very soon.

### Quinn Barnette:

Thank you. Our next question is also for Dr. Kim and asks, "We hear the general guidance is delaying obtaining a vaccine after an infection by about three months. Was this considered in your analysis, and would your data support that this delay enhances antibody titers at all?"

### Dr. John Kim:

That's, again, another great question. So the question being, I think at least at the time when the vaccines rolled out, if you had a history of infection, it was thought that maybe get the vaccine three months after you're infected. That really didn't factor into our analysis or we didn't really even think of that as we analyzed the data. And then I would suggest that we probably can't necessarily make a direct correlation of our data in terms of clinical guidance of whether to delay getting your vaccine three months later.

I think our data, that first part I had showed shows that at least at 60 days after the first dose of vaccine, we do see this peak of the antibody level and does seem to wane over time. I'm not aware of any current research efforts to interrogate or elucidate that relationship between infection and vaccine and when to get it, but I don't think we can necessarily, again, extrapolate our data to that sort of clinical question.

### Quinn Barnette:

Thank you. Our next question is for Dr. Oelsner, and it asked, "Do you know the probability of non-recover after infinite time, i.e. non-recovery after that 90-day mark from your study?"

## Dr. Elizabeth Oelsner:

That's a really good question. I will say that I spoke to our bio-statistician about this, and she would give a better answer right now. But basically, in terms of the figure I showed you with the median times recovery over different waves, participants were only in one of those bars. So if they were infected in wave one, their recovery time was in that wave-one bar, and the median was the median across the group of recovery time for those people.

Some of those people, unfortunately, remain non-recovered up until our last observation of them, which could be ... I mean some of them are, as you can imagine, years long, but the statistical method of looking at the median is actually robust to many different treatments of recovery versus non-recovery. So I don't think it would be influenced.

We could talk about it further. There are a lot of statistical issues here, but the median remains true, depending on a range of assumptions about recovery time in those individuals where they're not observed to recover because the median is still going to remain stable.

We are identifying in our preliminary wave-three data, people who have not recovered for years, and we have many people meeting that criterion. We also have people who suffered for many years but then did recover. So we think these are really important subgroups to assess in terms of their pre-long COVID risk factors and their current health conditions and their prognosis.

So we are actively looking at this and recognize that the range of periods of recovery is extremely wide, including very, very, very long non-recovery periods that remain non-recovered up through the wave-three questionnaire administered in 2023 through 2024.

## Quinn Barnette:

All right, thank you. Our next question is also for Dr. Oelsner and asks, "Were pregnant women included in your study on the time to recovery? And if so, did you see any differences?"

## Dr. Elizabeth Oelsner:

Pregnant women were, unfortunately, not included in the study, and that's an area that I think certainly demands research but was not covered with the work that we did.

## Quinn Barnette:

All right, thank you. Our next question I think can be directed to the entire panel, and it asked, "There's some general concern from the audience about risk of triggering long COVID after a vaccination. Could you comment on the evidence we have about how protective vaccines may be specifically for long COVID and if there's any data for potentially triggering long-COVID symptoms?" Maybe, Dr. Oelsner, If you want to start?

## Dr. Elizabeth Oelsner:

I think it's a really interesting question. I have seen, by and large, in analyzing our data for many different research questions, a compelling, consistent protective effect of COVID-19 vaccination versus risk of more severe acute illness and risk of prolonged recovery. That is what I have observed. I have not very specifically examined the question that you're raising, and I think it's something that we should do.

I think that we do expect, particularly at this time, a very wide range of vaccination histories. We see that in our wave-three questionnaire. We have people who have had zero vaccines by 2024 and people who've had seven or more. I think trying to look into the sequencing of vaccinations around symptoms is going to be a really critical next step for us.

It's going to be complicated, but I think the question you're asking is really, really a question that I hear in my primary care clinic all the time, which is what about me? What do I do? Should I get another vaccine or should I get my first vaccine? Given that the picture is very complex and certainly a lot of people do feel ill after the vaccine and that could be due to the vaccine effects, there's a lot of questions there.

So I hear that question as a really patient-oriented, patient-centered question that we want to dig into more as we get our wave-three questionnaire closed.

## Quinn Barnette:

All right, thank you. Our next question is also for Dr. Oelsner and asks, "If you can comment on the C4R cohorts having pre-existing conditions compared to those who do not have pre-existing conditions, is that something that you analyzed for the current study or are planning to analyze in the future?"

## Dr. Elizabeth Oelsner:

The original participants were generally recruited into cohorts as healthy adults, and some of them had some pre-existing conditions before they joined their studies. Many of them developed those conditions over time while they were in the study. So maybe they didn't have hypertension when they joined in 1971, but maybe in 2018, they did have hypertension.

So in the C4R population, we have many people who have zero clinical conditions prior to 2020, who have multiple clinical conditions, and among those who have clinical conditions, we often know when they were diagnosed over our period of observation. We also, relatively unusually because of the research nature of our cohorts, we have information on people who don't have a disease yet. They have maybe a preclinical or a subclinical difference that doesn't qualify as disease but is a little bit different than normal.

So we're able to compare people without disease, with the disease, and with some preclinical or subclinical elements of disease and assess their risk to see if there's really a graded association of risk, like the more the disease, the more the risk, which would suggest not prove that it's part of a biologic continuum.

Or we can also use some of these data to create subtypes of disease, different types of a disease with our quantitative data, with our biomarker data. Because diseases such as diabetes are probably many, many, many diseases in there with a similar major phenotype, but we're able to use different biomarkers that we have to try to understand subgroups of diabetes and look at whether they have differential risk associations with something like long COVID.

## Quinn Barnette:

All right. Thank you. I think we have time for one more question, and this one will also be directed to Dr. Oelsner and asks, "Will C4R and RECOVER, which is another long COVID cohort study, be collaborating for a cohesive combination of research and cohorts? Are there any activities planned?"

### Dr. Elizabeth Oelsner:

Could you repeat the last part of that question? We will C4R and recover be collaborating ...

### Quinn Barnette:

"For a cohesive combination of research and cohorts."

### Dr. Elizabeth Oelsner:

Yes. Thank you. I was assuming my answer would be yes, just wanted to make sure. So we work very closely with RECOVER, and we are complementary in many ways. We bring different things to the research table, and so we hope to provide opportunities to take RECOVER results and validate them in C4R or vice versa, and then in some cases, maybe pool our resources if we have special case types.

If there are 100 people meeting a case type in RECOVER and 75 in C4R, given how linked or harmonized our studies are, we should be able to pool resources to do additional investigation collaboratively.

### Quinn Barnette:

All right. Well, thank you so much. I think that is going to conclude our Q&A session for today. I want to say thank you to our presenters again for such a wonderful presentation and rich discussion and to our audience as well for attending this seminar and engaging with the Q&A.

As a reminder, a recording of today's seminar will be available on recovercovid.org within a couple of weeks, and we'll also be posting a Q&A document that has responses to the questions that we received today, including some that we didn't have time to address.

But before we conclude, a reminder to researchers both within and beyond the RECOVER Initiative, you can now apply to use RECOVER data for ancillary studies. This does include data from three RECOVER cohort studies, adults, including pregnant adults, pediatric, autopsy, and biospecimens collected from cohort study participants.

Any interested researchers have to apply using an ancillary study proposal and receive approval, and researchers must also have independent funding support to conduct the proposed study. To learn more about that, you can visit recovercovid.org/ancillary.

And with that, we do hope that you'll join us again. Please keep an eye on recovercovid.org for updates and for a list of future seminar topics as we enter the new year. Additionally, you'll see a short survey come up on your screen in just a moment. It'll ask for your feedback on the seminar, and we would appreciate if you could just take a brief moment to fill out the survey.

With that, I thank all of our panelists again. Thanks to the audience for joining today, and I hope you all have a great day.