Responses to Participants' Questions

The overarching goal of the R3 Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses* to questions raised by seminar participants related to the following presentations at the R3 Seminar ***Vaccine response and time to recovery from COVID-19 in a multi-cohort collaborative (C4R)*** held on November 12, 2024:

- ***Introduction to C4R* and *Epidemiologic features of recovery from SARS-CoV-2 Infection***
  Elizabeth C. Oelsner, MD, DrPH
- ***Anti-S1 response to vaccination in U.S. adults***
  John S. Kim, MD, MS
- **Discussant: Wendy Post, MD, MS**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. What do you think might have led to greater risk of slower recovery after COVID infection in American Indians in C4R?

Response:

Dr. Oelsner: 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. 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, body mass index (BMI), and 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 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. We have this additional biologic data and social data to interrogate these questions more deeply and hopefully get answers that help our communities.

Q. Do you think dried blood spots testing might be an approach that could be used clinically in the future to do clinical testing?

Response:

Dr. Kim: Truthfully, I was really surprised about the dried blood spot data, and one big feature of it in C4R Dr. Oelsner highlighted in her first presentation was we had a lot of participants send samples. So, I think it reflects the ease and 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. 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 think an exciting opportunity, and I'm not aware of anything right now that's looking at this, would be 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 this is really just the start of it.

Maybe 10, 12 years ago, the technology wasn't there 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 we have a lot of different independent studies looking at the potential utility of these dried blood spots. I think it's exciting. I think it's just getting back to more prospective research is needed.

Q. Do you think there's any clinical utility in monitoring antibody levels?

Response:

Dr. Kim: I don't know. That's the simple answer. I'm not sure about the actual clinical utility of measuring these antibody levels and monitoring over time. We're not sure of the optimal strategies if you do see a lower level. I think also we don't have sufficient standardization of these lab tests that measure these antibodies.
So there are a lot of things that need to be done before these are really implemented clinically. But I think the start is to look at this with the research so that it can propel other studies and eventual potential clinical utility.

Q. Can you comment on additional research that's being done in C4R, either related to time to recovery or in general?

Response:

Dr. Oelsner: 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 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. We're 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 and 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 we're 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 and 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? That's a body of work we're 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.

Q. 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?

Response:

Dr. 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, as 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's certainly a question that we're all asking. We'll 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.

Q. 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?

Responses:

Dr. Kim: 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, 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. 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 also at 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. 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.
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.

Q. Did you have the opportunity to look at vaccine response trajectories from patients who indicated they already had Long COVID? If not, are there any plans to look at this?

Responses:

Dr. Kim: 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 had that data to incorporate. 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. 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.

Q. 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?

Response:

Dr. Kim: That's, again, another great question. So, the question being, 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 didn't factor into our analysis or we didn't really even think of that as we analyzed the data. And 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.

The first part of the data I presented 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 extrapolate our data to that sort of clinical question.

Q. Do you know the probability of non-recovery after infinite time, i.e., non-recovery after that 90-day mark from your study?

Response:

Dr. 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 of 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 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're 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.

We're 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.

Q. Were pregnant women included in your study on the time to recovery? And if so, did you see any differences?

Response:

Dr. 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.

Q. 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?

Response:

Dr. Oelsner: I think it's a really interesting question. I've 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's what I've observed. I've 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. 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.

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

Q. Have you or will you analyze differences between C4R cohorts that do or do not have pre-existing conditions?

Response:

Dr. Oelsner: The original participants were generally recruited into cohorts as healthy adults, and some of them had some pre-existing conditions before they joined the 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 and people who have multiple clinical conditions, and among those who have clinical conditions, we often know when they were diagnosed over our period of observation. 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 (but 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 of diseases such as diabetes, there are probably many diseases 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.

Q. 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?

Response:

Dr. Oelsner: Yes. 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.

Q. How are C4R and RECOVER related? Are they funded separately? If so, how is C4R funded?

Response:

Mr. Sean Coady (NIH): C4R is currently funded under the RECOVER Other Transaction umbrella. It's important to note that C4R was initially funded under the CARES act as part of CONNECTS. As the pandemic evolved and Long COVID emerged, a second phase of C4R was funded to continue to collect emerging data on COVID in these long-running cohorts. Currently, C4R oversight by NIH lives at the National Heart, Lung, and Blood Institute (NHLBI).

Q. Can you please explain what harmonization of the data means?

Response:

Dr. Oelsner: 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.

Q. I'm surprised that age was not a risk factor. Would older groups have died, instead of surviving to experience Long COVID? Likewise, males, especially older males, I think would be more likely to die from COVID.

Response:

Dr. Oelsner: We performed sensitivity analyses that treated death due to COVID-19 as "non-recovery" (i.e., a Long COVID phenotype). In those analyses, we still did not see any significant association with age.

Q. Please share your thinking about your findings related to women in your study.

Response:

Dr. Oelsner: Our results of significant sex differences are consistent with many other reports and require further study. Sex differences in risk of PCC could be explained by multiple mechanisms, including differences in the immune response and higher risk of autoreactivity and thrombosis in women (vs. men).

Q. Why are there different opinions regarding antibodies levels not being accurate in any type of clinical study?

Response:

Dr. Kim: We're unable to answer this question as it is beyond the scope of our study and we don't have the expertise to speculate why there are different opinions, but it continues to be an important issue. We hope our findings can help others look into this.

Q. Blood spot metabolomics are used in sports sciences (cycling, etc.) and it would be useful for Long COVID fatigue and neuromuscular function.

Response:

Dr. Oelsner: This could be a very interesting ancillary study—thank you for the suggestion.

Q. Are you looking at Paxlovid as a way to prevent Long COVID development? If so, when can we expect some data on this?

Response:

Dr. Oelsner: We'll test associations of Paxlovid use with Long COVID outcomes after completion of our wave three questionnaire. Data should be available in Summer 2025.

Q. Do the data showing a decreased time to recovery as the waves continued, taking into account patients with Long COVID who saw an increase in symptoms and the decreased available population to experience new COVID infections?

Response:

Dr. Oelsner: It's possible that attrition bias could have contributed to our results, as you suggest. Nonetheless, given that SARS-CoV-2 infection rates remained relatively low until the Omicron period, we don't believe that it fully explains our findings.

Q. Has Rheumatoid Arthritis been identified as a risk factor for Long COVID?

Response:

Dr. Oelsner: We haven't explored this in C4R.

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