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 R3 Seminar ***Characterization of Long COVID Among Children and Adolescents, Cohort Insights*** presentation held on September 10, 2024:

- ***Presenters***
  Melissa Stockwell, MD, PhD
  Tanayott Thaweethai, PhD
  Rachel S. Gross, MD, MS
- ***Discussants***
  Andrea Foulkes, ScD
  Megan Carmilani

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. What do children and adolescent Long COVID symptoms have in common with those of older populations, and how might they differ?

Responses:

Dr. Stockwell: To me, what was really interesting was that it's almost like a gradation. So, there's sort of this overlap, the adult findings, and there's an adolescent overlap, particularly with the loss of taste and smell. And then there's some of those that overlap with the school-age children.
To me, that makes sense, and it goes along with what Dr. Gross was seeing, in terms of as children are growing and developing, their symptoms could look different. That makes sense why there's going to be some overlap with adolescents and adults and then some overlap with school-age children and adolescents as well. I think that take-home finding is interesting, and I think will also help as we're trying to tease apart the pathophysiology and the biology behind it.

When we talk about the clustering and the phenotypes, we saw this overlap between children and adolescents, but then there were these phenotypes that were very different in school-age children. A lot of things that Ms. Carmilani talked about that Long COVID families are seeing in school-age kids, they're not seeing in adolescents. And there are some phenotypes in adolescents that we weren't seeing among the younger kids as well.

Dr. Gross: When we think about the clusters of groups of symptoms that we described, we are seeing the first grouping where children, teenagers, even adults, are experiencing symptoms in almost every organ system of the body. So, that particular type seems to be crossing all of the ages, but where we are starting to see these similar but distinguishable differences, or when we're seeing types of Long COVID that may involve fewer symptoms, but that they may be more specific to different stages of development.

Ms. Carmilani: In addition to the difference in symptoms, children express symptoms differently, and I think that's really important to pay attention to and highlight. Some of the common things we've been hearing is that a child may say that their legs hurt, and what they're trying to explain is that they feel fatigued. Or a child will say, "I can't think." And they're trying to explain cognitive difficulties, or they'll say that their head hurts. What they're really trying to say is, "I can't think. I'm having a hard time." A very common one is that a child will talk about not being able to breathe, and it turns out to be more heart palpitations or tachycardia, which is a rapid heartbeat.

Part of what we've learned in our community of trying to help Long COVID kids is to really pay attention to the way they express things and not insert an adult perspective on what that means. Really try to figure out what the child's saying. Another common one is that children have often said that their throat hurts, but if you ask them where on their body, they'll point to the back of their head. And we've learned that's a common way for little ones to say they have a migraine. So really, just pay attention and try to think of it through the eyes of a child and what they're trying to communicate about the symptoms.

Q. Are there current or future plans to capture related illnesses and measures of Long COVID prevalence? For example, people with mild myalgic encephalomyelitis/chronic fatigue syndrome or those with related complications such as mast cell disease?

Responses:

Dr. Gross: We collect a lot of diverse data about all of the participants in the study. While this first analysis focused on the symptoms that are being experienced by the children, many of our next steps are to look more broadly at that conceptual model that Dr. Stockwell talked about in the review paper; we are collecting data about other medical problems, specifically the ones mentioned in the question, as well as a diverse range of other past medical history and special healthcare needs that children are experiencing, to see how they influence the development of Long COVID, but also how they develop over time. So, we ask about the emergence of new conditions over time as well, so we can begin to look at them as we're following children over time.

Dr. Stockwell: Importantly, symptoms and phenotypes are beginning to emerge. Because as Dr. Gross mentioned, it may be that one of the gastrointestinal symptoms, I'm going to quote Megan, might be associated more with certain underlying conditions or certain things, and it might be the multi-system grouping that is different. I think we're really trying to look by age, but again, by symptom cluster as well. As Dr. Gross said, it's not going to be a one-size-fits-all by age, but also inclusion of the phenotypes and really interrogating at that level.

Q. Are there any plans for the PASC research index to be independently validated externally before moving forward with more research?

Responses:

Dr. Thaweethai: That is a great question. Since we have the RECOVER data, we have developed a research index for identifying participants who are likely to have PASC. We will be, as the other panelists have mentioned, looking at how other clinical tests may correlate with higher scores on this PASC index. Looking at other physical assessments, for example, we could look at how they relate to the PASC index.

But I think my answer to the question is that the purpose of this presentation is to open the door to other people who are studying Long COVID, who have participant data, and who can validate what we've found. We have identified the symptoms that are most important. If you ask participants about these symptoms and you calculate their PASC research index as we've outlined it, does it correspond to whether the clinical diagnosis, perhaps, of Long COVID in other populations?

So that's really important. And we're so excited. We're hoping that people will take what we've presented here and validate it in the populations they're studying. And I think that will help us understand better. I think importantly, this is a definition, or rather an index and an algorithm that's used to identify people for research. I think it would require additional validation in other groups, in other cohorts, before we can approach a way to truly diagnose in the clinic. That will be a really essential part on the path towards being able to diagnose people in a clinical setting.

Dr. Stockwell: And can I just add one thing? I think, also, one important part about the research index is that it's a smaller number of items and isn't comprised of 88 questions. I think that part of the point was for us to be able to use something—and again, we would love for other people to use it and validate it and look at other contexts for research—that it is a shorter number of questions than 88. This is a lot of information to ask as a researcher, but also for the patients and participants over time. And obviously, we do know that we have many dyads where the caregiver and the child have Long COVID. We always think about the participant burden. For the caregiver, if they're filling it out for their child with Long COVID, or if it's a young adult who's filling it out for themselves, we hope this shorter list of questions for research will also be helpful.

Q. How do you view the progress in developing diagnostic tools for the condition? Do you believe a quantitative biomarker would be the most effective method for assessment? And what do you think are the main challenges and advancements for diagnostics?

Response:

Dr. Gross: Thank you for that question. I think it is such an important one, and really what this type of foundational work is aiming to help with. Because we need a way to be able to easily identify, in clinical practice, a way to diagnose Long COVID, first is acknowledging that it is a very heterogeneous condition, meaning that some people's Long COVID looks different from other people. I'm hopeful that we will be able to identify a biomarker in the future, but it's unclear right now what exactly that is. And so, one of the things that we're trying to do in RECOVER is collect blood and other specimens from children, as well as the adults in a similar way, so we can do the foundational research to try to identify such a biomarker, based on the underlying mechanisms and pathophysiology that we can identify as we follow these participants and families over time.

Dr. Stockwell: I think we all would love to get to a place where there is a biomarker. In the interim, from the pediatrician perspective, even just understanding what some of the common symptoms are that we saw in school-aged children is important. So even if we're putting aside the research index part of it, just that information is incredibly important for pediatricians and families to know. I think one thing that's great about kids is, in general, oftentimes whenever there are symptoms, they're self-limited. But in this case, these kids, it's not self-limited.

If you're seeing a child who's having prolonged symptoms in these groupings or not, and they had a COVID infection—many of them have, and it doesn't have to be that they had a COVID infection today and this started a week later—put that together and I can't tell you how many times I've had that conversation with pediatricians and there's this aha moment of like, "Oh, I didn't think that those could be related. That all makes sense now." I think it is what families have been trying to say. And I think while we want to and hopefully get to a biomarker, in the meantime, even sharing these symptoms and getting that information out there is incredibly important for families and for pediatricians as well in the interim.

Dr. Thaweethai: I would like to address one of the challenges of finding a biomarker. Something we've mentioned has been the idea that Long COVID presents in many different ways. It suggests that there may be different mechanisms of disease that may mean that there are different biomarkers. It’s related to this one-size-fits-all, but I think what we've discussed is that Long COVID doesn't look the same in all kids across age groups, but even within the same age group, Long COVID still looks different.

Trying to do an analysis, I'm imagining trying to plan what an analysis would be—it might be pertinent to think about specific types of Long COVID and whether there are specific biomarkers that are associated with particular types, rather than kind of looking at everything in aggregate, which is challenging. I don't know what we'll eventually find about a single biomarker, but I think it's possible that the story could be quite complicated.

Q. In this analysis or in other analyses that you've done, did you find any differences in prevalence or phenotype by sex similar to what's been seen in the adult populations?

Response:

Dr. Thaweethai: That's a great question. For the present analysis, we accounted for sex in fitting the statistical models, but we didn't specifically look at whether the symptomatology was very different by sex of the participant. I think what we know, based on emerging evidence in adults, is that participants assigned female at birth tend to have higher rates of Long COVID. I think that would be worth investigating in pediatric populations as well, but unfortunately, I don't have a concrete answer to that at this time.

Dr. Gross: I was just going to say that some of our next steps in this work is to try to understand why some children are experiencing these prolonged symptoms and others are not. Some of our next manuscripts that we will be working on and publishing are related to those very questions. Are there sex differences? How do vaccines play a role? What are the other factors that might influence the development of these symptoms or not? That is one of the main questions that we are also working on within the RECOVER Pediatric Study.

Q. Is RECOVER doing any assessments of downstream effects of Long COVID in children and adolescents, such as functional outcomes and schooling outcomes, for example?

Response:

Dr. Stockwell: Yeah, thank you for that question. It's very important for us. One of the things that happens in our tier two study is that we're seeing families more often—6 months, 12 months, 24 months—we ask them some functional questions, and also questions about school. We want to really understand days missed from school, and also if they have an individualized education plan (IEP) or not, how they're doing in school, and the impact of physical activity and nutrition and other issues for them. So it's really important.

I think one of the nice things about RECOVER, because we can ask participants directly, we can capture a lot of things that a medical-based study may not necessarily capture. Those include the educational outcomes as well. I would say that's probably one of the most important things that we want to be focusing on going forward. We worry a lot about how kids are doing right now, but again, as it's been mentioned, it is important to know how kids do as they develop and are they able to be in school as much as they can? Are they able to learn? Also, how is this school accommodating them? I know there are some questions in the chat about accommodations. We can definitely tell, just from our participants, that when kids are not granted accommodations, it also affects their trajectory. So that's important for us to be looking at.

Dr. Gross: Yeah, and one of the main assessments that we are doing every time children are coming in over time, is taking an extensive look at neurocognitive development. And these are things that can be subtle. So, we are doing assessment of memory, assessment of language, of motor skills, of executive functioning. These are things that people, schools, teachers, families, or physicians may not necessarily pick up as a change that's happening over

time. We're hoping that having these extensive assessments at every time point will really help to answer some of those questions.

Q. How are findings raising awareness of the impact of COVID on children and adolescent health, and informing policy to help address screening and treatment and accommodations for children?

Response:

Ms. Carmilani: As far as informing policy, we are in the very, very early stages. So we are, I would say, two to three years behind where the adult population is as far as awareness in general. So, we're still in the awareness phase, and that's why we're emphasizing it so very much. We're still having debates with policymakers about whether or not Long COVID is real in children.

That's where we are, unfortunately. And there may be potentially six million children out there that are waiting on us to find some solutions for them. I would invite everybody listening to help us to raise awareness. Knowing the symptoms that have been outlined today has been really, really helpful. We have heard from both families and educators and other doctors in the community. And so, we can start there and with awareness, then we can start pushing for the policies our families need.

Q. Did any in your study group receive the vaccine and/or boosters?

Response:

Dr. Stockwell: We had participants who were vaccinated and those who were not.

Q. Are you enrolling Canadian children?

Response:

Dr. Stockwell: The enrolling sites are all US based.

Q. Is the data indicating the numbers in the study who were vaccinated and boosted? Where can we get that data?

Response:

Dr. Stockwell: The paper includes vaccination as part of the description of participants in the study.

Q. Did you collect information on hyperflexibility or Beighton score? It seems some Long COVID centers are seeing a trend there which may lead to identifying a biomarker.

Response:

Dr. Stockwell: Yes, the Beighton score is part of our Tier 2 testing, and is something we plan to look at.

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- For medical/scientific terminology: https://medlineplus.gov/healthtopics.html