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 panel at the R3 Seminar *PASC in Children: State of the Science and Future Directions* held on April 23, 2024:

- **What is Known About Long COVID in Children**
  Suchitra Rao, MBBS, MSCS

- **Functional Outcomes in Children and Adolescents with Long COVID**
  Abigail Case, MD

- **Discussant:** Melissa Stockwell, MD, MPH
- **Representative Discussant:** Rebecca Letts, BA

* Responses may have been edited for clarity.

**All Presenters: Questions and Responses**

Q. Is being unvaccinated a risk factor for Long COVID?

Response:

**Dr. Rao:** A very important topic that has been coming up is what is the role of vaccination in Long COVID. Can it prevent symptoms from occurring or prevent the development of Long COVID?

We conducted a study that was published very recently in *Pediatrics*, and there was an R3 seminar where Hanieh Razzaghi—one of the first authors on that paper presented. For folks more interested in that in depth, I highly recommend watching that YouTube webinar. We looked at our data from multiple different health centers across the country, over a million children, and looked to see whether vaccines could prevent development of Long COVID.

And we looked at different definitions of Long COVID. One was sort of a stricter, more stringent definition. When you looked at that definition, we found that there was a protective effect of vaccines against the development of Long COVID. It was around 42% for that more stringent definition, and it was even more protective, so closer to 60% for adolescents within that first 6 months after receiving a vaccine. We did see that that effect waned over time. I think promoting the benefits of getting booster doses or the recommended schedule of those vaccines is justified. But, yes, vaccination did appear to have a protective effect.
Q. Do you have any recommendations for parents who have been referred to a rehabilitation doctor who might not know as much about Long COVID? Are there important highlights to share?

Response:

Dr. Case: We’re a small field, so in terms of working with a rehabilitation specialist, we operate under diagnoses of impairment. We work with children that have cerebral palsy or muscular dystrophy and they may have muscle weakness, but we're treating the muscle weakness, not necessarily the diagnosis of cerebral palsy. I think about that for families or patients and parents that are coming to talk about Long COVID. While it would be really important to highlight the context of the functional change, potentially, "We all had an infection. We tested positive for SARS-CoV-2. Six to 8 weeks later, X, Y, and Z happened," but then really highlighting what the patient was able to do before and what they want to get back to.

It may be crossing different spans or domains. It may have some cognitive pieces as well as physical. But if you can highlight what you want to work on, then a rehabilitative specialist can troubleshoot different techniques, referrals to different specialists like neuropsychology or psychology to work on memory retraining, or maybe it’s partnering. One of the things I’ve done commonly as a rehabilitation specialist is partnering with schools as to what exactly a patient needs in an individualized education program (IEP) to be successful. And so just really having them help walk with you in this impairment and try to return to optimal function.

Q. Is there evidence of symptom flare ups in individuals with Long COVID after subsequent non-COVID infections?

Response:

Dr. Rao: We’ve certainly seen anecdotal reports of people having another viral illness and then having flares of their Long COVID symptoms. It’s not something that’s reported a lot in the literature. I think it’s a very important topic area. But it is something that we see with our patients that we’re following over time, that this can happen, not just with SARS-CoV-2 positive infections but we’ve seen it occurring with others potentially as well.

Q. You mentioned the allergies that put children at higher risk of developing Long COVID. Is that any kind of allergy or can you expand and provide a little bit more detail around that?

Response:

Dr. Rao: There was a report that came out of Nature that was looking at risk factors for Long COVID. This study was done in adults, and some other studies in kids have shown this association as well. If you have a history of allergies—and they looked at any kind, seasonal as well as some food related allergies—if you had that
predisposition, that that was considered a risk factor, which is an interesting thing to see being reported in different types of studies.

Those types of studies as well as other ones looking at pathophysiology wondered about a mast cell activation syndrome as being a proposed mechanism for some of the features of Long COVID – the tachycardia, the flushing, some of the POTS manifestations, even some of the neurocognitive things. There have been some folks that have looked at whether we can do anything to minimize the histamine release and will that impact treatment? Still work that needs to be done in this area as it was just a risk factor that was picked up, a theory that makes a lot of sense, and now studies need to explore that association more.

Q. Have you found that any treatments or medications are working differently in children than they are in adults for PASC?

Response:

Dr. Case: There is not a lot of medication in rehabilitation at this point, although maybe in the future. But right now, some of the treatments that we have found to be more effective in clinical experience (anecdotally), are some of the brain retraining and cognitive behavioral therapy. In general, it's thought that pediatric brains have more neuroplasticity, but again, this is all still very new in terms of tracking outcomes and potential.

Q. Are there any short-term trainings that providers could undertake to feel better equipped to provide care or referrals for Long COVID patients?

Responses:

Dr. Stockwell: The American Academy of Pediatrics (AAP), on their website, actually has a really great outline for pediatricians about Long COVID and walks through a lot of the domains like what Dr. Rao has done and talks about each domain and when you might want to refer. That's often where I'd point pediatricians to if they want to learn about Long COVID. We definitely hear in RECOVER from a lot of the families in the study that their pediatricians don't really know about Long COVID and they are finding that they have to do the education, similar to Becky's experience. I can also see from some of the questions that are coming in the chat that parents unfortunately feel they have to be educating the pediatrician about it as opposed to the pediatrician already knowing about it.

I think one of the reasons we published the paper in Pediatrics that Dr. Rao mentioned was really to try and get out information about Long COVID very broadly to pediatricians. RECOVER also has a really nice tip sheet regarding how to talk about Long COVID to your pediatrician if your pediatrician doesn't really know a lot about Long COVID. That's something that came out of the RECOVER pediatric cohort as we were hearing from families that they really needed help talking to their pediatrician about it. We have a long way to go, but hopefully we're starting to make some changes.
Dr. Rao: I was actually going to say the exact same things you mentioned, and I really like the AAP website. I know the CDC has put out some materials as well. When I talk to providers about these types of things, I think it's obviously important for us to learn more about the conditions. It’s important for us to think about that biosocial model of how we can support and help the child and the adolescent really be at their best capacity and their best potential. And I think just as important is to really take the time to listen to the child, to the families, to the parents, to their stories and what they’re experiencing.

There's still some disbelief out there about the extent of these symptoms and conditions. One of the most important things is just to take that time to hear what's happening. It’s an evolving field. We’re learning more and more by the month. And I wish that we could proceed at a faster pace, try to come up with answers and treatments and make this all sort of go away. I think that validation of, "This is not in your head. This is real. We believe you. We'll help you through this," can really go a long way.

Q. What’s being done to look for the possibility of a new autoimmune disease occurring because of Long COVID or COVID infection? Do you think Long COVID will increase the risk of a future autoimmune disease?

Response:

Dr. Rao: That's such a great question and such an intriguing area of research. As you've heard me mention, there's been associations with autoantibodies in people after having acute COVID infection. For example, there was a study that looked at adults who were hospitalized with COVID. They found that 50% of them ended up having some sort of autoantibody in blood work compared with only 15% of controls.

We've been seeing that there are some antibodies that are directed at specific organ systems versus other ones that might be more general. We're trying to learn the association between finding them and relating that to what symptoms and conditions people are experiencing. We know that this is true of other autoimmune conditions. We know that when people get a virus or some sort of infection, even after that virus clears, the autoantibodies can continue and then can cause chronic disease. We've been accruing more data on what some of those conditions look like, trying to figure out a way we can look for them. They're going to be outside of what we can do clinically a lot of the time in terms of the panels that we currently have available, but it’s definitely a very active area of research.

And I think we also need to know that this risk may not just be in that short term, within a few weeks after infection. That’s why we're doing a lot of these longer-term studies, enrolling people over longer periods of time to see if something might develop even years after the initial viral infection.

Q. What is the state of the research around cardiac manifestations of Long COVID in children, such as microvascular inflammation, chest pain, and micro-clots?
Responses:

Dr. Rao: In terms of some of the cardiac manifestations, we talked about how some of these can be presenting as chest pain in individuals. Some of it might be respiratory related, more cough and respiratory system that’s involved, but some of it could be related to that cardiac presentation too.

If people are exhibiting chest pain, we really want them to be referred to the cardiologists and to undergo a cardiac evaluation. That usually looks like getting an electrocardiogram (EKG), looking at the heart rhythm, and then potentially going on to get an echocardiogram to look at the structure and the function of the heart. And then the next step is ruling out other potential reasons to have chest pains. Is it respiratory, is it related to the GI system?

What we’re seeing in kids is not the same chest pain as what we might be seeing in older individuals where there might be ischemia or parts of the heart that are damaged because of clots in the larger coronary arteries. We’re seeing different kinds of manifestations that might be more global inflammation of the heart—myocarditis was something that we talked about, or completely normal echocardiograms, completely normal EKGs, but still there are ongoing symptoms that we can’t necessarily pick up on our clinical testing.

For some of these folks, we need to be very careful in terms of their returning to playing sports. We want to make sure that we’re not going to exacerbate things in any way. For that reason, we talk about referrals to cardiology. They can help with some of those return-to-play pieces, make sure that there’s nothing structural going on and can talk about whether there are any other steps that need to be taken treatment wise.

That’s a little bit different from talking about the micro-clots and the changes that we see within the vessels. Again, we call this micro vessel damage. It can be a predisposition to clotting and then it can cause some sort of distortion or changes to the lining of the vessels. That has been shown to be associated with some of these local symptoms and conditions.

In terms of what can be done about them, we know that with acute COVID, we will often give people preventative measures to stop them from having clotting problems. Sometimes they need to get specific treatment if they have a clot. It’s still unclear what we need to be doing with certain conditions that are associated with the micro-clots. Is anticoagulation therapy, the same way that you would do with a large clot, is that beneficial for these patients? Because obviously there’s going to be risks with any procedure that hasn’t been studied well.

I think there’s more to come in this space. We’ll see if there are any directed treatments to help any of those symptoms down the road.

Dr. Stockwell: I think the only thing to add is that there have been some interesting recent studies that have looked for micro-clots in the muscles, not only in the vasculature and whether that might be part of the link between Long COVID and other post viral conditions and post exertional malaise. As Dr. Rao said, more research still needs to be done as we’re trying to piece this all together.
Q. Are there any proposed studies that use whole genome sequencing to search for genetic variations which may predict PASC in kids? Is the quest for a unique diagnostic protein biomarker futile given the plethora of symptoms involved?

Response:

Dr. Stockwell: As part of RECOVER, we are collecting many different types of samples, including doing some whole genome sequencing as well. When we're looking for potential risk factors, not only for Long COVID itself but also for recovery, which is really important for all of us, we want to make sure we're looking at multiple levels, the social, the biological, as well as the genetic.

Q. How is Long COVID in pediatrics evolving post-Omicron?

Response:

Dr. Case: I think the way that we’re thinking about post-COVID or Long COVID conditions really stems from the fact that we don't have a great baseline or information to start from. It's a little bit of learning as we go, and that's been a big challenge. But one of the things I wanted to mention is the MIS-C—or multi system inflammatory syndrome in children—was something that I saw as a consultant in the intensive care units (ICUs) for a fair amount in the beginning and even during the Omicron wave and then that kind of trickled out. I think knowing that is one of the phenotypes of PASC, it's shown me that things have definitely shifted and evolved and potentially there are subclinical or more mild MIS-C but it's not to that degree where they're requiring ICU care. And so I wonder if everything has just shifted a bit.

In addition, we've also still seen a couple cases of MIS-C, but it's been in children under 2. So I wonder if this has been their first exposure to a SARS-CoV-2 infection, whereas maybe one of the larger takeaways is that a large portion of the population has been exposed or vaccinated.

Anyway, that's a great question. It has evolved. And I don't necessarily take it to mean that the outcomes are more mild, but I haven’t been as much as a consultant in the ICU type arena.

Q. Do you feel that most children with Long COVID can be managed by general pediatricians? Or do you feel that these children need to be referred to a pediatric rehabilitation or Long COVID specialist?

Response:

Dr. Case: I think there are many patients that can be treated by pediatricians. I think involving a multidisciplinary team can help with the more severe and more limiting presentations. I do think with better higher-powered
studies, there can be more education and best practices to equip pediatricians to also address Long COVID effectively.

Q. Why is there a need to still use both PASC and post-COVID conditions in children? The duration is different for these two terms and seems to only add to the confusion and makes it hard to compare studies

Response:

Dr. Rao: As discussed on this call, there are several definitions being used by different clinical and research groups, which include different time intervals, and currently there is no established standard definition. We agree that this makes it challenging to compare studies and leads to the variability in reporting data such as incidence in children.

Q. Are you seeing an increase of inflammatory bowel disease (IBD) ulcerative colitis cases in children/teenagers after COVID?

Response:

Dr. Rao: We personally have not seen increased cases in children and teenagers after COVID, but there are several reports of this in the literature. The underlying mechanisms for conditions such as ulcerative colitis can be from an infectious trigger stimulating an immune response which goes on to cause autoimmune conditions.

Q. The studies being shared in this webinar so far (we are well into Dr. Case's portion) are from 2021. Are there any newer studies?

Response:

Dr. Rao: The prospective branch of the RECOVER initiative will be publishing several studies related to Long COVID in children over the next several months.

Q. How can a researcher working in a similar or highly related area get connected into the larger program. Is it through local institutions or are there ways to engage nationally?

Response:

Dr. Rao: Interested researchers can use the RECOVER website to determine whether there are opportunities to get involved. https://recovercovid.org/contact-us.

Q. Is there a role of vitamin D3 and thiols status in the outcome of COVID-19 disease? Can you speak to the Nature article on this topic?
Response:

**Dr. Case:** The study referenced would suggest hypovitaminosis D may play a role in outcomes (both morbidity and mortality) for adults with COVID-19 infection. The pediatric cohort was small and with no mortality. This should be further explored but vitamin D levels have the capacity to affect outcomes based on its known role in modulating the immune system.

**Q. Is the role of joint hypermobility/Ehlers-Danlos syndrome in Long COVID in children being investigated?**

**Response:**

**Dr. Case:** There is an interest in how different medical conditions affect recovery from infection, including hypermobility or Ehlers-Danlos Syndrome. There was a recent prospective observational study out of the UK using COVID Symptom Study Biobank. In this large population-based study, an individual with generalized joint hypermobility (an index of variant connective tissue structure) was approximately 30% more likely not to have recovered after initial COVID-19 infection. This study suggests this should be studied with a more diverse sample to better understand.

**Q. I have heard a pediatric pulmonologist say that they have seen an increase of kids coming in post-COVID with new asthma that had not had asthma previously. Is there any data on the percentage of kids that recover completely and no longer have asthma? Is there anything we know specifically about pediatric post-COVID asthma?**

**Response:**

**Dr. Rao:** There have been several reports of asthma symptoms developing after acute COVID infection. In one study of 69 children who were hospitalized with COVID-19, 58.5% were not affected by asthma-like symptoms. Of the 41.5% who did have asthma-like symptoms, there was a family history of asthma in 63.0%, a past medical history of asthma in 33.3%, and allergic rhinitis in 85.2%. Another study suggested that the inflammatory effects of COVID-19 on the lungs can last long after recovery from the infection. Researchers found evidence of these effects 3–6 months after recovery but found that they usually resolved after a year.

**Q. Has the data shown that children who have had COVID may get sick with other viruses more frequently than they did prior to their infection?**

**Response:**
Dr. Rao: Several studies have demonstrated suppression of immune responses controlling antiviral activity, which have the potential to persist several weeks to months. In some of our earlier work, studying over 600,000 children across the US, we observed a higher rate of tonsillitis, bronchitis, and pneumonia in the 1 to 6 months following PCR-confirmed SARS-CoV-2 infection compared with test-negative controls. We are currently exploring this question further by looking at whether SARS-CoV-2 infection increases the risk of subsequent respiratory syncytial virus or other respiratory infections compared with someone with influenza infection and other control groups.

Q. What is the general prognosis for these children with Long COVID? Are some of these children felt to be disabled for the long term and need to apply for long-term disability?

Response:

Dr. Case: This is a great question. The longer-term outcome and prognosis for children with PASC is still being studied. In one study, PASC symptoms resolved in the majority of children over the course of several months with one-third of children having ongoing symptoms at 12 months. The prospective studies underway should provide more insight into this.

Q. What percentage of children have a SARS-CoV-2 viral reservoir explaining their symptoms?

Response:

Dr. Rao: While immune dysregulation is proposed as one of the most important reasons for Long COVID, viral persistence has been described in some studies, and may be one potential reason for persistent symptoms. For example, a study evaluating tissue samples collected from 225 adult patients infected with SARS-CoV-2 (some of whom had Long COVID symptoms) showed residual viral RNA in 16 (30%) of 53 solid tissue samples collected at 1 month, 38 (27%) of 141 collected at 2 months, and seven (11%) of 66 collected at 4 months. Further research is needed to explore this association in children.

Q. What is the effect of vaccination on children who are presently suffering from Long COVID? Is there a worsening or prolongation of symptoms?

Response:

Dr. Rao: There have been reports of vaccination improving Long COVID symptoms, but data is lacking in children. In a systematic review of 11 studies (n=36,736 COVID-19 survivors) investigating changes in Long-COVID symptoms after vaccination (infection-Long COVID-vaccine design), seven articles showed an improvement in Long COVID symptoms with at least one dose post-vaccination, while four studies reported no change or worsening in Long COVID symptoms after vaccination.

Q. Since only 45% of kids exhibit a fever in acute infection, how can we communicate this to the medical community?
Response:

Dr. Rao: It’s important to convey to the medical community that Long COVID can occur after mild or even asymptomatic SARS-CoV-2 infection, which can make diagnosis challenging. Testing during the acute illness phase wasn’t done because its presentation overlaps with many other respiratory viruses.

Q. How many children also have autoimmunity and/or herpesvirus reactivation, and/or other underlying causes of their Long COVID symptoms?

Response:

Dr. Rao: A number of studies including the ones presented in the webinar have demonstrated the presence of autoantibodies following infection, as well as herpesvirus reactivation (such as Epstein-Barr virus), but the precise number is unknown in children at this time and is the subject of further study.

Q. How is the pain being treated in pediatrics?

Response:

Dr. Case: Currently, guidance remains limited regarding the assessment and treatment of manifestations of PASC in children and adolescents including pain. Recommendations for headache evaluation and management are in line with pediatric headache guidelines from the American Academy of Neurology and American Headache Society. Based on the Multi-Disciplinary Collaborative Consensus Guidance Statement from the American Academy of Physical Medicine and Rehabilitation (AAPM&R) task force, a stepwise approach should be taken, starting with conservative treatment and referral to physical therapy and psychology for cognitive behavioral therapy and coping. If conservative measures fail and patients are interested in a trial of medications, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, anticonvulsants (gabapentin or pregabalin) and low dose tricyclic antidepressants, can be considered. More diverse and larger studies should be done to provide more evidence-based guidance.

Q. What are the timeframes a parent might expect for the histamine research being done, and is there an interim path to choose for care until a study is done? What kind of doctor would be the right field?

Response:

Dr. Rao: We recommend seeking guidance from a rheumatologist regarding mast cell activation syndrome and the role of antihistamines while we await further study in this area.
Q. Is BC007 from Berlin Cures being tested in children? Is the NIH connecting with Berlin Cures?
Response:
Dr. Case: Based on a literature review, this doesn’t seem to be in children yet.

Q. Has low-dose naltrexone been tried in children to see if it will help?
Responses:
Dr. Case: At this point, low-dose naltrexone doesn’t have any evidence for pain relief from Long COVID. I’m aware that its effects are being explored for pediatric chronic pain and could be an intervention to be explored in future work. Please refer to the question regarding pain in children above.
Dr. Rao: There is a protocol for a study in adults.

Q. Do you feel like the schools should be implementing mitigation measures? It looks like reinfections only cause them more and more damage?
Response:
Dr. Rao: There’s certainly a need to balance the need to be in school for the educational and social benefits, while also minimizing the spread of infectious disease. While we are not carrying out the same mitigation measures as we did during the early phase of the pandemic, there are certainly steps that can be taken to reduce the risk of infections in school settings. These are summarized in a new report from the CDC for schools, and includes the following steps:
- Teach and reinforce proper hand washing and respiratory etiquette.
- Take steps for cleaner air by improving ventilation in schools. Schools should consider ventilation enhancements and design when undergoing remodeling or when undertaking new building construction to optimize clean air.
- Clean, sanitize, and disinfect, when appropriate.
- Promote vaccinations for students and staff.
- Have staff and students stay home when they are sick. The guidance makes clear what specific symptoms necessitate staying home.
- Hand washing, respiratory etiquette, cleaning, sanitizing, and disinfecting remain important.

Q. Do children tend to develop POTS at the same rate as adults or are they developing other types of symptoms?
Response:
Dr. Case: The literature continues to vary quite a bit, suggesting anywhere from 2% to 15% of any patients developing POTS following infection. I have not seen any specific literature on the frequency in children yet.

Q. Is anyone planning a trial of hyperbaric oxygen therapy (HBOT) in children?

Responses:

Dr. Case: I’m not aware of any HBOT trials now. Studies have validated indications for HBOT to date, among which carbon monoxide poisoning, decompression sickness, arterial gas embolism, and necrotizing soft tissue infections due to anaerobic or mixed bacteriologic agents, are well-known. There have been recent HBOT treatment studies for more chronic conditions like cerebral palsy that have not shown to be effective.

Dr. Rao: There will be a trial exploring longer dosing of Paxlovid in adults, through the RECOVER initiative, but no trials are currently being planned in pediatrics at this time.

Webinar Slides

To request a copy of the R3 Seminar slides, please email RECOVER_ACC@rti.org.

To Learn More

- Information about RECOVER research and to volunteer for studies: https://recovercovid.org/research
- Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs
- For medical/scientific terminology: https://medlineplus.gov/healthtopics.html