# 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 for the following panel at the R3 Seminar ***SARS-CoV-2 infection during pregnancy and development of Long COVID*** held on May 14, 2024:

- ***Pregnancy & PASC***
  **Ann M. Bruno, MD**
- ***Development of Post-Acute Sequelae of SARS-CoV-2 After Infection During Pregnancy: NIH RECOVER-Pregnancy Cohort***
  **Torri Metz, MD, MS**
- **Panelist: Chengxi Zang, PhD**
- **Discussant: Valerie Flaherman, MD, MPH**

* Responses may have been edited for clarity.

# All Presenters: Questions and Responses

### Q. How does infection during pregnancy impact the offspring?

**Response:**

**Dr. Metz:** I reviewed this topic a little bit on one of my slides that showed the offspring neurodevelopmental assessments that we're doing as part of RECOVER-Pregnancy. We have a very robust set of neurodevelopmental assessments that we're completing on the offspring of these participants. These data will lag behind the data that is shared from the adult cohort, just because we have to wait until the children are old enough to assess them. The last RECOVER-Pregnancy participants delivered in December of 2023, and so all of them will reach 1 year of age by December of 2024. We are starting to look at those data and are really interested in seeing them.
There are a couple of publications like this one looking at offspring assessments, outside of RECOVER, using data from other large administrative datasets, examining if offspring have abnormal neurodevelopmental diagnoses in their medical records. The researchers found a signal that those who had been exposed to SARS-CoV-2 in utero appeared to have a higher rate of abnormal neurodevelopmental diagnoses. I think it's hard to know whether they

were just more closely followed. These offspring were certainly more likely to be born premature and are often followed in specialty clinics where those diagnoses may be made more often. I think that there is really interesting work that's already been published, but it will be important to validate that work in a prospective cohort, like the RECOVER cohort.

There was another publication looking at using the Ages and Stages Questionnaire looking at using the Ages and Stages Questionnaire, which we're also using in RECOVER, to examine outcomes. The researchers used some control groups of children who were born prior to the pandemic. It's going to be really important to sort out the pandemic effects of children being born during the pandemic—in a period where patients were masked, where people were masked, where there was less social contact—and how that affects neurodevelopment in socio-emotional development in comparison to SARS-CoV-2 itself, that exposure and that inflammatory response. They're really important questions that we're excited about examining, and Dr. Flaherman can also maybe pitch in there since she's involved in the pediatric aspect of this cohort as well.

**Dr. Flaherman:** Yes, this is something that RECOVER has really focused on. In our prospective pregnancy cohort, we are doing these careful assessments of the offspring through 4 years of age. And one thing I'm really hoping to be able to look at is how exposure to SARS-CoV-2 affects the developmental trajectory of children over time. I think one thing that RECOVER is very suited for is adjusting for the effects of the pandemic itself, because we have those actual controls that are contemporaneous to the exposed participants. I think there will be some great things in the future and I'm glad to see that there seems to be some audience interest in it. So hopefully, we'll see you all at another seminar, not too far from now.

## Q. What are the benefits and advantages of the prospective data collection, and the benefits and advantages of the electronic health record (EHR) data collection? These are two unique data sets that might have different sorts of biases. The pregnancy cohort could be a good opportunity maybe to think about the unique contributions of each cohort.

**Response:**

**Dr. Zang:** Maybe I can start with the EHR cohort. I think one of the biggest trends is sample size of the EHR cohorts and thus, potentially more generalizable, real-world evidence. Actually, based on Dr. Bruno's work, we're continuing our efforts to collect a bigger cohort. Currently, we're targeting a cohort that's five to 10 time bigger, so we can study more, trying to analyze by different variants of COVID, different trimesters, and so on. I think that's the first power: we have a bigger sample size. Potentially, we can generate helpful evidence or hypotheses in a timelier way. This is more timely and cost-effective than the prospective cohort. And this is real-world evidence we are collecting to inform the real-world of treatment and real-world outcomes. Which of course, will inform data collection from the prospective cohorts and vice versa. And prospective cohorts will also inform the EHR analyses.

**Dr. Metz:** I can speak to the prospective cohort. I think Dr. Zang is exactly right. It's super helpful to get that large population-based capture that we can get with the electronic medical records. I alluded a little bit to the fact that with the prospective observational cohorts, we worry a little bit more about bias in terms of people who were already affected with PASC, then wanting to enroll (not surprisingly so) in a study that's investigating PASC. We worry that their participation may inflate the prevalence a little bit in the observational cohort. I think there is a little less concern about that in the pregnancy cohort, just because of the way we did our recruitment, and that we really weren't recruiting specifically from Long COVID clinics.

But that is a concern that the EHR cohort can fill and really complement the two. The advantage of the prospective cohort is that we can really collect detailed data on every single participant, really make sure that we understand all of their past medical history very well, take laboratory assessments, really extensive symptom surveys—things that we just can't get from just pulling information from a medical record. So, they really do work synergistically to try to get us research answers.

## Q. Have your groups looked at some of the risks and benefits of COVID-19 vaccination during pregnancy? How do you think about that in terms of RECOVER data?

**Response:**

**Dr. Bruno:** I would just say outside of the two studies that Dr. Metz and I presented today, there is quite a bit of literature now supporting COVID-19 vaccination in pregnancy. As was stated, earlier in the pandemic, this was a big worry. Just like when there's any vaccination or medication, it's very important to include pregnant and postpartum individuals in those analyses and studies. Over time, that has successfully been completed and the overwhelming evidence supports the safety of COVID-19 vaccination in the course of pregnancy and the postpartum period, both without any evidence of teratogenicity or other specific complications in pregnancy, but also, as highlighted in some of the prior work of Dr. Metz, with reduced acute risks related to SARS-CoV-2 infection in pregnancy.

We're also starting to see that in some of these longer-term studies looking at PASC and the EHR data set, we included documentation of vaccination and analyses. In general, we identified that pregnant individuals were less likely to be fully vaccinated. That likely reflects some of the time period that we were utilizing, because it crossed to the period before the data around safety for vaccination was as robust. That is something that's also been included in the ongoing prospective cohort with Dr. Metz. I think we'll continue to get more and more data from that component. I will say clinically, that as maternal-fetal medicine physicians, our national societies all highly support the use of COVID-19 vaccination before and during pregnancy. It's also nice to see that those recommendations are bearing out in data now to support that they are likely safe and demonstrate long-term protective ability as well. But I think future analyses that are more specific and focused on COVID-19 vaccination to look at PASC will be necessary within this population.

## Q. Have we flipped the research question to look at pregnancy in participants who already have PASC? Has RECOVER started to look at that?

**Response:**

**Dr. Metz:** This has come up. All of these cohorts have coordinated committee groups that meet, and we have patient representatives that are part of those committees that help lead the work that RECOVER's doing. It actually has come up there where they have asked, "What can we look at? What about..." Now that somebody has a diagnosis of PASC or Long COVID, and they want to get pregnant, how is that subsequent pregnancy going to be affected? How is their fertility going to be affected? I think that those are really important questions that are definitely on our radar. I don't have any data to share about that today. But it has been brought up in our group that is helping to lead this work, and we definitely think it's an important question.

I think we can get at this question with the prospective observational data. We collect data on subsequent pregnancies on all of the adult participants, not just those in the pregnancy cohort. For any adult participant who was enrolled, we have information about when they met a diagnosis of PASC, and if they had any subsequent intervening pregnancies after that time. We've talked about trying to get data about how many participants have had a subsequent pregnancy. But I also think it's something that will be very ripe for investigation in the EHR cohort, where we take these patients that have computational phenotyping and have identified them as people with PASC, and then looking at subsequent pregnancy in them.

**Dr. Zang:** We must acknowledge that our current analysis focuses on incident PASC, in which individuals begin at a normal baseline and develop symptoms. The challenge with examining pregnancy in participants who already have PASC is how to distinguish between worsening PASC symptoms and the conditions common to the gestational or postpartum periods. This may be cause for revising our definition of existing PASC, since we can see the gap between the general population and those with incident PASC.

## Q. Has there been thought given to the different stages—or perhaps trimesters—of pregnancy, and how this may impact the physiology of the individual, and the outcome of PASC?

**Response:**

**Dr. Bruno:** I think that's of interest. In the analysis that we presented today, while we did have a large sample size—which is a major positive of using this data source—we were still limited in our ability to complete sub-analyses by trimester of infection. That’s something we’re working on for future work in a larger EHR data set. So, thinking about how we might be able to consider what we've highlighted earlier about vaccination status a bit further.

Also considering bivariants of SARS-CoV-2 infection has been of some interest. And as it relates specifically to pregnancy, thinking about the trimester of infection and how that might alter the interval development of PASC. That's something we're currently working on. We'll hopefully have more information in the future. This highlights an important question that comes up as we think about pregnancy and whether it matters at what point during pregnancy an infection occurs as it relates to interval PASC.

## Q. Since SARS-CoV-2 has changed over time in its acute form, would it be reasonable to think that PASC itself might also be changing? And if it is, how can we track that in the data?

**Response:**

**Dr. Metz:** It's a question to address on an ongoing basis. It does seem like with infection by the earlier variants, people are more associated with PASC. But perhaps that's because of how we've defined PASC. I think we may see differential symptoms in severity of PASC with different variants. I think uniquely with pregnancy, there were definitely variants—specifically the Delta variant—that were particularly harmful for pregnancies. As in the general population, we saw a lot higher rates of intensive care unit (ICU) admission, but we also saw much, much higher rates of stillbirth and placental effects of that particular variant of the virus. I also think it is important to look at differences in the offspring outcomes by variant differences and PASC by variant.

And those are all things that are certainly at the forefront of people's minds when we're thinking about this. Pregnancy is a little tricky, because we presented data showing that people who are pregnant who got SARS-CoV-2 are more likely to be admitted to the ICU and die. Epidemiologically this is true and has borne out over and over in the literature. It's probably because their immunologic response is a little bit different than people who aren't pregnant. That's why we also see with other viruses, pregnant women tend to get more ill. And that's because they're a little more immune-tolerant in pregnancy. They have to tolerate a fetus that doesn't have their maternal DNA. In order to do that, a lot of changes happen with the immune system that adapt, that allow more tolerance, which then results in sicker patients.

So then you'd say, "Well, if they got sicker, why isn't their PASC worse?" Well, maybe it's all interrelated, that even though they got sicker, it was because they didn't have quite as robust of an inflammatory response that's involved in the pathophysiology. I think next steps, if this continues to be demonstrated that there's a lower prevalence among people who had SARS-CoV-2 in pregnancy, we'll be examining why. And can we look in terms of pathophysiology? Can we look back at the bio-specimens that we've collected, and really demonstrate if there are differences there?

**Dr. Zang:** PASC can vary by different SARS-CoV-2 variants suggested by our epidemiology study. For example, in New York's data, we just found a bigger hazard ratio, bigger burden on the pulmonary arteries, and more gastrointestinal conditions compared to the ancestral variants. But as these are findings from the general

population, I think it will be a question mark for the pregnancy cohort, how they evolve over time. It's a big question mark.

## Q. Could you talk a little bit more about the specific indications, such as the immune changes, and why that might be hypothesized to be a protective factor during Long COVID?

**Response:**

**Dr. Bruno:** In prior evaluations of other infections during pregnancy, there has been data supporting that there can be immune changes. Both Dr. Metz and I talked through that a little bit, that in the presence of a developing fetus, there are natural physiologic immune changes that allow for a tolerant state, because there is "foreign DNA" in the setting of the fetus as well as other immune regulatory aspects. So, while that is a hypothesis, because it's been borne out with other infections, it's still technically a hypothesis. As Dr. Metz highlighted, in future work it will be interesting to use bio-specimens to look more specifically at cell regulation and the pathology within specimens to try to confirm or deny that a bit further. But because of existing data for other infections and the hypothesis from a biologic plausibility standpoint, that is something that would make sense to us clinically.

## Q. Regarding the apparent lower incidence of PASC among people who were pregnant during infection, do you think this could have been influenced by the perception of fatigue and brain fog that's associated during the postpartum period?

**Response:**

**Dr. Metz:** We were worried, for sure, about overlapping symptoms that we see between many of the PASC symptoms that people have as well as what is more just being postpartum—feeling fatigued, obviously, from interrupted sleep with a newborn. The vast majority of our cohort, their pregnancy did result in live births, about 96%. Actually, we're trying to enroll people whose pregnancies resulted in live birth, just because we want to also follow their offspring. For the analysis that we did in the prospective observational cohort, we did that second sensitivity analysis where we took out anybody who was being assessed for PASC while they were either still pregnant or while they were within the first 12 weeks postpartum, and just tried to make sure that we were still seeing the same prevalence of PASC, which we did.

I think it’s important to try to tease those things out. Also, our comparison group is other people who had a pregnancy who didn't develop PASC, and so similarly, those people also have a newborn at home and would, in theory, have similar symptoms related to just being postpartum. So, I think we have an appropriate comparison group for that. And we also did that additional analysis where we looked only at people who are assessed further out from their birth.

## Q. Dr. Metz' study uses the definition of PASC that was from the recent JAMA article. Can you talk about if that included pregnant individuals in their algorithm, and if there's any distinguishing symptoms that are seen in the pregnant sub-cohort that maybe might not be as frequent in the rest of the population?

**Response:**

**Dr. Metz:** Yes, the initial publication included pregnant individuals, and so they helped drive that initial PASC score development. Although, I will say that it is only about 10% of the overall adult cohort population, and so that was not largely driving that. It was largely driven by people who had SARS-CoV-2 outside of pregnancy. But we really have been trying to say—on general principle and broadly—that pregnant people should be included in analyses, they should be included in research, they should be included in studies. Across the whole RECOVER Consortium, unless we have a really good rationale for excluding them from these analyses, they are being included.
I think more broadly, in terms of the symptoms that we saw, they really were the same in terms of the most prevalent symptoms between the initial adult RECOVER population and the subset of this pregnancy population. We looked at it specifically. Really, the most prevalent symptoms in both cohorts were very much the same. We didn't see a difference in those, which might be a little bit surprising because you may think that you would see a difference in those, especially with what we've been talking about in terms of differences being postpartum and being pregnant. But they really were consistent across the two cohorts.

## Q. Is there a discernible impact on breastfeeding success or failure rates related to perinatal COVID infection or postpartum Long COVID that you're aware of?

**Response:**

**Dr. Flaherman:** This was something that RECOVER is very focused on answering. We have a good assessment of breastfeeding practices in our infant outcomes. It was a major concern of pediatricians in the early pandemic, when mothers who delivered with SARS-CoV-2 were actually separated from their infants. And there was a lot of concern about breastfeeding during SARS-CoV-2 infection. Of course, as I think everyone knows at this point, breastfeeding is very much to be encouraged. We really want to look into what happened at that time, and whether there was an impact of early infection on breastfeeding. I look forward to hopefully presenting those findings later this year.

## Q. Will you also look into other symptoms among offspring beyond neurodevelopmental symptoms?

**Response:**

**Dr. Metz:** I can maybe answer that from an obstetrician (OB) perspective, then maybe Dr. Flaherman can answer from a pediatrician perspective. From an OB perspective, we worry a lot with infections that we see a lot of. We can see maternal fever, we can see maternal inflammation. All of those things in other conditions have been associated with adverse neurodevelopment in the fetus. So, that's the rationale for really focusing on that. I think early in the pandemic, there was a lot of concern for vertical transmission of SARS-CoV-2—meaning the virus actually crossing the placenta and infecting the fetus. We have found that that it is extraordinarily rare for that to actually happen.

I think that allows us to shift our attention a little bit more to not those acute effects of the fetus actually being infected with the virus, but the effects of the fetus being in an inflammatory maternal environment with things like a fever that can really affect that neurodevelopment. That's why we wanted to focus on that from an OB perspective.

**Dr. Flaherman**: It is very difficult to assess child neurodevelopment through, for example, an electronic medical record—especially in early childhood—and we didn't want to wait 10 years until these kids were in the middle of their school age and we could actually demonstrate a drop in test scores, or something like that. We wanted to do the assessment early so that we can really inform public health preparedness for the future. The only way to do that is through a detailed neurodevelopmental assessment that really has not been done with the sample size that RECOVER is going to be able to do it.

Having said that, we are also looking at a wide variety of other childhood outcomes, including growth, body mass index, child health services utilization, sleep quality, behavior, different aspects of child well-being that we'll be able to report on. And I think one of the unique things about RECOVER is that we have this detailed information on both the pregnant individual and the child, and we have the ability to follow them together, which is really unique across cohorts. That cohort will have to age somewhat before we can do our final neurodevelopmental assessments. But I think we should be able to get some of the highest quality data on this topic of any studies that I'm aware of.

## Q. How do you hypothesize that sequelae of SARS-CoV-2 infection during pregnancy might influence trends and severe maternal morbidity and mortality?

**Response:**

**Dr. Metz:** It's definitely an area of interest and research for me. The CDC has released data about maternal mortality in the period of the pandemic as well, and we definitely did see an increase initially in maternal deaths

during the pandemic. Which, if you really broke down that analysis in detail, could be largely attributed to SARS-CoV-2 itself, so COVID-19 itself. But I think in the pregnant population, like any population, we also saw increases in all-cause mortality.

Certainly things like mental health disorders, suicide, and drug overdoses have gone up in the pregnant population, just like they have in the non-pregnant population. The most recent maternal mortality data that have come out actually started to show a decline again. But we certainly saw an increase over the early pandemic years, related largely to COVID-19 and maternal deaths from that, but also other causes of mortality that were influenced by just living in the time of the pandemic.

## Q. What supports can we offer women at risk for Long COVID and the transition from antepartum to postpartum care?

**Response:**

**Dr. Bruno:** That's a great question in regards to how do we apply clinical research to our actual clinical practice? That is one piece that's exciting about these findings, from both of the studies presented today, is how those can be utilized to counsel patients. Although there's a lot of additional work still needed, as we have highlighted today, we want to see future prospective work and hopefully replication of our findings. These data can be utilized to start to counsel patients on what we have identified as far as associations between COVID-19 during pregnancy versus outside of pregnancy and interval PASC.

Currently, there's somewhat limited availability of Long COVID clinics, as it relates to postpartum patients. Because for many of the other reasons discussed from our research as well as clinical aspects, unfortunately sometimes our pregnant patients fall out of some of those mechanisms of support. I think these findings also can lend support to policy change as far as available resources through hospitals, communities, and wider policy around that. So I'm hopeful that that would be a change that we could see.

## Q. Has there been any interest or have you seen any differences in findings based on the multiparity of your participants that are reporting symptoms? The notion behind this is a previous pregnancy might affect their reporting of symptoms.

**Response:**

**Dr. Bruno:** From the EHR dataset, that is more difficult for us to get at in regards to considering prior pregnancy history, while we have obstetric history as it relates to prior history of certain health conditions. Our ability to understand how that might alter presentation as far as symptomology is somewhat limited when we're using EHR diagnoses. So that, I think, going back to the pluses and minuses of different datasets or data sources is something that's of benefit, thinking about the prospective cohort.

**Dr. Metz:** Yes, and we definitely are collecting pregnancy history in the prospective cohort in terms of whether people have had pregnancies in the past, and also if they've had pregnancy complications—because pregnancy complications can predispose or unmask underlying tendencies to other comorbidities, things like diabetes or high blood pressure. We did not examine that specifically in the analysis we've already done, but I think that's a great question and something we should definitely keep in mind.

## Q. Is there any interest or any current evidence that the length of time that someone has Long COVID might differ for pregnant populations versus the general adult population?

**Response:**

**Dr. Metz:** That is a focus currently of RECOVER broadly. The RECOVER adult cohort has a writing group that's working specifically on that question now, "What does the trajectory of PASC look like?" This would be a great opportunity to also look at it in the subset of pregnant participants to see if it actually differs in our pregnant population. But really, RECOVER broadly is just starting to do that work related to trajectory.

I think I emphasized a little bit in my presentation but want to reemphasize here—we really are looking at a snapshot in time, and at a median time of 10 months after the infection. But that time differed from as soon as 4 months to as late as a year—or even a year and a half actually, in one of the participants. So really, it's these little snapshots we're getting. As RECOVER, with all the thousands of participants that it has, with these really robust analyses and interactions with participants every 3 months, we're really going to be able to get a much better look at what that trajectory looks like over time as we gather data. And I think is going to be super interesting. It's a really important question, and we are actively working on it.

## Q. Is there any evidence that offspring from mothers who are infected during pregnancy might be more likely to be infected with COVID, as newborns or as offspring?

**Responses:**

**Dr. Flaherman:** I have not seen that. But one of the things we are collecting data on in RECOVER is offspring infections. And we actually assess those periodically throughout follow-up. So, we will be able to look at whether infants whose mothers had SARS-CoV-2 during pregnancy are more or less likely to get it in the first years after birth.

**Dr. Metz:** I would just add briefly that we know that maternal vaccination is protective against neonatal infection, and so that's just circling back a little bit to the vaccine conversation earlier. I mean, that data has been published demonstrating that moms who've been vaccinated, their neonates have a lower risk of being hospitalized for COVID-19. But we have that information too, in terms of vaccinations. It's going to be interesting to look at both of those things.

**Q. Were there any significant findings regarding any tests that are more diagnostic—for example, lab test results? Did you find any difference noted between reported severity of symptomology and these test results among the participants?**

**Response:**

**Dr. Bruno:** In the EHR dataset, we used ICU admission as a surrogate marker for disease severity. Individuals acquiring SARS-CoV-2 infection during pregnancy as compared outside of pregnancy were more likely to be admitted to the ICU.

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