Dr. Nedra Whitehead:
(silence).

Dr. Nedra Whitehead:
So, the goal of the R3 seminar series is to catalyze the shared understanding of the research of the scientific stakeholder community within the Recovery Consortium. Today, this seminar is focused on the clinical spectrum of the post-acute sequelae of SARS-CoV-2 infection. Thank you. Next one.

Dr. Nedra Whitehead:
(silence).

Dr. Nedra Whitehead:
We have three speakers today and a panelist, as I said, I'm Nedra Whitehead, I'm the principal investigator of the RECOVER Administrative Coordinating Center and I'm the moderator for today's session. Ms. Hannah Davis is a co-founder of the Patient-Led Research Collaborative and we're presenting research that she did previously. Dr. Sindhu Mohandas is an assistant professor of Pediatrics Infectious Disease and at the Children's Hospital of Los Angeles, University of Southern California and she’ll be discussing the clinical spectrum of PASC in children. Dr. Igho Ofotokun, sorry, I practiced that before and I still didn't get it right, is a professor of medicine at Emory University. And Dr. Bernard Dreyer is our discussant, he is a professor of pediatrics at the NYU School of Medicine.

Dr. Nedra Whitehead:
As Sean mentioned, please put any questions you have in the chat. Today, we’ll be addressing questions that are directly relevant to the speakers. Questions that come in that are about RECOVER more broadly or other scientific questions will either be addressed in future seminars or will be put on the question and answer document that's on the recovercovid.org website. Thank you. Next slide. As I said, we're going to start with Ms. Davis talking about characterizing long Covid in an international cohort, seven months of symptoms and their impact. And then, Dr. Mohandas is going to talk about the pediatric clinical spectrum of PAS. And then, Dr. Ofotokun is going to talk about the post-acute sequelae of Covid 19. Dr. Dreyer will wrap up, summarize and provide the first few questions and then we'll open the session after questions and answers. Thank you. Hannah.

Dr. Nedra Whitehead:
(silence).

Hannah Davis:
Hi everyone, so my name’s Hannah Davis and today I'm going to be talking about characterizing long Covid and also some interesting data biases we found along the way.
Hannah Davis:
(silence).

Hannah Davis:
So, for those of you who don’t know us, we’re from the Patient-Led Research Collaborative and this is a team of now over 40 members who are all long Covid patients, who also have some research or data or medical research background. We have health policy advocates, we have health activist advocates, so it’s a very interdisciplinary group. And we were formed out of the Body Politic support group on Slack and we have our IRB from University College London. And we’re very interested in patient involvement in research more broadly, we work with different models that already exist to co-create research together with patients and researchers.

Hannah Davis:
So, we’ve put out in total eight papers, three on our own and five with other collaborators. So, we put out the first research on long Covid back in April, 2020. The second paper on patient involvement in research in November, 2020 and then more recently, a third paper looking at over 200 symptoms of long Covid over a time course of seven months. And this has been one of our biggest successes. We have almost 260,000 downloads and it’s been able to influence a lot of the long Covid research that already exists. So, this is the one I’m going to be talking about today. We also do a lot of advocacy work, we have ongoing advocacy projects with the WHO and CDC, we work with Congress, et cetera.

Hannah Davis:
We’re working on a patient engagement model and research with the Council for Medical Specialty Societies. And we’re doing a lot of new work around reinfections, mental health, phenotyping for long Covid, qualitative research, as well as work with N3C. So, for the paper I just discussed, all of our respondents were from the first wave so this is a very particularly focused paper. Almost 92% were not hospitalized. It was a 500-question survey that took on average 70 minutes to complete, which was pretty amazing that we got that response rate for so many patients. But we built in times where they could take a break and then come back to the survey and I think that really helped to get the responses we did.

Hannah Davis:
So, we found that on average for people who did recover, they recovered around three months after an average of 91 days of symptoms. And their symptoms interestingly peaked in week two, compared to those who didn’t recover their symptoms peaked a little later in month two. And on average of the 200 symptoms we looked at, patients experienced 56 of those symptoms. So, we organized these into 10 categories. Systemic gastrointestinal, pulmonary, dermatologic, immunologic, cardiovascular, musculoskeletal, reproductive, head, ears, eyes, nose, throat and then neurological. And because we had so many neurological symptoms, they were about half of our symptoms, we further subdivided those into nine subsections.

Hannah Davis:
And of those subsections we actually found that sensory motor symptoms were the most common overall and that's interesting because we don't see a lot of sensory motor research in long Covid research. And this was of course, followed very closely by cognitive functioning. The top symptoms at any point were fatigue, post-exertional malaise, which is different from fatigue. This is a feeling of either flu-like symptoms or a recurrence of symptoms after exertion, either physical or cognitive. Shortness of breath of course, concentration issues, tight chest, muscle aches, insomnia, heart palpitations, which we now know are likely POTS. And interestingly, the top symptoms that persisted at month six, the top three were the same.

Hannah Davis:
So fatigue, post-exertional malaise and brain fog, as well as sensory motor symptoms, headache, memory, et cetera. And we really focused a lot on cognitive dysfunction and memory because we know how debilitating that symptom is for long haulers. And 86% of people with brain fog found that it impacted their ability to do work, to make serious decisions, to communicate thoughts, to converse with others, even to drive. And to me, one of the biggest findings from our paper was that the cognitive dysfunction in memory was the same in 18 to 29-year-olds as in people over 60. And so, for a while in the beginning of the pandemic, people were talking about the memory loss but said, "Oh, this is only happening to older people," it's absolutely not, it's happening equally across all age groups.

Hannah Davis:
So, one of the things that's valuable about our data set is being able to see which symptoms resolve or not over time. So, you can see on the middle left, the pulmonary and respiratory symptoms are actually more likely to decrease. You see a pretty obvious slope down where a lot of the systemic and neurological symptoms increase over time or remain consistent over time. And one thing that's interesting for me is that a couple of these symptoms, including bone ache and burning and ear and eye symptoms actually seemed to increase after the six-month point. And since our study's been published that has been validated by other studies that after the six months' point, there's this weird surge of eye and ear symptoms as well.

Hannah Davis:
And this is a graph of the onset of the average onset of these symptoms. So, you can see at the top, the acute symptoms stand out pretty obviously. Fever, dry off, shortness of breath, fatigue. But then the neurological symptoms actually have a delayed onset. So, a lot of people who get or basically two-thirds of people who have cognitive symptoms, have those symptoms happen after about a delay of a month or two months after their Covid onset. And that's also something that has been validated in other studies. And other studies have actually shown that having a delay in the cognitive impacts is associated with a younger age. So, older people are more likely to get the cognitive stuff at the acute phase, younger people are more likely to get cognitive symptoms after the fact.

Hannah Davis:
We found a lot of immunologic and allergic symptoms. One thing that was interesting to me is we found 20% of people found a change in sensitivity to medications they had been taking for a really long time. So in both directions, people needing to adjust their dose up and down. We found heightened reaction to old allergies, new allergies, new and unexpected anaphylaxis reactions. Weirdly, we found disappearing allergies, including severe ones like shellfish. And of course, this wasn’t very known at the time but it’s more known now. We found a lot of post-Covid reactivations of EBV, HHV-6, CMV, shingles, et cetera. We found vision loss, hearing loss and facial paralysis.

Hannah Davis:

We also found a lot of reproductive health symptoms, including post-menopausal bleeding and early menopause, abnormal periods, including abnormal clotting in a quarter of people who menstruate, sexual dysfunction, pain and testicles and decrease in genital size in cis men, likely related to endothelial dysfunction. Two-thirds had their work impacted by long Covid, 45% required a reduced work schedule and almost a quarter were not working at all. And this did not include people who took early retirement because of long Covid. So, one thing we did was because in the first wave in March, 2020, only one to 3% of people were able to have access to PCR tests and so we accepted people who didn’t have PCR or antibody positives but were symptomatic and we compared the two groups.

Hannah Davis:

And what we found was that the biggest difference between these cohorts was not in the symptoms. As you can see, the symptoms are the same, even across time course. But the graph on the left shows that the positive group got tested at a median of six days and the negative group got tested at a median of 43 days. And I think that’s important to communicate that when you hear negative Covid test, it usually means didn’t have access to a Covid test, not that they weren’t necessarily true negatives. The one area that was different was the first week of change in smell and taste and that’s likely because the policy for most of the first wave was that you could only get tested if you had an obvious Covid symptom and smell and taste was an obvious Covid symptom. So if you had that, you were more likely to test early enough to test positive.

Hannah Davis:

We looked a lot at medical stigma, this is some work we’re doing right now. We’re looking at actually, a lot of stigma and the impact on the mental health component. The majority of patients don’t have anxiety or depression but of those who do, it can be very serious. And we found that medical stigma which means that having a doctor respond as dismissive, harmful, apathetic or skeptical actually increased depression, anxiety and suicidal thoughts. And so, one of the things I want to bring up is some of the weird biases that we found in long Covid research. My own background is in machine learning and I did a lot on identifying biases in machine learning, data sets. And so, this has been very interesting to me in particular.

Hannah Davis:
So, I mentioned that only one to 3% of cases from the first wave were confirmed and that was disproportionately hospitalized patients. To this day, only 25% of Covid cases are confirmed, which is fascinating and a really difficult research problem because what do you do? How do you make control groups when 75% of Covid cases don't have confirmation of it? We see a lot of research, bad research that's including PCR and antibody negative symptomatic cases as controls. And so, when you're making research, we always suggest to include those who meet the WHO definition for probable and suspected cases in cohorts and don't include anyone who could meet the definition in the controls.

Hannah Davis:
People without lab-confirmed testing experienced an additional eight-week delay in care. So, 16 weeks overall versus eight and a half weeks for those with lab confirmation. They're less likely to have adequate rest, they're less likely to have time off, more likely to experience both lost income and to be unable to live alone at six weeks. 63% more likely to have pain symptoms and 69% more likely to have anxiety and mood symptoms, likely from the disbelief and lack of care. And non-hospitalized patient are 75% more likely to not have lab confirmation. There's also a lot of confusion around antibodies and there are still doctors out there who are trying to test for antibodies months after the fact to see if someone had a Covid.

Hannah Davis:
But 24 to 36% of Covid patients don't make antibodies at all and this is more likely in female and mild cases. In one study, 28% seroreverted by 60 days, this was more likely in patients that had a low viral load and tested PCR negative but then went on to seroconvert. 65% of patients with low antibody levels seroreverted and low antibody levels are more likely in women. There are huge gender differences in antibody creation. So, men are four times more likely to retain antibodies, 80% of people who lose antibodies are female. In one study, 36% of female patients lost antibodies between month three to six, compared to 8% of men. And women are also more likely to have waning antibodies post vaccination. And there's increasing evidence that women are more susceptible to reinfections.

Hannah Davis:
And to make this even more interesting, there's now a lot of evidence that low or no antibody response at all, and it is actually a feature of long Covid to the point where it can predict long Covid from the acute stage. So, the first two studies here basically look at the same thing. One looks at low acute IgG antibodies and one looks at low peak IgG antibodies. They both predict long Covid at six and seven months in both hospitalized and non-hospitalized patients interestingly. There's another study that showed that long Covid is negatively correlated with Covid-specific CD8 T-cells, RBD and S-specific total memory B cells. Another study that showed that viral persistence in the gut was associated with lower levels of and slower generation of antibodies.

Hannah Davis:
And then more recently, the big paper that came out in Cell showed that autoantibodies actually anti-correlate with protective antibodies. And we know now that long Covid patients have a lot of autoantibodies. And again, this was another piece that suggested that long Covid patients are likely to be more susceptible to breakthrough and reinfections. So, most people with long Covid were not hospitalized and that's hard to wrap your head around data-wise because if you have a severe case, you are more likely to get long Covid. But just because there are so many more mild cases out there, if long Covid happens after 10 to 30 of those cases, if you're looking at the whole collective of long Covid patients, most of those will have happened after a mild case.

Hannah Davis:

And I think it's also important to look at these groups differently because we get a lot of test results that are almost the opposite of severe hospitalized patients. And ferritin is one example where there's very high ferritin in severe patients, but very low ferritin in a lot of non-hospitalized patients. This also has an impact on the provider care, so this is looking at hospitalized versus non-hospitalized patients. As you can see, non-hospitalized patients were much more likely and 12% of them have not seen any physician. Most of them have only seen their primary care doctor where hospitalized patients have access to a lot of specialists more easily.

Hannah Davis:

And just some EHR biases, they're really interesting ones I think in the creation of this illness. From the longest time, the Covid was considered just a respiratory illness. So, those with neurological Covid, those with gastrointestinal Covid really couldn't get care for a long time. So, a lot of what's documented is disproportionately respiratory. A lot of long Covid symptoms exist but very few get written down and documented in EHR data. There's an overemphasis on anxiety and depression as a diagnosis, especially from the earlier waves when doctors didn't really understand what was going on because complex and uncoded conditions are usually not recorded. And when they don't recognize an illness, they disproportionately record mental health diagnoses like anxiety instead.

Hannah Davis:

Oh, and I would just add to that, a lot of symptoms that are very common to LC like post exertional malaise aren't recognized by doctors or asked about. So, some common long Covid diagnoses are of course, dysautonomia, myalgic encephalomyelitis, mast cell activation syndrome, connective tissue disorders, cervical spine issues, small-fiber neuropathy, neuralgias, more recently, we know that microclots are happening and becoming familiar with all those conditions helps recognize long Covid in EHR data as well. So to sum up, research needs a comprehensive selection of patients including non-hospitalized, non-respiratory, non-PCR, antibody positives patients. Many had mild acute cases, many never had low oxygen levels.

Hannah Davis:

When asking about questions on surveys, it's important to include neurological and cognitive and post exertional malaise questions and questions on relapses. And this is especially true when using machine learning because algorithms will be biased without a representative
symptom and patient data set. So, one thing I'm really excited about these days is that there's so much existing research both already about long Covid. The speed of the microclots research and the brain and hypometabolism and brain inflammation research has been pretty amazing. But I also want to just bring attention to existing research in the field of postviral research and ME/CFS already. There have been amazing findings in brain inflammation, neuroimmunology, metabolic profiling, mitochondrial fragmentation, et cetera.

Hannah Davis:
And if you're near any of these people who have been working in this field for decades, I would really recommend reaching out to them. Ron Davis at Stanford came up with the metabolic trap hypothesis. He, in my opinion, is the closest to not only finding a diagnostic test with his nanoneedle diagnostic project, but also is working on a trial for myalgia encephalomyelitis, which about half of long Covid patients are being diagnosed with. There's really interesting research around cerebral blood flow, hypoperfusion overlap with connective tissue disorders. Nancy Klimas at the Institute for Neuro-Immune Medicine is really interesting. She found that cytokines change over the first three years of onset from these conditions. And a lot of people right now are trying to use cytokines as biomarkers and I think her research shows that that might not necessarily be the case.

Hannah Davis:
Elevated blood lactate is another amazing finding. Dr. Prusty found that a small bit of HHV-6 RNA, which a lot of people are reactivating right now is able to stop mitochondria from joining together to participate in any viral defense. PolyBio Research, they just did an amazing overview of the long Covid possible pathophysiologies. Jarred Younger found elevated brain temperature and a new form of neuroimaging. Of course, I mentioned a bunch of times viral activations and their impacts. And again, this is one of the WHO's objectives for the long Covid global research roadmap. So, thank you so much for your time today and feel free to reach out to us if you have any questions.

Dr. Nedra Whitehead:
We're going to go through the presentations and do questions at the end. So, the next speaker is Dr. Mohandas.

Dr. Nedra Whitehead:
(silence).

Dr. Sindhu Mohandas:
Thank you Nedra, it's a pleasure to be here. I'll be talking about the clinical spectrum of the acute sequelae of SARS-CoV-2 infection in children today.

Dr. Sindhu Mohandas:
(silence).
Dr. Sindhu Mohandas:
So, when I think about sequelae of Covid-19 in children, the two broad categories that I think of, one is multisystem inflammatory syndrome in children, also called MIS-C or MIS-C. And the other is post-acute sequelae of Covid-19, PASC or long Covid. So, I'll touch upon briefly on the clinical spectrum of both of these conditions. The review of the multisystem inflammatory syndrome will be briefer since there's an upcoming session, which will concentrate specifically on MIS-C. So, in the spring of 2020, that was the first time the Pediatric Intensive Care Society received an email alert from the NHS England highlighting a small increase in the number of critically-ill children seen in their PCUs.

Dr. Sindhu Mohandas:
They found that these children had unusual symptomatology and who had overlapping features of toxic shock syndrome and atypical Kawasaki disease, with blood parameters of severe inflammation. Around the same time soon after, an outbreak of severe Kawasaki-like disease was reported at the Italian epicenter. Soon, it was put together that these patients have a temporal timing relationship to acute Covid infection. And this syndrome occurred a few weeks after exposure to Covid-19. And multiple initial names were proposed for this. The one that finally stuck is MIS-C and CDC published the definition for MIS-C by May.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
And since then, we have seen 7,459 patients as of March 1st this year in the United States, of which 63 deaths have occurred attributed to MIS-C. So, if you look at the map of the United States, you can see that cases have occurred from almost every state, more in some states than other. And if you see here, California is one of the states with the higher cases in excess of 400 cases. And here at Children's Hospital Los Angeles, we have seen nearly half of that, we've seen nearly 200 patients with MIS-C. The graph here shows the daily MIS-C cases and Covid-19 cases and you can clearly see the temporal relationship. Spikes in Covid-19, which is the gray line are followed a few weeks later, usually four to six weeks by spikes in patients presenting with MIS-C.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, when they looked at the demographics of these patients, most of the patients fell in the five to 11 year age group and majority were male, 60.49% patients were male. And the race and ethnic distribution showed that 58% of patients were in the Hispanic, Latino or the Black non-Hispanic group. A group also known to be more represented in acute Covid infections.
Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, the CDC case definition pretty much presence of fever for at least 24 hours, elevated inflammatory markers, multiple system involvement, at least two or more, without any alternative plausible cause. Also required is some evidence of recent or current SARS-CoV-2 infection. That's either respirology, PCR or even history of exposure to a person with SARS-CoV-2 in the family or direct contact. And the signs and symptoms of Kawasaki disease, so this picture shows the signs and symptoms of Kawasaki disease, which was how the first cases were picked up. This is not the only presentation of MIS-C but quite a number of patients have been seen with these symptoms.

Dr. Sindhu Mohandas:
So, these pictures highlight those presentations. So, [inaudible 00:26:52] inflammation, oral mucosal changes, cervical lymphadenopathy, rashes, changes in the extremities, all of these can be seen in patients with MIS-C. And if you see below this patient, the other reported findings include coronary aneurysms, which are also seen in patients with Kawasaki disease.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, the cardiac manifestations of patients with MIS-C are two main kinds. One is coronary artery aneurysm and the other is left ventricular dysfunctions. And since MIS-C was recognized as a clinical entity, several researchers have looked at comparisons between Covid-19-related MIS-C and Kawasaki disease. This paper summarizes the number of patients, this is the one on top, the JAMA article, is a multi-center study, which found an incidence of 13.4% of four coronary aneurysms and 34% of these patients had LV dysfunction. The paper at the bottom, The Journal of Pediatrics is data from our institution. We have found a much higher rate of coronary aneurysms. 43% of our patients had coronary aneurysms and 39% had LV dysfunction. It's not really clear why we have a much higher coronary aneurysm rate but it could be related to the ethnic distribution of our patients, which is largely Hispanic.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, it's clear that MIS-C has overlapping presentation with other diseases seen in children, including Kawasaki disease and toxic shock syndrome. And again, researchers have tried to see if there are differentiating features which can help us diagnose MIS-C in a clinical presentation. So, some of the things that have been found include that MIS-C tends to be seen
in older age group rather than Kawasaki disease and they also are more likely to have gastrointestinal symptoms.

Dr. Sindhu Mohandas:
And when looking at the labs, they're more likely to have lymphopenia, thrombocytopenia compared to leukocytosis and thrombocytosis in patients with Kawasaki disease. Again, multiple researchers have looked at these differences to be able to come up with specific diagnostic criteria. At our institution, the table here, we also found that patients with MIS-C were older, were more likely to have GI symptoms and also we're more likely to need intensive care and with reactive infusions.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, at the time when the MIS-C cases were at the highest number, there were several patients, children evaluated for MIS-C who eventually went on not to be diagnosed with MIS-C. So, we were interested to see what kind of diagnosis these patients have. And if you look at the alternative diagnosis, almost 80% of the alternative diagnosis were infections, both bacterial and viral infections. And within the bacterial infections, UTI and pneumonia were the more common bacterial infections that we saw. So clearly, there is a need to be able to differentiate MIS-C from other childhood febrile illnesses as well as Kawasaki disease.

Dr. Sindhu Mohandas:
And for a more objective approach to this, there is a machine learning algorithm created by Dr. Burns and the CHARMS Study Group, which attempts to objectively identify patients with MIS-C. So, I have to say that this study is in pre-print and has not been peer reviewed. But inputting certain data, which is clinical criteria and easily available labs, leads to an output of the likelihood of the child having MIS-C, Kawasaki disease or other febrile illnesses. And I think this will be a great tool for clinicians in the future.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, since the spring of 2020, we have learned a lot about MIS-C but there's still a long way to go. It's clear that more Hispanic, Black and mixed race patients get severe Covid-19 infection as well as MIS-C so it's important to understand the risk factors. And large scale genetic profiling will help to identify genetic factors if they exist. Better understanding of mechanisms leading to cardiac dysfunction, further research on immune mechanisms develop more targeted treatments will all help in developing more specific treatments. And there is research ongoing to study the long-term implications.
Dr. Sindhu Mohandas: (silence).

Dr. Sindhu Mohandas: I'll now talk briefly about the clinical spectrum of post acute sequelae of Covid-19, also called PASC or long Covid.

Dr. Sindhu Mohandas: (silence).

Dr. Sindhu Mohandas: So, we are still learning about long Covid, particularly in pediatrics. And this is a heterogeneous condition without a super clear definition at this point. And there are multiple terminologies used for this as you see here. And of these, the most commonly used now is long Covid and the post-acute sequelae of SARS-CoV-2 infection or PASC in the research and scientific community.

Dr. Sindhu Mohandas: (silence).

Dr. Sindhu Mohandas: Multiple institutions have come out with a suggested definition and initial guidance on long Covid nationally and internationally. And the most accepted definition seems to be, this is the definition by the CDC, new, recurring or ongoing symptoms and clinical findings four or more weeks after infection. Just as Hannah mentioned, it's important to remember that this can occur even after mild or asymptomatic infections. And as you've seen before, this is an area of active investigation in medicine.

Dr. Sindhu Mohandas: (silence).

Dr. Sindhu Mohandas: What I'll do now is go through some of the studies that have been done in children specifically. So, this is a systematic review not specifically focusing on children but I included this to see this map shows that where the studies have been done. So, really patchily all over the world and this looked at 39 studies across 12 countries. And they did use that this long Covid effects, both previously hospitalized and non-hospitalized people and the primary symptoms include fatigue, weakness, general malaise, breathlessness and concentration impairment. They also found a wide diverse area of secondary symptoms.

Dr. Sindhu Mohandas: (silence).
Dr. Sindhu Mohandas:
This is the number of symptomatology that they found in the patients and as you can see, this is an extensive list. What they've done here is given the dots here, the larger the dots, the more frequent these symptoms were. And if you'll see here in both the hospitalized and the non-hospitalized patients, the biggest dot is for systemic symptoms, which includes fatigue and weakness and psychological and social symptoms, which is anxiety, depression and sleep disorders, closely followed by neurocognitive symptoms. This is pretty much a similar distribution also seen in the non-hospitalized patients.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
This is a study which looked at long Covid in children and adolescents and it was a cross-sectional survey done three months post-discharge. In Fars Province in Iran, they followed 58 children and adolescents and found a 44.8% prevalence of long Covid symptoms. The most common symptom they found was fatigue followed by shortness of breath. They also classified symptoms in terms of whether they were mild and tolerable, moderate or severe and incapacitating. So, as you can see in this table, most of the symptoms were in the mild and tolerable range, though we did have a couple of patients with severe and incapacitating symptoms.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
This is a study done in Rome, which was a cross-sectional survey of 129 children and adolescents who were assessed 30 days after infection. Again, they included both asymptomatic, symptomatic and hospitalized patients. And they had an average follow-up of 162.5 days. They found that 41% fully recovered and the rest of the patients had persistent symptoms and 22% or more had greater than three symptoms. The most frequent symptoms they found was insomnia, respiratory symptoms and nasal condition.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
And this is a study that came out of a long Covid clinic. So, this was a pediatric multidisciplinary clinic study out of Israel, where they followed 90 children who were referred to this multidisciplinary long Covid clinic. The mean age of the patients was 12 years and the median follow-up was around 112 days. And they found that of the patients that were referred 91% had mild disease and six had moderate and there was a small percentage of 2%, those who had
severe infections. They also broke the patients into two groups greater than 11 years and less than 11 years. And they found that the group of patients who were older than 11 years were more likely to have symptoms, including fatigue, dyspnea, myalgia, chest pain, [inaudible 00:36:52] and anosmia.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
Another study, this was in Moscow, prospective cohort study of hospitalized children that followed 518 children after post-hospitalization. So, this clearly focuses on the hospitalized patients. They had 2.7% of the patient had severe disease. They found a 25% rate of persistent symptoms and if you see this graph here, it shows that the most common symptom was fatigue, which decreased with time, but not to the extent that the other symptoms decreased. And those symptoms closely were followed by disturbances in taste and smell and sleep problems.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
Then we come to this very interesting study done in the UK. This was self-reported data collected through a mobile app. This was a prospective cohort study, which looked at UK school-aged children between five to 17 years testing positive for SARS-CoV-2. This study also included asymptomatic controls. And the data was analyzed within two age groups, younger children who were in the five to 11-year age group and older children who were in the 12 to 17-year age group. And as you can see here, this shows the distribution of symptoms in the two age groups and the older children are in blue and the younger in pink. So, the older children were more likely to have symptoms of headache, fatigue, sore throat and anosmia and the younger children were more likely to have fever and abdominal pain.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
They also looked at the duration of symptoms. Again, they found that older children had a longer duration of symptoms compared to the younger children. And this is a heat map, which shows the duration of symptoms in children and clearly the most impressive symptom which persisted the longest was fatigue. Headache tend to occur more early on in the illness and decreased as time passed. And another interesting symptom, anosmia, just as Hannah mentioned regarding the sensory symptoms, they can sometimes appear later on in the illness and not necessarily present early on. So, they found that prolonged illness in the Covid positive
patients was 4.4% for LC28, which is a 28 days and 1.8% at 56 days. Again, a very different prevalence rate than seen in the other studies.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
So, we've seen a brief smattering of studies across the globe and we've seen the different rates and the different symptomatology that's been found in it. This is a review which looked at all the pediatric studies and the studies with controls are on the top and the studies without control are at the bottom half. And if you look at this, it's just staggering, the big difference in the percentages that was found in all of these studies. So, if you see here, the number ranges from 5% all the way to 66% as prevalence of long Covid. And risk factors, couple of studies looked at risk factors and they saw that children, older age was consistently at risk to have long Covid. Muscle pain on admission and ICU admission had an increased rate of long Covid. Also history of allergic diseases tend to be an increased risk for long Covid.

Dr. Sindhu Mohandas:
(silence).

Dr. Sindhu Mohandas:
Management, there is no clear pharmacotherapy available at this point but relies on holistic support with a rehabilitation plan, including physical and occupational therapy, speech and language, neurological rehab and counseling on lifestyle components with an aim to gradual return to exercise. It's important to remember that there are patient groups with special considerations and racial and ethnic minority groups have a higher burden of Covid-19 and long Covid is also more likely in these patients. So, it is necessary that more resources may need to be allocated to these communities.

Dr. Sindhu Mohandas:
So there, we still have a long way to go to understand long Covid, particularly I would say in pediatrics. Features of long Covid are poorly characterized and as we have seen in the studies, there are major limitations, lack of clear case definition, variable follow-up times. Many studies with no confirmation of the SARS-CoV-2 infection and reliance on self or parent-reported symptoms. And quite a few studies have an absence of control group. We are hoping that through the RECOVER, we can address many of these limitations and give a clearer idea of the clinical spectrum, risk factors, incidents and prevalence of long Covid in children, which will ultimately be helpful in developing better treatment and management strategies.

Dr. Sindhu Mohandas:
(silence).
RECOVER Research Review (R3) Seminar:
Clinical Spectrum of PASC: Overview

March 22, 2022
12:00 – 1:30 PM EDT

Dr. Sindhu Mohandas:
Thank you, these are my references. Thank you.

Dr. Nedra Whitehead:
Thank you, Dr. Mohandas. So, we are now going to hear about adults from Dr. Igho Ofotokun and I mangled it again, my apologies.

Dr. Igho Ofotokun:
No problem. Thank you very much. My name is Igho Ofotokun, I am a professor of medicine at Emory University. I’m also the PI of the RECOVER hub here in Atlanta. So today, what I plan to do is to review with us what is known about the clinical spectrum of post-acute sequelae of SARS-CoV-2 or now known as PASC in the adult population. What I decided to do because there is so much out there already done in this study was to really focus on key papers that I’ve actually looked at this in depth. The first one is a systematic review that was published earlier in the course of the pandemic. It captured all the papers that were published between the beginning of 2020 and the end of 2020, early 2021. This paper was from the group at Columbia University.

Dr. Igho Ofotokun:
The second paper I really wanted to focus on, it’s from multiple institution but the senior author is from Cornell. This is both a systematic review and a meta-analysis of all the studies that were done up until the middle of 2021 on this topic of long Covid. And then the third one, which is a combination of two paper came from the group at Washington University in St. Louis using the VA large database. They published their first paper, I think in June of last year. And then, the second paper came out recently, I think last month, really focusing on a cardiovascular outcome. And the last paper which has been referred to by my other co-speaker was the Cell paper that came out about two weeks ago that really did a deep phenotyping of what are the predictors of a post-acute sequelae of Covid.

Dr. Igho Ofotokun:
One of the things we can appreciate from all of these studies, a lot of them was that, like has been already mentioned, there has been really no universal case definition of this phenomenon. It’s a lot of heterogeneity in the clinical studies, many of them are electronic data review, some of them were just retrospective chat review, DIY surveys, phone survey and a few of them were prospective study. But you can see that the design of the study are all over the place. And it’s therefore not surprising that these studies came up with a wide estimate of the burden of disease. So, the prevalent estimate very widely between five and 80% depending on which study you look at. May any of them cluster around 10 to 30%. And then, there’s no uniform name.

Dr. Igho Ofotokun:
So, if you look at NIH website, it is referred to as post-acute sequelae of Covid-19. CDC website, it is post Covid-19 condition. The WHO website is post Covid-19 and in the lay literature, it's long Covid, it's long hauler, long-term Covid or LTC-19. But one thing that everybody agrees on is that regardless of the prevalence, whether small or large, given the magnitude of this pandemic, close to half a billion people have been affected globally and 80 million people in the US, regardless of the prevalence, this is likely going to be a huge health issue. And we are already beginning to see that in our respective practices.

Dr. Igho Ofotokun:
(silence).

Dr. Igho Ofotokun:
So, let's look at some of the emerging consensus definition. The WHO definition of post-acute sequelae of Covid. So, they define this as a post Covid-19 condition. Of course, an individual with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of Covid-19 symptoms and that last for at least two months and cannot be explained by any alternative diagnosis. So, common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. So, symptoms may be new onset following initial recovery from the acute Covid-19 episode or persist from the initial illness. Symptom may also fluctuate or relapse over time. So, this is the WHO definition.

Dr. Igho Ofotokun:
And then the CDC website, which was mentioned earlier on is widely accepted. They define this condition as the continuation of Covid-19 symptoms or the development of new symptoms, four or more weeks after recovery from acute Covid-19 infection. So, the question is why four weeks? So, we do know that it's generally believed that most people with acute Covid infection would clear their viruses within the first two weeks of onset of symptoms. And overwhelming majority definitely by the fourth week of infection. So, acute Covid-19 usually lasts until four weeks from the onset of symptoms beyond which replication [inaudible 00:48:50] SARS-CoV-2 has now been isolated. So, the post-acute Covid-19 is defined as persistent of symptoms beyond this time point.

Dr. Igho Ofotokun:
(silence).

Dr. Igho Ofotokun:
So, how does this manifest in adult? So, this is the large systematic review and meta-analysis that was done earlier during the course of the pandemic. There were about 18,000 studies that were reviewed for this meta-analysis. And eventually, they narrowed it to 21 studies. They included only study with 100 or more participants. And this 21 study included about 48,000 people all adult aged 17 to 87. So, a couple of findings from this study. First of all, almost every system that they looked at was affected. So, they were looking for symptoms, for signs,
laboratory abnormalities. They were able to identify 55 different symptoms, signs and laboratory abnormality associated with this phenomenon.

Dr. Igho Ofotokun:
Second point. 80%, at least 80% of people that were included, so remember almost 50,000 people. 80% have at least one symptom, 80% complained of something that they could identify by their definition was related to this post effect of Covid. And every organ is affected. And the most common symptom, the five top most symptoms are fatigue, which was reported by 58% of those included in this analysis, headache 44%, attention disorder in 27%, hair loss in 25% and dyspnea in 24%. So, this is a disease, a condition that affects almost every system. So, whatever complaint you're looking for, whatever abnormality you're looking for, you'll find it associated with this condition.

Dr. Igho Ofotokun:
(silence).

Dr. Igho Ofotokun:
So, this study I found, thought was really interesting. This was the group from St. Louis who took the VA database and they did what they described as high dimensional characterization of the symptoms of PASC. So in this database, this first of two studies that they published, this in June of last year, there were 73,000 cases of Covid-19 and then they had close to five million cases of control, essentially everybody that was in the VA system nationwide that did not have Covid was a control. So, what was interesting about this study was that first, they looked at incident diagnosis that is new diagnosis that occur after they have their acute episode, they look at incident medication used, they also look at laboratory abnormalities.

Dr. Igho Ofotokun:
And because of the size of the population, they were able to look at people who had mild infection that did not require hospitalization. Those who had moderate to severe that require hospitalization and those with severe infection that were in ICU. So, they look at two things, they had hazard ratio of developing symptoms of post-acute sequelae of Covid, they also look at assessing burden above and beyond what you expect compared to the control population. So, they noted that beyond the first 30 days of illness, people with Covid-19 exhibit a higher risk of death and then the use of health resources.

Dr. Igho Ofotokun:
And they were able to characterize the body, the excess body for a broad area of systematic manifestation, including respiratory conditions, neurologic conditions, mental health, metabolic disorder, cardiovascular disease, GI disorder, pulmonary embolism, malaise, fatigue and anemia. And the top thing that they actually did that was interesting was that they were able to show that your acute experience, whether you have a mild, moderate or severe Covid predict whether you would develop a post-acute sequelae of Covid-19. So, the less severe cases in green that is a non-hospitalized, hospitalized cases in orange and ICU cases in purple.
Dr. Igho Ofotokun:
Whether you're looking at the hazard ratio of developing long Covid or the excess burden, you find out that there are several magnitude of [inaudible 00:54:07] higher risk when you have moderate to severe disease compared to those with the mild infection. So, they repeated the same analysis but this time, they focused on cardiovascular outcome. This was published in February, about four weeks ago. So here, they had larger size, about 153,000 cases. And then, they had two sets of control, about 5.6 million historical control and then another 5.8 million current control. And so, what they did was similar to what they did in the previous study but this time focused on the heart. They look at both individuals that were hospitalized, those that were not hospitalized and those that were in the ICU.

Dr. Igho Ofotokun:
And then, they found again that, this is after 12 months, they found that beyond the first 30 days after infection, individuals with Covid-19 are at increased risk of incident cardiovascular disease, including cerebrovascular accident, dysrhythmia, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic diseases. There was more than a 50% increase of major event, cardiovascular event with Covid and then 63% increase in any risk, meaning risk of any event. So, major event about 55% increase in risk, any cardiac event at all about 63% increase in risk. Again, they were able to show that the risk is higher the more severe your disease is.

Dr. Igho Ofotokun:
So, people who are not hospitalized compared to those who were hospitalized and compared to those who were in the ICU, the risk of having post-acute sequelae of Covid dependent on what your experience was during the acute illness. So, the question is what is really driving this? That is a big question. Because if we can answer that question, then we can actually look for target for intervention. Is it that with the virus is persistent in sanctuary sites? People have told us that within two to four weeks, most people clear their virus. But we’re only looking at the respiratory tract, the nasopharynx, the saliva. We know from autopsy study that every organ in the body is affected by Covid. The spleen, the appendix, uterine lining, the testes, the thyroid, the esophagus, the adrenal gland, ovary, they’re all affected by this virus.

Dr. Igho Ofotokun:
So, this unpublished work from South Africa I think was published in [inaudible 00:57:03] and The New York Times. The people from South Africa look at the intestinal lining. They look at the proximal and the intestinal lining using immunohistochemistry staining. They were able to detect the presence of virus three months out of the acute infection. The question is that are these dead virus, are they replication competent virus? We do not know. Then, the second question is the issue of inflammation. We know of the acute inflammation during the cytokines during the acute inflammation. This poor response of the immune system, it's like a tornado of cytokine that sweeps through every organ in the body leading to the severe illness that we see in some individuals. Does that storm inflammation, immune activation? Does it completely resolve after the acute process?
Dr. Igho Ofotokun:

We know now by looking at some of these various organs in the body, look in hematologic system, the CNS system that for example, the platelet. During acute phase, you have activation of platelet in people. During the post-acute phase, you also see that the platelets are activated. They are big, they are clumpy and likely to cause a microtrauma within the various organs and tissue in the body. And if you look at the brain, you also see marked amount of activation, the microglial activation during the post-acute phase in some individuals. So, do all of these changes contribute to the development of this phenomenon? This is a question that is yet to be answered. So, the last study I just wanted to refer to is the Cell study that was published on the 3rd of March, this month, about 300 individuals were involved in this study.

Dr. Igho Ofotokun:

It was a deep phenotyping single cell, multi-omic, plasma, assay of various viruses within the body. And this gained a lot of attention in the lay press. There were four key things that these people came up with, things that happened during the acute phase of Covid that predict what happens post-acute. One of them was the peak of SARS-CoV-2 viremia during the acute infection. So, the higher the peak, individuals with high peak of virus, regardless of whether they have severe disease or mild disease, the peak of viremia is high during the acute infection. They are likely to develop a post-acute sequelae of Covid. The second thing they saw was the activation of viral infection, particularly Epstein-Barr virus, EBV.

Dr. Igho Ofotokun:

So, if people have activation of EBV, that also predicts whether they would develop acute sequelae. And then, comorbidities, particularly type-2 diabetes and then the development of autoantibodies, especially those that are related to lupus. All of these predict the development of post-acute sequelae of Covid. So, we're now beginning to come up with some form of biomarkers, which hopefully can be refined and be taken into clinical practice to be able to target those who are more susceptible, more at risk. So, when you take all of these together, all the existing data, like most studies they raise more questions than the answer. So, we still don't know the true prevalence or the incidence of this phenomenon. We don't know the cause of PASC disease and the trajectory of recovery.

Dr. Igho Ofotokun:

Some of the studies are beginning to touch on this but this is something we don't ... because we need a prospective study, we need to diagnose people at a time of the event and then follow them over a period of time to be able to discuss, map out the course of recovery or the progression of illness. How do the variants affect susceptibility and severity of PASC? These are questions that are yet to be answered. Does vaccine have a role in protection? We don't know. And what is the part of physiology? What is the [inaudible 01:01:58]? Is it related to viral persistence or is it related to ongoing inflammatory process? These are things we don't know yet. Finding solution to this, answer to this question will help us in looking for appropriate target for prevention and for treatment. So, we're hoping that with the RECOVER study, some of these
questions will be addressed. Thank you very much for your attention, I'd be happy to take your questions.

Dr. Nedra Whitehead:
Thank you very much, it’s really interesting, three really interesting talks. I have a few questions that have come in through the Q&A, but before I get to those, I'm going to ask Dr. Dreyer to speak, Dr. Dreyer?

Dr. Benard Dreyer:
Yes, I want to echo Nedra’s comment about these three great presentations and they basically covered such a large amount of ground that it's difficult to add very much. I would say a couple of things in summary. First of all, adults and children tend to have pretty similar symptoms in PASC. Of course, some of the adult patients also have some very serious symptoms like acute coronary artery disease, heart failure, thromboembolism that are not really seen in children with PASC. A number of people have commented in either direction on at PASC and symptomatology being much more likely after severe disease. But as I think Hannah Davis pointed out and some of the others as well, most of the people with PASC or long Covid are actually those with minor symptoms and not with severe disease. So, although severe disease is a very significant risk factor, most of the patients we’re going to be seeing with PASC are not going to be those with serious disease.

Hannah Davis:
I would make a note there that it’s not serious disease, that it's not pneumonia. A mild case is considered not having pneumonia, but I would definitely still consider long Covid pretty serious.

Dr. Benard Dreyer:
Yes. Okay. I meant a serious disease in the acute phase rather than in the long Covid phase. You're absolutely right.

Dr. Benard Dreyer:
(silence).

Dr. Benard Dreyer:
I think some of the questions that I would like to raise are primarily regarding children, one is that most of the studies that looked at children, looked at school-aged and as children and adolescents are not necessarily very many young children. Obviously, RECOVER is going to be trying to correct that but I wonder what we think we know about young children and PASC.

Dr. Benard Dreyer:
(silence).

Dr. Benard Dreyer:
I guess, I'm looking at Dr. Mohandas, specifically.

Dr. Sindhu Mohandas:
When you say young children, do you mean the infants?

Dr. Benard Dreyer:
I guess I mean, preschool-aged children, maybe infants but probably children under primary school-age.

Dr. Sindhu Mohandas:
Yeah. So, from the studies, we have seen that long Covid is more prevalent in the older children, adolescents. But to be honest, I don’t think that is completely true. It’s only because older children are more able to verbalize their symptomatology. And when many of these studies are asking parents for symptoms, there may be trouble with a younger child but the parents and the child may not be able to verbalize what the problem is. So, I think really more a targeted question as towards design specifically for this younger age group will help us figure out what the prevalence is.

Dr. Sindhu Mohandas:
So, I would say yes at this point what we know is that it's more common in older children, but I suspect we have just not figured it out in the younger children. So, I feel the younger children are just as much as at risk. And in our clinic, we have seen under one-year old coming in with prolonged long Covid symptoms. And their symptoms may be slightly different, like we saw fever, GI symptoms, and it's probably because the other cognitive symptoms are not recognized until they develop physical symptoms, which parents and doctors can then recognize.

Dr. Benard Dreyer:
Yeah, absolutely and well said. I think another issue for us to study in the future in children is that of course, children are developing, their brains are developing and their abilities are developing. And so, insults may impact them in different ways as they get older. So, that's another goal, I think of the RECOVER study is to be able to look at child development and their academic performance and try to understand the trajectory of long Covid symptoms as well there. Finally, I think you all mentioned or touched on the fact that the prevalence rates were vastly different from different studies.

Dr. Benard Dreyer:
And obviously, part of the problem is that there is lack of tight definitions. People who were entered into the studies at different times, et cetera. But it still seems to me that there is such a large variety of prevalence rates in the studies. But I'm just curious in addition to the obvious study design issues, if you have any thoughts regarding why the prevalence rates should be so variable.
Hannah Davis:
For me, I think that on the low end you really only see numbers below 10, where two things are happening. I mean, one of them was based on an app where basically, anyone who stopped using the app was counted as recovered, which we know that that's a user interface issue. Any symptom questionnaire that doesn't ask about the most common symptoms is going to look very low so we see a lot that don't ask about cognitive dysfunction, post exertional malaise, sensory motor symptoms. And then crucially, I put it in the chat but the biggest issue we keep seeing over and over is that people will exclude Covid symptomatic infected people from inclusion and studies because they don't have antibodies anymore. And it just speaks to this huge issue and huge lack of understanding of a really key concept in this pandemic, which is that not everyone make antibodies.

Hannah Davis:
And if you have mild case, you are way less likely to make antibodies and way more likely to lose your antibodies. And that's particularly true in children, which is why I think we see prevalence all over the place so much more wildly in children. And then at the high end, I think the reason you mostly see numbers over 30 or over 40 is when you have a very disproportionately hospitalized cohort. If none of those things are true, then the numbers almost always fall between 10 and 30%, which I think is a solid range. We know that after EBV 11% of people have myalgic encephalomyelitis and postviral symptoms. After the last SARS, it was 27%. So, that range feels very solid to be working with, I think but really we need more understanding and communication of the antibody issue.

Dr. Benard Dreyer:
Thank you very much, Hannah.

Dr. Sindhu Mohandas:
I had a comment on that as well.

Dr. Benard Dreyer:
Yes.

Dr. Sindhu Mohandas:
So, there are few ways to think about this. One is the differing prevalence rates, are they really just related to the study design and the questions we are asking? Because the questions that are asked then determine what the results you get. But the other question is, are there really differences across the world? Are there genetic susceptibility, are there regional and environmental triggers, which then dictate this difference in the prevalence rates? So, I think it's not an easy question to answer and I think we need a lot more research before we could say that more definitively.

Dr. Igho Ofotokun:
Absolutely. And I think the last point I just wanted to make is that as we understand this concept more, as we now have more consensus definition of what PASC is, as those consensus are being built into the more studies of PASC, that we're seeing that the variation of the more recent studies is not as much as the ones that were done earlier. And so, it's a question of really all of us calling it the same thing, defining it the same way and looking for the same thing.

Dr. Benard Dreyer:
Thank you all and I'm going to stop my part of this to make sure that the Q&A can be robust. So, back to Nedra.

Dr. Nedra Whitehead:
Thank you very much. And we did have a few questions come in. I'm going to start with the ones that are most specific to the presentations. Take a few more general questions as we can and anything that we don't get answered today, we're going to try to post with the recording of the session in a Q&A document. Those are questions that are specific to the presentation. Again, more general questions about RECOVER will be added too, if they're not already there, the frequently asked question document that's on recovercovid.org. So, for Ms. Davis, someone posted that as a scientist and long Covid patient had been disappointed that there was little overlap between the grassroots or patient-led surveys and medical units probably because of HIPAA. And he wanted to know if there's a way that patients could contribute their lab data from formal medical tests to help the grassroots survey efforts.

Hannah Davis:
That's a great question and that's actually one thing that's really exciting about our collaboration with N3C who is doing a lot of the data standardization and analysis for RECOVER. One of the things we see a lot of is that patient-led surveys include more comprehensive questions about the experience, include more symptoms. And some of the N3C team actually took all of our symptoms and translated them into standardized medical terms so that they can be used on surveys and EHR data and things like that. In terms of labs, we informally collect labs mostly to generate hypotheses, but obviously for the same reasons, the question described, we can't just release labs to the public but we can say, "Oh, on an aggregate, these labs are coming back abnormal. These labs are not coming back abnormal." That's why we say things like, "The ferritin, which is coming back very low." And a lot of the standard blood test and standard MRIs are not coming back abnormal. But when you look at antiphospholipid syndrome or the EBV or the HHV-6 reactivations, we know that because of the patient-led data for the most part. So, we're definitely working on ways. We have a lot of collaborations with organizations that actually have their own labs and can take what our initial findings are and do something more valuable with it.

Dr. Nedra Whitehead:
Thank you very much. I had a question for Dr. Mohandas but you all addressed it during the discussion. So, for Dr. Ofotokun, please comment on the prevalence information for symptoms given the lack of controls in many studies. Is the prevalence attributable to Covid? That the prevalence attributable to Covid maybe much less for some of these symptoms.

Dr. Nedra Whitehead:
(silence).

Dr. Igho Ofotokun:
I think that is a great question and I think that is one of the issues we’re still grappling with. The issue of control, especially in this study, what is a true control? How do you even know that you have a true control in your study? So, that is a big issue that we’re grappling with. And how do we then really determine the true prevalence in relationship to the general population that is excess burdening of some of these conditions. Even in RECOVER, we are dealing with that because just the size of the pandemic, even if you have somebody today who doesn't have Covid and the same road as a negative control, what happens two weeks from now if they develop Covid? So, it’s a big issue and I think that is contributing to some of the challenges and the variability we see in the prevalence of these conditions.

Dr. Nedra Whitehead:
Thank you.

Hannah Davis:
I would add to that there are, at this point, a lot of good prevalence studies with control groups that end up putting the prevalence rate in the same 10 to 30%. There's a big meta-analysis that just came out of 81 studies, looking at fatigue and cognitive dysfunction with many of them having controls that still found 22% of adults and 9% of children have cognitive dysfunction and fatigue.

Dr. Nedra Whitehead:
And it’s a related question there. Is there any information on the percentage of people with Covid that have PASC that last longer than three months?

Hannah Davis:
I can answer that too, if that's okay?

Dr. Nedra Whitehead:
Go right ahead. It's a general question so go right ahead.

Hannah Davis:
I've been tracking anything that has a timeline of over three months. And actually in the last, I would say last nine months, we've seen a switch from defining long Covid at four weeks to defining it at either usually around 12 weeks because we know a lot of recovery happens in the first three months. Basically, if you're still sick at four weeks, the chance that you're still sick at 12 weeks is halved. But after three weeks, the prevalence doesn't decline that much at all. It's like a couple percentage points over the next year. And the percentage of people still sick at 12 weeks is again, still 10 to 30%.

Dr. Nedra Whitehead:
Yeah. Anyone else have anything to add on that question?

Dr. Sindhu Mohandas:
So, I may be a little biased because we see patients in the long Covid clinic and just the trouble with finding care or finding medical care. Most of the patients we see in our clinic are two to three months beyond. So, we see a skewed and most of our patients have had symptoms for three months or more.

Hannah Davis:
We also know that looking at the respiratory long Covid and the neurological long Covid, the respiratory long Covid is much more likely to recover than the neurological long Covid in part because there are more treatments for it.

Dr. Sindhu Mohandas:
I agree with that. A lot of our patients with persistent symptoms fall in the neurological category.

Dr. Igho Ofotokun:
The other thing to add to this is also that the [inaudible 01:19:37] that have fluctuating symptoms, they get better, they get worse, they get better, they get worse. So, there's a period of time when they feel like they're better and then the symptoms come back again. So, there’s a wider spectrum here of presentation and persistence.

Dr. Nedra Whitehead:
So, I got a couple of questions on this topic. I'm going to paraphrase them both but that is, have you seen any difference in whether or not there's either a qualitative or difference in the presentation of long Covid with people who got Covid before they were vaccinated or after? Or whether vaccination has any impact on long Covid symptoms, either onset or change if they already had long Covid.

Hannah Davis:
I just did a big review of this. There's apparently eight studies now looking at the impact of the risk of long Covid. So, in people who don't have long Covid but did get vaccinated and then got infected, it seems that vaccination pretty solidly reduces the risk of long Covid by 40 to 50%.
That's very good news. But the other side of that is that it means between 9.5 and 14% of breakthrough infections still lead to long Covid. And that's really bad news because it's basically the only tool that we're using to protect people right now. And then, on the symptoms side, there's really, really mixed reviews.

Hannah Davis:
There's a lot of stories that long Covid or that vaccine improved long Covid symptoms. An interesting study just came out recently that showed that some people are improved by it but it's a small 10%. Some people are worsened by it but that the people who are worsened by the vaccine actually have higher levels of antibodies. So again, that's another clue that this is a place where we should be looking to get a predictive sense of how people are going to respond to the vaccine.

Dr. Nedra Whitehead:
Thank you. Anyone else want to comment on that?

Dr. Sindhu Mohandas:
I agree with Hannah on this one. The response to vaccine is not uniform. I'm talking about patients who already have long Covid. We've seen a few patients at least, whose symptoms have improved. But this response is not uniform. There are patients whose symptoms may not improve after vaccination but it's definitely a thing to try if the long Covid symptoms resolve. For example, I had a patient who want a booster dose and his persistent neurological symptoms improved soon after, within the next two or three weeks, most of his symptoms resolve. So, it's something to think of and possibly try.

Dr. Igho Ofotokun:
The other thing to just add to this is that we now know just from looking at the studies that have been done, that the milder your experience, your acute Covid is, the less severe, the lower your risk of developing long Covid. It's also possible that given that vaccine reduces the severity of illness, that there might be some protection in that regard.

Dr. Igho Ofotokun:
(silence).

Dr. Nedra Whitehead:
Thank you all. I think I'm going to end the questions there. We have quite a few but they're pretty involved. We will try to address those in the Q&A. And the timeline approximately for having the recording and the Q&A on the website is about two weeks. I also got a couple questions about having transcripts. We will discuss that internally and see. There are requirements about how things are posted on the web that might have an impact on that. So, thank you very much. Catherine or Shane, do you have anything in closing?
Catherine:
No, just thank you all for being here. As you can see from this last slide, we have a number of interesting topics coming up. As Dr. Whitehead mentioned, some of the questions that came in today will be the focus of future webinars so stay tuned and we will, as she said, be posting this on recover.org soon. It'd be opportunity for you all to look at the slides in greater depth then so thank you.

Catherine:
(silence).

Dr. Igho Ofotokun:
Thank you.

Dr. Nedra Whitehead:
Thank you everyone and especially, again, thanks for our speakers and our discussant.

Dr. Nedra Whitehead:
(silence).