RECOVER Research Review (R3) Seminar:
Epidemiology of Post-Acute Sequelae of SARS-CoV-2 Infection: Current Understanding and Key Questions

March 1, 2022
12:00 – 1:30 PM EDT

Dr. Nedra Whitehead:

Thank you everyone for coming today to our seminar. I'm Nedra Whitehead and I'm the principal investigator for the RECOVER Administrative Coordinating Center and the moderator of today's webinar. So welcome to the first RECOVER research review or R3 webinar. The goal of this webinar series is to catalyze a shared understanding of the research within the RECOVER consortium. I want to start by thanking everyone who submitted questions early, please submit any questions that arise today using the Q&A feature in Zoom.

Dr. Nedra Whitehead:

After the presentation, we will answer as many questions about today's topic and presentations as possible. Some questions may also be answered within the Q&A. An FAQ document for the seminar will be posted with the recording of the seminar on recoverCOVID.org. It will include the answers for all the questions relevant to the seminar that were submitted today. Questions about other side scientific topics will be addressed in future webinars and answers to the broader questions about RECOVER will be available in the FAQs at recoverCOVID.org. Today's speakers will discuss what's known about the epidemiology of PASC, the gaps in our knowledge, and how RECOVER will contribute to filling those gaps.

Dr. Nedra Whitehead:

Our presenters today are Dr. Sharon Saydah, Dr. Beth Unger, Dr. Steven Deeks, and Dr. Valerie Flaherman. Dr. Sharon Saydah is an epidemiologist and senior scientist at the US Centers for Disease Control and Prevention, Division of Viral Diseases, respiratory viruses branch. She received her PhD in epidemiology from Johns Hopkins Bloomberg School of Public Health, and joined CDC as an epidemiologist intelligence service officer in 2003. Prior to the COVID-19 pandemic, Dr. Saydah's Work focused on the surveillance of diabetes among youth and young adults and the prevention of diabetes and its complications. She is currently serving in the CDC COVID-19 response and is deputy team lead for the applied epidemiologic studies team in the respiratory viruses branch at CDC, which leads investigations and research on the natural history of SARS-CoV-2 infection, including prospective cohort studies focused on post-COVID conditions.

Dr. Nedra Whitehead:

Dr. Beth Unger received her PhD and MD from the University of Chicago and completed her residency and fellowship at... Excuse me, pathology at the University of Chicago and Pennsylvania State University Hershey Medical Center. She is currently chief of the Chronic Viral Diseases Branch in the US Centers for Disease Control and Prevention, and is responsible for guiding research in public health studies encompassing molecular pathology and epidemiology of human papillomavirus associated diseases and myalgic encephalitis/chronic fatigue syndrome. As part of her CDC tender, Dr. Unger has served as a consultant on ME/CFS to the FDA and US National Institutes of Health. She recently joined the CDC COVID-19 response as a co-lead of the post-COVID conditions team to leverage understanding of

ME/CFS to address post-COVID conditions and advance research and treatment for both conditions.

Dr. Nedra Whitehead:

Dr. Steven Deeks is a professor of medicine at the University of California, San Francisco. He's a recognized expert on the antiviral infections on inflammation and immune function and health. He is one of the principal investigators of the Delaney AIDS Research Enterprise, an NIH funded national collaboration aimed at developing therapeutic interventions to cure HIV infection. In April 2020 he leveraged his HIV research program to construct the longterm impact of infection with novel Coronavirus for lead cohort. And he's one of the principal investigators for the UCSF RECOVER adult cohort.

Dr. Nedra Whitehead:

Our final speaker is Dr. Valerie Flaherman. She is a professor of pediatrics in epidemiology and biostatistics at the Institute for Health Policy Studies at the University of California, San Francisco. Her primary research focus is preventative interventions in the newborn period and newborn care. She's the managing director of the Better Outcomes in Research for Newborns or BORN network. She's the co-principal investigator of the pregnancy and coronavirus registry or PRIORITY study, and a RECOVERY US UCSF pregnancy cohort.

Dr. Nedra Whitehead:

Our discussor today is Dr. Lorna Thorpe, who is an epidemiologist with the RECOVER Clinic and Science Core at New York University, and the CSC project co-lead for the RECOVER Electronic Health Records [inaudible 00:05:21]. Please welcome all of our speakers. In our first talk today, Dr. Saydah and Dr. Unger will provide a broad overview of the current understanding of PASC in this epidemiology. Dr. Deeks will then discuss REOCVER adult cohort and how it contributes to our knowledge of epidemiology PASC among adults. And, Patrick, I think you can go to the next slide. Dr. Flaherman will provide an overview of the epidemiology of PASC among children and other RECOVER pediatric cohort and its contributions to our knowledge of that. I will now turn it over to Dr. Saydah out and Dr. Unger.

Dr. Sharon Saydah:

Good afternoon. Thank you very much for inviting us to speak today. As mentioned, I'm joined to here by my colleague, Dr. Elizabeth Unger, and together we co-lead the Post-COVID Conditions Team and the epidemiologic task force for the CDC's COVID-19 response. Next slide. CDC is taking a public health approach to addressing post-COVID conditions. Our work is aligned around these three main goals.

Dr. Sharon Saydah:

The first is to define and assess post-COVID conditions and the risk factors and provide estimates of the prevalent incidents by demographic groups. And also describe the symptoms in new diagnoses and identify groups disproportionally impacted, and also describing the disability. The next is identifying successful interventions to help prevent and mitigate the impact of post-COVID condition. This includes the understanding of risk reduction associated with vaccination and developing and evaluating models of care that promote equity in access to and quality of healthcare for post-COVID conditions.

Dr. Sharon Saydah:

And finally, we're working to disseminate clinical guidance and other educational materials for healthcare providers, patients, and the general public to improve our understanding and reduce associated stigma and support recovery. We continue to establish and maintain partnerships to achieve all of these goals and are collaborating with other federal agencies and organizations to assure an effective response. Next slide.

Dr. Sharon Saydah:

To begin our discussion, we need to address the variety of terminology that's in use. Long COVID is a term used by many patients experiencing these problems. Similar terms are long hauler or long haul COVID. CDC uses post-COVID conditions, which is similar to the World Health Organization. NIH uses the term post-acute sequelae in SARS-CoV-2 infection or PASC. This variety of terms does reflect that we are still learning about the longer term consequences of SARS-CoV-2 infection. And while there are minor differences in what is meant by each of these terms, they are often used interchangeably. In any discussion of these conditions it's always best to start with the description of what is being covered. Next slide.

Dr. Sharon Saydah:

Post-COVID conditions refer to a wide range of physical and mental health consequences present for four or more weeks after SARS-CoV-2 infection. These conditions occur for patients with severe disease, and also for patients who had mild or asymptomatic acute infection. Post-COVID conditions include a range of symptoms and conditions following infection. And patients are medically complex with a variety of processes ongoing and occurring. We are proposing this general framework for describing these processes with the understanding that it is likely to change as we learn more and that these groups are not mutually exclusive.

Dr. Sharon Saydah:

On the left are conditions that occur as a result of many severe illnesses, hospitalization, or treatment, such as post-intensive care syndrome. On the right are processes that are more specific to infection with SARS-CoV-2. These include system-specific pathology and clinically significant symptoms with an unclear pathology. Multiorgan effects following acute SARS-CoV-2 include new or newly identified neurological conditions, kidney damage or failure, diabetes, cardiovascular damage, and skin condition. And symptoms with an unclear pathology include a range of problems that can last for months after being first infected with SARS-CoV-2, or it can even first appear weeks after the acute phase of infection has resolved. This unexplained group has many similar features to myalgic encephalitis/chronic fatigue syndrome, dysautonomia/POTS, and other post infectious syndromes. Next slide.

Dr. Sharon Saydah:

There are a number of symptoms... Sorry. Sorry, lost my train of thought there. There are many challenges in research and surveillance of these conditions. As noted in the previous slide, there's a wide range of symptoms and effects in the spectrum of severity. The wide variety of these conditions may be identified, and whether from worsening or underlying conditions or a direct effect. Studies vary in the symptoms and conditions that are considered and in the methods for evaluating them in the time after acute illness that is used for data collection. Studies to date also include different patient populations. Some focusing only on hospitalized patients and others on outpatient. Many of these studies do not include control groups making attribution to SARS-CoV-2 infection difficult and preventing an estimation [inaudible 00:12:06].

Dr. Sharon Saydah:

And more importantly, few studies include measures on severity and the impact of symptoms on quality of life for day to day activities for people. Next slide. The number of symptoms experienced can be quite extensive and involve multiple [inaudible 00:12:29]. The list showed here is from the CDC's website, but is certainly not exhaustive, as indicated by a recent publication by the patient-led research collaborative that monitored 203 symptoms. Dyspnea or increased respiratory effort, fatigue, post-exertional malaise, brain fog, cough, and chest pain are some of the most common symptoms reported by patients with post-COVID condition. In addition, anxiety, depression, post-traumatic stress disorder are all common.

Dr. Sharon Saydah:

Next slide. Given the widely different study designs used and patient populations included, there's a wide range in estimates for the prevalence of post-COVID conditions. Identified, easy and self-report are based on what's available in electronic medical records. Based on self-report using a mobile app, 13% of people have incident cases with COVID-19 followed prospectively in the UK, reported ongoing symptoms more than one month after COVID-19 and 2.5% reported ongoing symptoms three months more after COVID-19 illness.

Dr. Sharon Saydah:

Using electronic health data, even among adults who are not hospitalized, 7.7% had one or more of 10 common post-COVID conditions. Severity of acute COVID illness is also associated with the occurrence of at least one symptom at six months. Among the VA population, the burden of post-COVID condition increased from 44 per 1,000 non-hospitalized patients to 217 per 1,000 hospitalized patients and to over 360 per 1,000 ICU patients.

Dr. Sharon Saydah:

Next slide. The duration of post-COVID conditions can vary and is still unknown. Many patients appear to recover from the acute illness with 4 weeks. This is the reason that CDC considers illness persisting beyond four weeks as warranting initial clinical evaluation and supportive care. However, as highlighted in this figure from the UK Coronavirus Infection Survey, the proportion reporting ongoing symptoms continues to decrease from 4 to 12 weeks. Improvement then slows around 12 weeks after infection. This slowed recovery after the 12 week point is the reason that the WHO uses persistence beyond 12 weeks to define post-COVID condition. This curve is showed for men and women, and when stratified by sex, the pattern is similar, with a higher proportion of women reporting symptoms compared to the men at each time point. Next slide.

Dr. Sharon Saydah:

These next two slides present results from the study we recently published using the CoreNet data. CoreNet is a distributed research network with 42 participating healthcare systems that uses a common data model. Starting in April of 2020, 42 healthcare systems within the network began supporting rapid query twice monthly to allow the capture of recent data on patients with viral illnesses for testing for SARS-CoV-2.

Dr. Sharon Saydah:

In March of 2021, 40 sites responded to a query to assess the current symptoms and conditions in the 31 to 150 days after SARS-CoV-2 testing. We compared patients 20 years and older against less than 20 years at these healthcare systems from March to December of 2020, that had received medical care for any reason in the 31 to 150 days after they were tested. Children and adults with a positive SARS-CoV-2 test were more likely to receive a diagnosis for a new

condition or symptom in the five months after acute infection, compared to those who had received a negative test.

Dr. Sharon Saydah:

These figures present the unadjusted prevalence ratios of patients who tested positive compared to those testing negative. The data for the adult is shown in the top figure. And prevalence ratios are broken down by illness severity with non-hospitalized light blue, hospitalized in orange, and mechanically ventilated in gray. Fatigue, shortened of breath, heart rate abnormality, were the more common among those testing positive, especially with more severe illness. Data for children and young adults are shown in the bottom figure, stratified by non-hospitalized in gray or hospitalized in orange. Fatigue and shortness of breath were more common in children testing positive. Again, particularly among those who tested positive. Next slide.

Dr. Sharon Saydah:

We also observed several conditions more likely to be newly diagnosed among adults in the top figure and children in the bottom figure, testing positive compared to those testing negative. These included neural disorders in adults and type 2 diabetes in both children and adults. Similar to what we observed with the symptoms. New conditions were common among those more severe COVID-19. And this also illustrates the importance of having a control group.

Dr. Sharon Saydah:

Next slide. As mentioned earlier, post-COVID conditions may also include conditions newly diagnosed after SARS-CoV-2 infection, possibly due to direct effects of the virus unmasking or worsening of underlying conditions. In the fall and summer of 2021 we started hearing reports of increases in newly diagnosed diabetes among children and adolescences. One question posed during our investigation into these reports was whether this observed increase in cases was greater among children who had had COVID-19.

Dr. Sharon Saydah:

To investigate this we used a different electronic health data source to examine newly diagnosed conditions... newly diagnosed diabetes in children and adolescents. The IQVIA data source is a large commercial healthcare acclaims data system that was analyzed for this study. We compared children and adolescents to those without COVID-19 during the same period, time period. As well as a group with acute respiratory illness in a pre-pandemic period. We found that children and adolescents who had COVID-19 were 2.7 times more likely to have newly diagnosed diabetes in the months following infection compared to those without COVID-19, or those diagnosed with other respiratory infections before the pandemic. And there have been other observations made, especially in the VA population, in the adult population, related to newly diagnosing.

Dr. Sharon Saydah:

Next slide. Factors associated with the increased occurrence of post-COVID conditions are just now being identified. As noted earlier, severity of initial infection is associated with increased occurrence of persistence symptoms. And a higher proportion of females compared to males report post-COVID condition. Pre-existing medical conditions, also often a risk factor for severe COVID-19 are associated with an increased occurrence of post-COVID condition.

Dr. Sharon Saydah:

And age is also a factor. With adults more likely to experience these conditions compared to children, and older adults more likely to experience them than the younger adult. And finally, those unvaccinated persons who are affected with COVID have an increased occurrence of post-COVID conditions. The known drivers of increased susceptibility of severe COVID-19 is illustrated in this figure, will likely extend to a higher risk for post-COVID condition. Related to this is the fact that many of these groups also experience more challenges and difficulties in accessing care, and therefore health disparities associated with COVID-19 are likely to persist with post-COVID condition. Next slide.

Dr. Sharon Saydah:

One of these last factors, vaccination, is worth emphasizing. Vaccines are effective at preventing post-COVID condition by protecting against initial infection from SARS-CoV-2. In an Israel study, while post-COVID conditions do occur among those infected after vaccination, the frequency appears to be lower. In addition to the data shown on the slide, there's a new review by the UK Health Security agency that shows people who have had one or more doses of COVID-19 vaccine are less likely to develop long COVID than those who remained unvaccinated. I'm now going to turn it over to my colleague, Dr. Unger. Next slide.

Dr. Beth Unger:

Thank you, Sharon. So I'm going to shift a little bit to talk about the disability associated. We do have evidence that disabilities associated with post-COVID conditions. CDC conducted a study collecting data from a network of rehabilitation clinics in 36 states and the district of Columbia. Compared with patients referred for cancer rehabilitation, patients with post-COVID conditions had poor physical health in many measures.

Dr. Beth Unger:

In addition, patient and patient advocacy groups have brought attention to the profound disability associated with post-COVID conditions. Individuals report cognitive problems, post-exertion malaise, and fatigue that has persisted for extended periods of time. And that they've not been able to perform essential activities, such as work and home life. The reports from patients emphasize the importance of including patients and caregivers in related research. The next slide. Just as a reminder, under the American with Disabilities Act, long COVID is recognized as a physical or mental impairment that can substantially limit one or more major life activities. However, an individual assessment of whether long COVID does substantially limit these activities is required when determining disability.

Dr. Beth Unger:

The extent of associated disability is still being investigated. One study from China found that 88% of patients returned to their original work by 12 months, indicating that 12% did not. Further, this return to work excluded 62% of the COVID patients who were retired or not employed prior to infection. Given the size of the pandemic, even a 1% associated disability at one year will have a significant impact. Can I have the next slide? Patients with post-COVID conditions often present with a complex clinical picture that makes diagnosis challenging.

Dr. Beth Unger:

There is no single diagnostic test to identify patients with post-COVID conditions. In many cases, COVID-19 may not be documented with a positive SARS-CoV-2 test. Reasons include lack of access to testing, testing prior or after viral [inaudible 00:25:06] were detectable, or in early test platforms, a false negative result. They should not exclude the clinical diagnosis of

post-COVID conditions. Diagnosis relies on the clinical history and clinical evaluation to identify other conditions.

Dr. Beth Unger:

As we indicated, patients may report numerous symptoms. And the number and temporal fluctuation in intensity of symptoms reported may not fit recognizable clinical paradigms. Clinicians can have difficulty accepting patient reports. And this is particularly problematic when routine tests are normal. As a result, patients feel misunderstood and stigmatized by their care providers. In addition to date, no clinical trial or evidence-based management outcomes are available to guide clinicians.

Dr. Beth Unger:

Have the next slide. To support clinical care of the large number of patients with post-COVID conditions, CDC prepared interim guidance that was published in June of 2021. It was informed by the experience of healthcare providers caring for patients with post-COVID conditions, as well as by experience with similar conditions, such as post-treatment line and ME/CFS. We anticipate that the guidelines and information for healthcare providers will be updated as more information becomes available.

Dr. Beth Unger:

The guidance encouraged primary care providers to diagnose and manage these patients and emphasizes good medical practices in history, physical examination, and use of routine screening tests. Conservative management with supportive care is appropriate, particularly within the first three months. Listening and believing the patient is emphasized as many patients' symptoms are not explained by test abnormalities and these patients have been misunderstood. There has been an ICD-10 CM code for post-COVID conditions that became available in October of 2021.

Dr. Beth Unger:

The next slide. The subgroup of post-COVID conditions that are not explained by routine test abnormalities present unique challenges to clinical care and to research. They share features, particularly the course symptoms of fatigue, cognitive dysfunction, sleep disturbances, and pain, with a wide variety of post-acute syndromes as illustrated here.

Dr. Beth Unger:

Many of these post-acute syndromes have been recognized and described for years, and yet progress in identifying the underlying pathogenic processes have been stymied. Systematic study of the large number of post-COVID condition patients in comparison to these other conditions may begin the process of understanding how to intervene and treat these chronic syndromes. One additional comment about the similarities of these conditions is that they can be difficult to capture in electronic health records because of incomplete coding of symptoms and varying approaches to diagnosis and coding.

Dr. Beth Unger:

The next slide. In summary, post-COVID conditions are not uncommon and may occur among patients of all ages with COVID-19, regardless of acute illness severity. The duration and extent of impairment varies. While we presented our current understanding, additional work is clearly needed. Key studies that... Our CDC studies will continue to answer and explore are defining

the frequency, severity and duration of post-COVID conditions, identifying groups disproportionately impacted by these conditions, association of SARS-CoV-2 variants and vaccination with the incidents of post-COVID conditions, and developing models of care to assure equity and access.

Dr. Beth Unger:

Have next slide. CDC is involved in a multi-pronged approach to understand, characterize, and provide clinical for post-COVID conditions. This table highlights the key questions and the varied approaches that we're taking to address the questions, along with the status of these activities, where they're currently ongoing or planned.

Dr. Beth Unger:

The key questions are what are the characteristics of post-COVID conditions? What is the burden of post-COVID conditions in the population? What are the effectiveness of COVID-19 vaccines against post-COVID conditions? What management strategies are being used and how can they be improved? We're approaching these questions through a range of activities spanning prospective cohort studies, analysis of electronic health records, population surveys, medical chart reviews, dissemination of clinical guidance, implementation, research, outreach, informing partnerships. Next slide.

Dr. Beth Unger:

Finally, while we're still learning about post-COVID condition, there are several important messages. First is the importance of the S on post-COVID conditions. Post-COVID clinical outcomes are complex and not likely to be one simple entity. This makes case definitions impractical, simple ones at least, and presents challenges for standard surveillance methods. In addition, the clinical complexity precludes detailed and specific clinical guidance. Continued surveillance and epidemiologic studies characterizing the different phenotypes, risk factors, and biomarkers are needed for an effective response.

Dr. Beth Unger:

The follow-up times will be measured in years, rather than in weeks or months. Due to the long duration of illness, post-COVID conditions will remain a public health concern after the response and similar post-infectious syndromes can be expected in future pandemics. Lessons learned from the COVID-19 response about post-COVID conditions can help us prepare. An ongoing response to post-COVID conditions will require a heightened commitment by CDC and other government agencies of resources, personnel, and organizational support for surveillance, implementation, research, and education.

Dr. Beth Unger:

Nationally, increasing the clinical capacity to meet the needs of patients with chronic illness following COVID will be needed. And this needs to be done with a focus on assuring equity and access to care. Finally, it is clear that the patient advocacy community has concerns about how well the whole of the government is able to meet their needs.

Dr. Beth Unger:

Improved intra- and inter-agency collaboration is necessary to provide better integration of the ranges of services needed, including healthcare, rehabilitation, workplace and school accommodations, and disability insurance. Understanding and meeting the ongoing complex

needs of patients and their families for clinical care, workplace and educational accommodations, disability support, and rehabilitation will require co-ordinations of efforts and communication. And we thank you for the opportunity of starting that through this webinar. Thanks.

Dr. Nedra Whitehead:

Thank you, Dr. Saydah and Dr. Unger. We are now going to go to Dr. Deeks who will talk about the RECOVER adult cohort and how it will contribute to knowledge of the epidemiology of PASC.

Dr. Steven Deeks:

Thank you, Nedra. Hey, everybody. Can I get the next slide? So as Sharon and Beth just outlined, there's a massive amount of data that we've already developed as it pertains to long COVID or PASC. And there are papers being deposited daily on these pre-print servers. And I think we're going to actually see an acceleration of this over the next few months.

Dr. Steven Deeks:

So it's already a massive amount of work going on globally to try to figure this out. And the question is, well, why do we need RECOVERY then? And so what I want to do is to describe real briefly what RECOVERY is, and then go through all the questions being asked, and note what's been found, but also note what's not been found. And I'm going to argue that ultimately to get a definitive answer to what we're trying to do here, we need a massive prospective, well-curated, well-performed, well-resourced type of initiative of that RECOVER is. Next slide.

Dr. Steven Deeks:

So here are the objectives for RECOVER. It's essentially to characterize the epidemiology of PASC and to begin to address some of the clinical biologic characteristics, and importantly to describe these very important phenotypes or subclinical phenotypes or distinct flavors of PASC, which I think is going to be really important before we can begin to do the mechanistic work. To describe its natural history over time, and also to begin to do some of the mechanistic and biologic work. Next slide. All right. So I'm not a card-carrying epidemiologist. Some of this terminology is new to me. I admire people who can build cohorts. My role is to actually use the cohorts and that's what I've done in the past.

Dr. Steven Deeks:

But RECOVER is an ambi-directional longitudinal meta-cohort study that's going to have these nest case-control studies. The design is in the figure here, and it's actually quite clever, I think. We're going to try to go out and identify people in the acute setting, the first 30 days of the infection, bring them in to RECOVER and then begin to follow them forward in time.

Dr. Steven Deeks:

And the idea here is that is based on the... This work is based on the assumption, reasonable, that a lot of the determinants of what happens in the future plays out in the first few weeks. But we're going to complement that with these existing cohorts, or people who've actually had COVID in the remote past. This will allow us to characterize what's happening in the first few waves, the individuals who were infected in 2020. And I do believe very strongly that what happened to them is quite distinct than what's happening now.

Dr. Steven Deeks:

So we need the first generation, second generation of participants in these studies. And here we're going to identify in a non-biased manner if we can, individuals who basically are long past their acute infection and who are being followed forward in time. We're going to try to select for individuals who are already in existing cohorts, and I'll talk about ours in San Francisco, called the link cohort, allowing us to leverage some of the existing specimens and so forth.

Dr. Steven Deeks:

Sample size is very big. It's about 17,000 people, including the uninfected controls. We are going to purposely try to recruit people who were not hospitalized in the past. There's a very important pregnancy cohort nested within this of a couple thousand individuals, a little less of individuals who acquired COVID during a pregnancy. And we're going to be studying both the mom and the kids going forward.

Dr. Steven Deeks:

And we're going to really... I mean, from day one in RECOVER, there's been this massive amount of energy and initiative, while making sure that we go out of our way to recruit a population that reflects what's actually happening in the United States. And this includes having the correct diversity in terms of the ethnic and racial backgrounds, but also to make sure that we actually obtain people who are living in urban settings and in rural areas. And getting people in the very rural parts of the United States into these types of intensive studies is a very big challenge, but the resources are hopefully going to be made available to make that happen. Next slide.

Dr. Steven Deeks:

This is just a list. So one of the great strengths of RECOVER that's going to make this an incredibly valuable database, isn't so much all the biology that's being done, because anybody could do the biologic stuff. It's the clinical phenotyping. This is what we desperately need. These individuals, we have no idea what's going on with them. We know they don't feel well, we know all the various symptoms. But beyond that, we don't really have any good diagnostic tests, any good biomarkers. And we haven't quite yet figured out how to break people into these various different bins. So we're doing in everybody, detailed questionnaires and a whole series of more basic types of assessments.

Dr. Steven Deeks:

And then about 30% of these individuals, based on whether or not they have certain symptoms or they're going to be a comparator individual, will get a bit more intensive studies as listed here. And about 20% of the cohort, again, based on symptoms so forth, will actually go to tier three, in which there's going to be implementation of much more intensive, much more expensive, and much more riskier types of interventions. So everybody's going to get the basic stuff and a subset of people with symptoms or without symptoms, are you going to get more detailed clinical phenotyping with these measurements and others. Next slide.

Dr. Steven Deeks:

All right. So I'll go real quickly through the various different objectives about what we know, what we don't know, and what we hope to learn. Next slide. And I'll start with this paper, which was a lovely paper. There's been a lot of great work that's come out of the VA. It's got a lot of attention, it's relatively recent.

Dr. Steven Deeks:

And this was an electronic healthcare record system study in which they went back retrospectively, identified about 150,000 people who had COVID and over 5 million people who did not. And they identified that across these two groups, the risk of a whole long line of cardiovascular outcomes was actually much higher, twofold higher, plus or minus, in people who had COVID or who did not. And there was a fair amount of media attention. A lot of stuff on Twitter, a lot of people saying this is definitive, that this basically means that this is a real issue. But when you dig down deeper there are limitations.

Dr. Steven Deeks:

Number one, most of the burden of disease that was in this study was in patients in the ICU and people who were hospitalized, not so much in people who were not hospitalized. They did not use a typical definition. They identified people as early as 30 days after their hospitalization or 30 days after the acute infection. And a lot of people are still recovering then, particularly those who were quite sick.

Dr. Steven Deeks:

So you can imagine people in the ICU, they could be out 30 days. So from their initial infection, I don't think that's necessarily passed. The population is primarily older white men. It's the VA, not generalizable. And importantly in all these EHRs... I'm a practicing clinician. I have patients come in, they tell me they have COVID, they feel a certain way. I go, "You've got long COVID," and I code very differently what they have than someone who else comes in with these vague symptoms.

Dr. Steven Deeks:

And I'll say that... And maybe I'm not going to be as aggressive as charting and so forth, or certainly not do those diagnostic tests that you might do. So there's a lot of bias, right? In terms of how clinicians are managing myocarditis, for example. You would not think in some vague symptoms that people are going to have myocarditis in the real world. But certainly with all the attention of this in the post-COVID type situation, it might get coded quite differently. And I also think that patients who actually are suffering from COVID are more likely to report long COVID type symptoms. Everybody's heard about this. And so this is actually a major... So I think the most significant source of bias in the current generations of EHR studies and they will be going forward perhaps more so.

Dr. Steven Deeks:

Next slide. Another big question is who will we study? And again, as I mentioned, RECOVER's making a huge amount of investment to make sure that we actually study everybody who's at risk, everybody who might actually acquire COVID, to do it in equitable manner. And there was a very nice paper in Nature Medicine that's shown here. That really details if we rely on our current standards of clinical research, EHRs, which are not necessarily able to characterize what's happening all across the country. [inaudible 00:41:08].

Dr. Steven Deeks:

Most of the studies require people to have a positive PCR, access to testing, not fair, not equitably distributed, certainly not that common back in the first generation, which I think is an important issue. I do believe over time, we're going to learn that having access to vaccines,

having the ability to take a vaccine, being in an environment in which vaccines are encouraged. All that will have a huge impact on who gets PASC and what happens longterm.

Dr. Steven Deeks:

Having access to antivirals, having access to monoclonals is certainly, I think, going to actually affect the amount of virus early on, which could affect longterm. And then, of course, even in the types of prospective studies that we do, in which we try to bring people in and then really dig down deep and try to capture as much information in these patient oriented types of cohorts, one-on-one, even there there's issues. A heavy reliance of our group and other groups on digital technology and, of course, most of the stuff is being done [inaudible 00:42:06].

Dr. Steven Deeks:

So these are big issues with the current database. The data's affecting everything that RECOVER's going to try to address. Next slide. And what should we measure? So we are starting off rather agnostic. Perhaps a bit too aggressive. We're struggling, everyone's struggling to implement the full RECOVER protocol, because we're starting off saying we need to measure everything. I'm beginning to wonder if we can begin to use the existing data to whittle this down a bit. Our own group has been led by Matt Durstenfeld and Priscilla Hsue, working with Michael Peluso in San Francisco, have done a very detailed assessment of the cardiovascular version of PASC. And when they compare people with PASC or without PASC, most of the time what we've been measuring hasn't been all that different.

Dr. Steven Deeks:

Now our sample size is much, much smaller than we have with RECOVER. Not saying that we shouldn't do these. But I do think that there are some data emerging, that there are certain types of type diagnostics that are going to be very, very informative. Our group in particular, Matt had a late-breaker CROI last week showing really striking differences on cardiopulmonary exercise testing needs between those who had COVID, got PASC, versus not. And this is consistent with some of the emerging data from some of the other postviral infections. Anyway, so we're measuring everything in RECOVER. We may be measuring too much, perhaps this will get whittled down. I'm hoping if it does, it'll be driven by data like this. Next slide.

Dr. Steven Deeks:

How about the natural history? Next slide. So I think Sharon may have mentioned this. That this is actually where I think we are beginning to get some consensus, who gets long COVID or PASC? Clearly every single study has found that the acuity of your initial disease is hugely impactful. Now that could be because a lot of people who are really quite sick don't necessarily have PASC but have a post-ICU syndrome, which is biologically quite distinct, hard to tease that out.

Dr. Steven Deeks:

But clearly acuity of the initial disease is a really massive predictor of badness in the various EHRs. But you look at it a little bit deeper, clearly people who were not hospitalized and people who were minimally symptomatic, still are coming up with symptoms. And clearly in our cohort and everyone else that's seen this, the most striking cases are the people who were absolutely healthy, got COVID, weren't particularly sick, then may have recovered, may not, and now a year later are quite disabled. It happens.

Dr. Steven Deeks:

It clearly happens in people who have less symptomatic disease, but less so than those with more symptomatic disease. And the female sex is a very consistent predictor. And not too surprising considering that a lot of the autoimmune types of syndromes that we're used to studying that are quite similar to PASC in certain regards, are also much more common in people of female sex. Other predictors, including age, BMI, comorbidities are not as consistent in the literature, but I suspect they're going to prove be important. Next slide. The controls. Okay. There was a lot happening in the world in 2020, 2021 and not all of it was good. Most of it was bad for people's health. And so there was lots of stuff happening in people who had never had COVID. And a lot of that could look like some of the stuff that's associated with long COVID.

Dr. Steven Deeks:

And so these EHRs and other types of studies have tried their best to find relevant controls. That's very difficult to do retrospectively. But when it's been done, it generally has shown that there is certainly long COVID-like stuff of happening in the background. Depression, there's a bunch of symptoms, weight loss, that might be related to what was actually happening in the pandemic. But it was typically happening about rates about 50% lower than those who had COVID. But the more data are needed.

Dr. Steven Deeks:

Next slide. What happens over time? I think if you talk to clinicians who are dealing with this phenomenon or patients and patient groups and advocacy groups, a couple things are very consistent. One, the symptoms. Everyone experiences this differently. A lot of people can have no symptoms early and they can emerge late. Those who do have early symptoms can have symptoms that wax and wane. People have good days and bad days and so forth. And this applies to all the different symptoms. And so this actually is going to be something that's going to be very important to capture as we move forward, get more definitive studies, figure out why this might be. And is it true for each of the different distinct clinical phenotypes?

Dr. Steven Deeks:

Next slide. What happens over time? I think this was shown earlier as well. People do... Again, this is debated, but for the first three to four months, people do get better. There's no question about that. But around four months, there's a small subset of individuals who have profound disease and who might actually be much more disabled and so forth, who don't necessarily get better with time. And what proportion of it is, is unknown. Next slide. Preexisting comorbidities. People with autoimmune diseases. HIV, for example, in our cohorts are probably more likely to be going to develop long COVID. Time will tell. Next slide.

Dr. Steven Deeks:

What about the various different waves of this pandemic? I personally am hopeful that the amount of PASC in people who got Omicron will be a lot less than we've seen in the past, but time will tell. Certainly most of the disease that we've seen are from the first couple generations. That's in part because in San Francisco, most of the Delta was at least in vaccinated people.

Dr. Steven Deeks:

Next slide. Will antiviral therapies help? Will therapy during the acute setting work? We have no idea. I'm hopeful that it will. Next slide. And what's going to happen in people vaccinated and get COVID or people who get COVID and early vaccinated? The early data suggests that being vaccinated will be very, very helpful, but again, the data are a bit messy. Next slide. And then

finally, let me just highlight a different part of RECOVER that we're not talking about today, but just to let you know it's happening. Next slide.

Dr. Steven Deeks:

And that's a question of what are the biologic predictors? What are the factors that predict bad outcomes among people with COVID? And are these actually mechanistic? And can they be targeted with therapies? And there again, there are studies coming out left and right. And I know a lot are about to come. They're looking at inflammation, they're looking at the role of acute viral loads, they're looking at the role of virus persistence, EBV reactivation, autoantibodies. All the studies so far have told inconsistent stories. These studies have been somewhat limited in size. They've defined PASC differently and so forth. And so the data are a bit of a mess right now. And again, we're hoping that RECOVER will be more definitive going forward. Next slide. Nedra, I'm going to go ahead and just leave the conclusions here and send it back to you because I think we're a little bit behind time.

Dr. Nedra Whitehead:

Yes. Thank you. Thank you very much, Dr. Deeks. And we will move on to Dr. Flaherman, who's going to talk about pediatric PASC. Valerie?

Dr. Valerie Flaherman:

Great. Sorry. Thanks so much, everyone. It's a pleasure to be here today talking about RECOVER and our investigation of pediatric PASC. And I'm going to be talking today about RECOVER in the context of the work that Steve and [inaudible 00:50:53] have been discussing. So in overview, for pediatric PASC, there are 74 million US children. And of these, there have been 12.5 million reported positive cases of SARS-CoV-2. But of note, Seroprevalence study reported in November, showed that among 5 to 17 year olds, prevalence of positive serologic status was 38%. And, of course, that was before the recent Omicron strike. So this condition is affecting a large portion of US children.

Dr. Valerie Flaherman:

And this is important because while severity of illness is lower for children, prolonged illness and longterm consequences can occur for both children and young adults with persistent symptoms over time and end organ damage leading to cognitive, psychiatric, and neurodevelopment mental impairment, as well as other systems. And today I'm going to talk about the pediatric RECOVER study and our investigation of post acute SARS-CoV-2, looking at clinical characteristics and epidemiology, and then focusing on key populations that are at risk and will be examined in RECOVER. Including children with chronic illness and are health disparities. And I'm going to conclude by just some of the details of pediatric RECOVER and how it is similar and different from the adult work.

Dr. Valerie Flaherman:

Okay. Starting with pediatric PASC. Much of this has already been reviewed by the previous speakers, but just to remind everyone that although PASC is new, post-viral conditions in children are not uncommon. With long term symptoms occurring in children following viral infection. And, of note, these sometimes manifest in different ways than they would for adults. And I think the classic example of this is infection with respiratory syncytial virus, which usually has benign longterm consequences in older children and adults, but can cause profound wheezing in infants, sometimes leading to serious lung disease. Especially true for infants born prematurely. And other post-viral syndromes are also prevalent in children and some of them

have been touched on by my colleagues speaking previously. In light of this, it's important to remember that when we think about the [inaudible 00:53:28] definition of long COVID or post-COVID condition in children, as noted by the WHO, a separate definition of long COVID, or post-acute SARS-CoV-2, may be appropriate for children.

Dr. Valerie Flaherman:

And here's some of the first epidemiologic examinations of this condition in the world population. This study presents data from a population based cohort in Denmark that looked at post-acute SARS-CoV-2 in children 15 to 18 years old. And you can see that conditions like chest pain, headache, sore, throat, dizziness, trouble breathing, palpitations, and cough were all more common in children following SARS-CoV-2 infection than controls. And here's a similar cohort available now in pre-print looking in a German population study of children and adults. The children here are marked in blue with blue dots and blue bars. And you can see that following SARS-CoV-2 infection, children were more likely to have cardiac, ENT, gastrointestinal, psychiatric, musculoskeletal, neurological, pulmonary, and vascular and coagulation problems than matched controls.

Dr. Valerie Flaherman:

Metabolic derangements have also been noted in our young population. And I'll speak more about that in a bit. But this is some also very new data from a study of youth in the Swiss Army. So this is 18 to 30 year old, mostly males. And following SARS-CoV-2 infection, they had an increased BMI, decreased aerobic capacity, and higher levels of LDL and cholesterol noted.

Dr. Valerie Flaherman:

So these early changes following COVID infection may have longterm downstream effects for our future population health. RECOVER is going to be investigating these important questions, focusing on some key populations at risk. And I think this is work that is somewhat unique and specific to pediatrics. So I wanted to look at it. As the previous speakers have noted, although predictors of developing PASC are not certain. It is generally true that PASC tends to be more pronounced among those with more pronounced and more severe initial SARS-CoV-2 infection.

Dr. Valerie Flaherman:

And even for children, severity of SARS-CoV-2 infection seems to be correlated with comorbidities. The figure here from work by Woodruff, et al. shows that in the top panel children under age 2 were more likely to have severe COVID if they had chronic lung disease, neurologic disorders, cardiovascular disease, or prematurity, which importantly was defined here by these investigators as birth at gestational age less than 37 weeks. So that's a large portion of the US population. The panel below shows predictors for children 2 to 17 years. And here you can see that chronic diseases like diabetes, obesity, chronic lung disease, and developmental delay, really dominate.

Dr. Valerie Flaherman:

When we look at infants, which is my own area of interest, you can see that younger age during infancy predicts more severity of disease with children less than 100 days old, which is roughly 3 months old, being much more likely to require hospitalization. Another aspect of the study population and the impacted population to consider is the disparities, the health disparities, that we see in so many aspects of pediatric and, of course, public health as a whole. Which show up in the case of SARS-CoV-2, both in testing and in illness. This is recent work by Bailey, et al. showing that in the US, Hispanic, Asian and non-Hispanic black children were much less likely

to be tested for SARS-CoV-2 than non-Hispanic white children, and were much more likely to test positive.

Dr. Valerie Flaherman:

And that may translate into differences in morbidity where we can see that race and ethnicity, both in the US on the left and in the UK on the right, are impacting outcomes. Another key population that RECOVER considers is children with multisystem inflammatory syndrome with childhood, or MISC, which is a unique constellation of symptoms. Including fever, multisystem organ dysfunction function, and an increase in inflammatory biomarkers that can result in myocarditis, potentially leading to heart failure, starting about two to six weeks after SARS-CoV-2.

Dr. Valerie Flaherman:

Although MISC occurs in only a small fraction of children infected with SARS-CoV-2, it is a severe condition requiring hospitalization, often because these children become hypertensive. And striking neurologic impairment is possible in this setting where there is no definitive treatment. Good recovery is common, but these children are quite ill. Another key population that will be investigated by RECOVER is infants who are exposed congenitally to SARS-CoV-2, meaning their mothers had infection during pregnancy. As we know from other viruses, preterm birth, congenital anomaly, and metabolic disorders can occur following maternal viral infection. We saw this in the influenza pandemic, but also other viruses such as Zika and CMV may cause specific associated anomalies.

Dr. Valerie Flaherman:

One of our collaborators in the RECOVER pregnancy cohorts, Torri Metz, presented this data in JAMA this past month, looking at the increased risk of premature birth of mother with moderate or severe SARS-CoV-2. And the last population that's considered by pediatric RECOVER is children who develop myocarditis and pericarditis post-vaccine. You can see that in post-marketing surveillance from Italy in this recent pre-print, indeed relative incidents of myocarditis and pericarditis are greatly increased.

Dr. Valerie Flaherman:

So with these important needs, I think pediatric RECOVER is well designed to address some crucial research questions. Our objectives are to characterize the incidence and prevalence of post-acute SARS-CoV-2, as well as the spectrum of clinical symptoms, subclinical organ dysfunction, natural history in phenotypes that are seen, and to look at the biological mechanisms that are the underpinning of this and may provide clues toward therapy. Our cases are going to be those key groups we talked about. Children 0 to 25 years with current or recent SARS-CoV-2 infection, children who have or have had MISC, children with heart inflammation post-vaccination, and these congenitally exposed infants. And a key part of RECOVER is going to be our control population.

Dr. Valerie Flaherman:

And I think this was provided by the previous presenters. But is also of great importance for the pediatric population because the pandemic has had such a devastating impact on so many aspects of the health of our children. Decreased educational attainment, decreased activity levels and increased screen time leading to BMI, increased onset of type 2 diabetes has been discussed. Mental health issues for the pediatric population increased ER visits related to

depression, anxiety, and suicidal ideation. And these impacts may be profound even when they're not obvious.

Dr. Valerie Flaherman:

So this is some work that came out just a couple weeks ago, done by Shuffrey et al. in New York City, looking at six month old infants born during the pandemic and some screening results on an early neurodevelopmental screener called the Ages and Stages Questionnaire, third edition. In this figure you can see that in the bottom panel B, the pandemic cohort compares negatively to historic controls for gross motor, fine motor, and personal/social subscales.

Dr. Valerie Flaherman:

Suggesting that even at six months of age, the impact of the pandemic may be seen for both exposed and unexposed infants. And my own team's work with the Pregnancy and Coronavirus Registry Study, just reporting on the first several hundred infants in this study, although grossly these children appeared well. Looking at neurodevelopmental screening at, in our case, 12 months of age, showed that children scored lower than reference norms, or than basically a historic cohort, in gross motor, fine motor, problem solving and personal/social.

Dr. Valerie Flaherman:

So choosing those controls appropriately is going to be really important. And I think in particular it's important because measures of quality of life, physical health, and mental health may vary inversely with SARS-CoV-2 status, as was shown in that Danish cohort that I mentioned earlier. Where you can see here on the right in this table, that pediatric somatization as measured by the CSSI-24 score was actually higher in the control group than in the case group. And quality of life was lower in the control group than in the case group.

Dr. Valerie Flaherman:

Now, the causal mechanisms for these relationships are unclear, but really flag the importance of using appropriate controls in RECOVER. Similar to the adult cohort, RECOVER is planning a very diverse enrollment across the country. And we'll use a large initial cohort of 19,500 children with tiered assessments so that the entire cohort receives only a small number of assessments and the additional assessments are targeted.

Dr. Valerie Flaherman:

Tier one, which will be received by all children will include survey data, neurodevelopmental screening, a little bit of blood work and saliva testing. Tier two will be a little more extensive with anthropometry EKG, spirometry, neurodevelopmental assessment, and wearables. And tier three, which are outcomes that will be assessed only among less than 10% of the cohort, will be some of these more intensive assessments.

Dr. Valerie Flaherman:

Overall we hope that pediatric RECOVER will help us in the future understand the epidemiology of PASC in childhood and develop strategies for ameliorating its effects on the most vulnerable. We also hope that we can describe those mechanisms of PASC that are unique to pediatrics to inform the prevention for PASC. And also for future postviral syndromes, as others have mentioned, and to develop treatments for those impacted to date.

Dr. Valerie Flaherman:

In summary, although SARS-CoV-2 infection is less severe for children and young adults than for older adults, its incidence is high. And pediatric PASC does appear to have unique characteristics that may have a profound effect on our future population and its health. The RECOVER pediatric cohort is designed to examine the impact of PASC in a large, diverse population of children, newborn to 25 years of age, and look at cardiac, pulmonary endocrine, neuropsychiatric, and cognitive function to identify the longterm effects of SARS-CoV-2 on our youth. Thank you.

Dr. Nedra Whitehead:

Thank you very much, Valerie. Now, Dr. Lorna Thorpe will give a summary of what we've talked about today and put it in context and start some of the questions. Lorna?

Dr. Lorna Thorpe:

Thank you, Nedra. I want to start by thanking our presenters for their presentations. We heard from a diverse panel, including our federal colleagues who are involved in setting public health and clinical guidance nationally, as well as our clinician scientists from UCSF representing both the adults and the pediatric RECOVER sides. And I thought the presenters did a fabulous job of presenting what we know to date, including the latest science. So I think it was a real treat and thank you for that. All of the presenters noted the challenges associated with characterizing the epidemiology of PASC. And it's fair to say that despite all of the studies we've presented today and despite the hundreds of papers that have been published on the topic, we still have more questions than we have answers around the lasting health effects of COVID-19.

Dr. Lorna Thorpe:

So one of the points I wanted to start with as a discuss, is to take a step back and ask the question, why do we care so much about the epidemiology of PASC, especially when, as you heard in detail today, the building of this knowledge is slow and painstaking? Should it be a priority for the RECOVER initiative? Or should we be focusing more of our attention on clinical trials, biologic studies on biology of PASC, et cetera? The reality is that the RECOVER initiative and other studies are doing all of these and the interplay between these different scientific disciplines is important. My own stance is that there are three reasons why the epidemiology is so key.

Dr. Lorna Thorpe:

One is that knowing the epidemiology of a condition expedites solutions. We do need to more crisply characterize the spectrum of recovery from COVID-19 and the various COVID profiles that Dr. Geeks talked about. That helps us determine what's causing the variation between groups. Why did we see more long COVID among women, among older adults, et cetera? And we look for clues initially, risk factors subsequently, and ultimately the biologic causal pathways. And that expedites our ability to identify effective treatments and solutions.

Dr. Lorna Thorpe:

So knowing the epidemiology of a condition expedites solutions. Knowing the epidemiology of a condition also allows healthcare providers to provide better care for their patients. When a physician understands the spectrum of recovery, that helps them support those with longterm symptoms and give a realistic and data driven sense of what the possible trajectories are and outcomes. And I think patients often have a great sense of comfort in really understanding where they sit in the context of a larger profile. It can also help clarify to the physician and to patients what is not likely.

Dr. Lorna Thorpe:

So, for example, we talked about many symptoms that are associated with long COVID, but we there are some things that we're not seeing. For example, we are not seeing new onset respiratory symptoms several months after infection. That's helpful to know. It's less clear about new onset, other metabolic [inaudible 01:10:00] and other conditions. And our prediction models are helping us identify who is at higher risk of long COVID early during the acute infection. And that helps us identify who might be a good target for early intervention or for clinical trials.

Dr. Lorna Thorpe:

So knowing the epidemiology of a condition expedite solutions, it allows healthcare providers to provide better care. And the third main reason is practically from a policy perspective, knowing the epidemiology of a condition helps us prepare and respond better. And this is often what policy makers need to know. They need to understand many people are experiencing long COVID in order to really provide the public health and societal supports that are needed. Whether it's the impact on the healthcare system, workplace policies, anticipated absences, disability, healthcare insurance, guidance, et cetera.

Dr. Lorna Thorpe:

And so that's a lot of the work that our CDC colleagues are doing. What we heard today was really valuable. I think we can say with certainty that long COVID symptoms are more common in certain groups. Women, older adults, depending on the severity of the illness for both children and adults, individuals with comorbidities prior to COVID infection, including diabetes, some autoimmune conditions. These are profiles that are becoming increasingly clear.

Dr. Lorna Thorpe:

We see that the proportion of patients with respiratory symptoms declines over time. People largely begin to improve over time. We still have a lot of unanswered questions around the trajectories of cardiovascular, metabolic, neurologic conditions. And research from a number of studies, including a recent study from Israel that was presented, show that vaccination does help reduce the risk of long COVID on average. Now there are some people who report worsening long COVID or worsening symptoms after vaccination, but by and large, the data shows fewer people develop long COVID after vaccination.

Dr. Lorna Thorpe:

That's really important and helpful. There's a lot we don't understand about long COVID, but also about COVID itself. If you take a step back and remember, we don't know why 40% of people who are infected with COVID don't develop symptoms, whereas 1 in 200 died from illness. So we don't understand a lot about COVID and we don't understand a lot about long COVID. But the key question is whether or not there are multiple phenomena, not just phenomena in long COVID. So it may be that some people have immune system responses or subclinical antibodies that get triggered by COVID and that continues to exacerbate symptoms.

Dr. Lorna Thorpe:

Other people are having COVID pneumonia, and yet other people are having neurologic concentration symptoms and many people are having combinations of those. So we can't necessarily assume that different conditions are caused by the same processes and that's what's being worked out now. You've heard about the RECOVER cohorts, the adult cohort and the child pediatric cohort. And the clinical characterization that will be taking part to really

understand the clinical epidemiology of PASC. Those are mainstay thrusts of the RECOVER initiative.

Dr. Lorna Thorpe:

There are a few other aspects of the RECOVER initiative that are underway. One is an autopsy study, and the other is a network of electronic health record cohorts that are providing some fast out of the gate... And Dr. Deeks did a nice job really characterizing some of the challenges associated with big data research initiatives. But they're a very important part of this ecosystem in understanding as quickly as we can, what are the characteristics and what is the epidemiology of PASC? While we are building the systematic perspective data and biospecimen collection that you just heard about and tracking rigorously people over time, we are working with three cohorts. N3C, CoreNet, and PEDSnet that have networks of electronic health records across the country, similar to many of the studies that you've heard today. And some of them were from these networks themselves.

Dr. Lorna Thorpe:

And they're beginning to provide early evidence that is helpful for guiding the larger RECOVER initiative. Characterization of children who have a diagnosis of MIS-C by age, race, and sex across the country. Really profiling those individual with increased diabetes risk among patients of COVID positive patients, six months after their COVID infection versus COVID negative patients. Looking at long COVID trajectories, depending on when people were infected.

Dr. Lorna Thorpe:

So do we see the relative fraction of long COVID differ with different variants of the illness? And also tracking [inaudible 01:15:17] measures in past patients over time. And what's the trajectory of inflammatory markers among patients with PASC? These are some of the early data coming out of the EHR initiatives. Currently the EHR cohorts are accepting queries from stakeholders from across the RECOVER initiative. There is a query request form that can be submitted and reviewed to assess whether it can be answered by these cohorts.

Dr. Lorna Thorpe:

An early query came to the cohorts just a couple of weeks to go by NIH leadership, asking about the identification in therapeutics to understand what are the treatments being used by individuals with PASC, and using that information from those queries to help begin to plan for clinical trials, which are hopefully going to be begin being launched this summer.

Dr. Lorna Thorpe:

So increasingly I think what we are aiming to do is have these different thrusts of the RECOVER initiative, these large prospective cohorts that take a lot of time but are incredibly detailed and rigorous, combined with fast strike EHR studies, combined with clinical trials, as we identify candidate therapeutics to try and build an orchestra of studies to help us understand PASC, working with scientists around the country.

Dr. Lorna Thorpe:

And so maybe I'll leave you with one final thought. And that is that science moves fastest when the knowledge exchange between these different scientific fields is optimized. And so perhaps to jumpstart the Q&A, if I could ask a question back to our presenters. And just say, can you provide an example, either from your current COVID and PASC work or from your prior work,

where epidemiology has really provided that knowledge and exchange to move to trials and to move to improving clinical solutions? And I'll turn it back to our presenters.

Dr. Steven Deeks:

I'll take a shot of that, Lorna. So, again, prior to COVID, I was full-time HIV and we built over 20 years of infrastructure that did this, right? We had in our cohorts, we made these observations that that antiretroviral drugs may not have been 100% able to block all virus replication and that that was causing inflammation and longterm health problems. And so we did an experimental medicine study in which we intervened based on those observations. And we actually learned something new when we did, that we weren't aware of. And we went back to the cohorts to begin to tease all this stuff out.

Dr. Steven Deeks:

So science advances, as you mentioned, when all these different lines of investigation, the EHRs can inform the cohorts, the cohorts can inform experimental medicine, experimental medicine can inform phase two and phase three clinical trials. There's a whole process and it's very iterative. And that's hopefully what we'll have with RECOVER and long COVID. And we're going to build it. Again, in the HIV world, we do this very well, but it was billions of dollars in investment over 20, 30 years to have that infrastructure. We're trying to do that very quickly with RECOVER.

Dr. Lorna Thorpe:

Valerie, Any thoughts?

Dr. Valerie Flaherman:

Yeah. I mean, I think I agree with everything that was said. And also I think that RECOVER itself provides really a platform for future work. And that's how it's intended. It's not just what we're going to learn from our initial study design, but how it's going to evolve and what else can happen with it.

Dr. Valerie Flaherman:

So I know in our work with the Pregnancy and Coronavirus Registry, many of our participants have expressed interest in participating in other studies from that study where we can use that information that we collected back in 2020 or 2021 to answer questions now that we would not be able to get that detailed data retrospectively from someone who was newly enrolled. So I think that's really another strength of this plan.

Dr. Lorna Thorpe:

And I don't know, Dr. Saydah or Dr. Unger, if you have anything you want to add here? If you do, please step in. Otherwise, we'll turn it back to Nedra.

Dr. Beth Unger:

No, I think those were good examples and you did a very good job of tying it all together. Because the epidemiology can't go in alone and it teaches us separate lessons from what happens from the basic science. And the basic science is going to miss looking at the correct patients if the epidemiology isn't right.

Dr. Nedra Whitehead:

Thank you very much, Lorna. That was very helpful in understanding the presentations. I'm going to prioritize questions that are about these specific presentations that go to the individual speakers since we don't have much time left. And then we're going to add the additional questions, as I said, to an FAQ that's available on the website. So the first question is for Dr. Saydah. And that is how do you define the severity of initial infection?

Dr. Beth Unger:

This is Beth. I'll go ahead and answer for Sharon. And usually we follow what the WHO has done, grading them based on the kinds of care that was required to get them through the severity infection. So hospitalization versus oxygen use, intubation, ICU. Those are the factors.

Dr. Nedra Whitehead:

Do you run into problems with access to care being different among different people? And so possibly the same kind of infection gets treated one way in one place and in one and another?

Dr. Beth Unger:

Yeah, that's always a possibility. Of course, with the most severe infections where people need intubation and ICU care, I think that people would end up there. But people that don't have good access to care may end up actually more likely to have severe disease because they weren't supported appropriately early on. But yes, it's a concern. But I think for the most part, this is a reasonable approach to looking at the severity.

Dr. Nedra Whitehead:

And the next question is also for our CDC speakers. It's how are long COVID cases being counted? And how will long COVID disease burden be estimated now that CDC has moved away from emphasis on case counts?

Dr. Beth Unger:

Well, the case counts of the acute cases is a very different problem from counting post-COVID conditions. And surveillance with post-COVID conditions is not straightforward, as I think we tried to emphasize in the presentation. And that's because they aren't easily coded or diagnosed and it requires a very multi-pronged approach to get an estimate. And so we are going to be continuing our studies and trying to do a combination of self-reported data along with deeper dive studies on cohorts that we're looking at. But it's not going to be a case counting kind of thing like we did with the diagnosis of COVID.

Dr. Nedra Whitehead:

Thank you. I'm going to ask an easy... What I think will be a fast, easy one here for Dr. Saydah. And then I have a few for Dr. Deeks. And that is whenever you talk about diabetes on the slide, is that diabetes insipidus or mellitus? And is it type 1 or type 2 if it's mellitus?

Dr. Beth Unger:

Right. So it's diabetes mellitus. And most of the studies have not differentiated type 1 and type 2, but there's evidence that both are occurring.

Dr. Nedra Whitehead:

Dr. Deek's question is people who self-identify as Asian American, Native American, Pacific Islander American Indian, or Native Alaskian, are only making up 4% of the adult cohort according to your slide. But they make at least 7% of the population. Can you discuss why that difference is there?

Dr. Steven Deeks:

I might ask Lorna to help. She may be closer to some of the decisions. But it's my understanding that these numbers were very carefully generated so they reflect the proportion of people who actually have been infected with SARS-CoV-2, and hence at risk for long COVID, which is different than the number of people. But I would've thought those subpopulations were more likely to become infected. But the goal was for this to reflect the population who have acquired COVID, not the American population. I don't know if Lorna wants to add to anything?

Dr. Lorna Thorpe:

That's correct, Steve.

Dr. Nedra Whitehead:

And I will add that it was based on the best information that was available at the time that the cohorts were being decided... The people that were making up the cohorts, were being decided on. Another question for Dr. Deeks and then I have one for Dr. Flaherman. And the other question for Dr. Deeks is you listed social determinants of health as data being collected in the adult cohort. Can you please elaborate on what this encompasses for this study and how it will inform [inaudible 01:26:09] research going forward?

Dr. Steven Deeks:

So yes, these assessments that are happening at each of these visits are very detailed to capture all the socioeconomic factors, education and income. It's actually become quite a burden on the participants, the degree to which... The amount of time it's taken to extract as much information as we can on that. And again, I'll maybe turn to Lorna. If she has anything to add to that?

Dr. Lorna Thorpe:

I do not.

Dr. Nedra Whitehead:

And the last question is for Dr. Flaherman, asking about whether any of the studies you discussed distinguished between the impact of the pandemic and the virus itself on mental health and neurocognitive outcomes.

Dr. Valerie Flaherman:

Yes. I think those are the questions that we're just starting to be able to answer. To understand the difference between participants with SARS-CoV-2 infection and without, we really need to see the different impact of the pandemic itself on the population. So the work that I showed today will be the foundation to build upon in RECOVER, where we'll be able to compare these two groups.

Dr. Nedra Whitehead:

Thank you. If we can put up the last slide now. It will show the upcoming topics for the webinar, for future webinars. And I typed this in the Q&A few times, but you'll see down here at the bottom, it says recoverCOVID.org. That's the website for the RECOVER initiative. And there's lots of information about the initiative there, including a detailed protocol for the adult cohort. And a summary of that protocol will be coming soon. And that is where the recording from today and the Q&A's will be posted. Thank you very much for everyone who came. We look forward to seeing you at future webinars.