**Speaker 1:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast*. I'm Lynn Yoffee, BioWorld’s publisher. Okay. Everyone who has COVID-19 news fatigue, please raise your hand. That would be everyone, right? BioWorld’s journalists are no exception. Even as we've cranked out almost 7,000 articles since the beginning of the pandemic, we're always looking ahead at what the next big impact will be and that's long COVID.

About half of all people who have had the virus will be affected by this complex syndrome that's still being defined. That's more than 100 million people globally, which is likely a low estimate. 19 symptoms related to the syndrome range from long-term fatigue to multi-organ failure so, this is about much more than just a respiratory illness. The impact to society could be enormous because we have no idea how long everyone will continue to experience the syndrome.

So we decided to analyse the research to better understand how the syndrome is even being identified and studied. We also took a deep dive into what kinds of treatments are in the pipeline. Today joining BioWorld’s Managing Editor, Michael Fitzhugh, to discuss these issues are Anette Breindl, our Senior Science Editor who reviewed all of the latest published research, and Lee Landenberger, our Staff Writer who dug into the pipeline of potential therapeutics to treat long COVID. They're going to discuss their findings which were just published in BioEorld. Over to you, Michael.

**Michael Fitzhugh:** Thanks, Lynn. So much about this pandemic has been eye-opening for me from the multinational emergence of agreement that we're in a public emergency in the first place, to the incredible pace at which scientists, policymakers, and everyday people just totally reoriented their waking hours to figure out what to do about it. With so much urgency and so much impact on our families and daily lives, the idea that we’d eventually begin to have the wherewithal to really start to come to grips with the long-term impacts of this global tragedy sometimes felt hard to imagine. That's really happening now.

Recently for our readers, but also for our own sakes we paused for a few moments to ask, do we really understand what long COVID is and how it's affecting people beyond those initial acute stages of the disease where so much of our attention has been focused? What does it mean for young people, especially those who too often in the industry are treated as an afterthought or only somewhat that are a later priority in the clinical sphere?

Anette, you've put together something of an answer for the staff and more importantly, our readers. Get us started. What did you learn?

**[00:03:30] Anette Breindl:** Thanks, Michael, for taking the time to talk to me. I'd say that there are several pieces of news that came out in the last few weeks that shed a little light on long COVID for both adults on the one hand and then children and young people on the other. For adults, the biggest news is probably on the cell biology side. There was a systems biology study published in *Cells* that identified four factors that increase the likelihood of developing long COVID.

A piece of good news is that you can see all of those factors quite early during acute infections and that there are ways to turn this into therapeutic strategies, probably. For example, high levels of SARS-CoV-2 virus in the blood but also reactivation of Epstein-Barr Virus, which is this usually harmless infection that 95% of us have without any symptoms, increase the risk of getting long COVID.

That would suggest that maybe aggressive antiviral treatment during the acute phase to bring those viral levels down could help prevent long COVID from being able to establish itself in the first place. Likewise, one risk factor is the presence of certain autoantibodies in the blood.

**Michael:** Remind me what autoantibodies are.

**Anette:** They are antibodies that bind to our own proteins and if they’re too many of them or they are the worst kind you get autoimmune disease. A lot of those actually have such antibodies and usually without any symptoms or a diagnosed autoimmune disease either. Maybe because the levels are too low, or for whatever reason, that is actually still very confusing.

Anyways, in this *Cell* paper, they found that the presence of autoantibodies to certain proteins that are important to the anti-viral immune response increase the risk of long COVID. Again that suggests that long COVID may be more likely to develop when the body is not that good at controlling acute COVID, and so aggressive treatment of acute COVID could reduce the risk of long COVID. That was the big recent news for adults.

For children, last week saw the publication of the most rigorous epidemiological study to date. The good news there was that they lowered the estimate of how many children and young people actually get long COVID. There have been wildly divergent estimates for that. The highest estimate so far has been 50%, 5-0. This new paper says that probably at the upper end it is 14%, 1-4. That's quite a bit less, it's still a big range, 1% to 14%, but that was good news.

**Michael:** I know when I read that in your story I breathed this sigh of relief as a parent of a couple of teenagers. When I read that 50% number, my eyeballs just freaking out a little bit, but took a breath. Thank you. [chuckles] Thank you, researchers.

**Anette:** I have a teenager too and I am very glad that her risk is lower than some people thought. What these wildly divergent numbers show us is that long COVID is literally still being defined on the research front. There was progress there too last week when a consortium put out a research definition of long COVID in children and young people.

**Michael:** With really complex conditions, sometimes there's a lot of divergence in thinking about what really comprises the condition, what symptoms should define that, why does it really matter to have a research definition?

**Anette:** A research definition is a way to standardise research so that you can compare different studies more easily. One of the issues was getting a handle on long COVID on the prevalence and other things about it is that different researchers do studies using different definitions, or use the data they have. Then if you want to pull together several studies in what's called a meta analysis to give you the numbers you need to be able to find, for example, rare symptoms, that's hard to do if the datasets are very different, because you're just tossing everything, things that may not go well together into one study.

A research definition helps people to think about, in the beginning, what they need to collect to really be able to not just show things in their study but perhaps be part of bigger meta analyses down the road. It's not a clinical definition in the sense that it should not be used to define who has access to medical services and the researchers were very clear on that.

The other important thing about this research definition is that like the long COVID definition for adults that was published by the World Health Organization last year, and that this is meant to complement, it was arrived at by consensus. A group of researchers but also service delivery folks and people with lived experience, which includes patients themselves and those who care for them, evaluated a number of statements about long COVID to see which were important enough to include and then that was decided by consensus.

Terence Stephenson is the chair of the Health Research Authority in Britain, he contrasted that it to what he called the GOBSAT method which is the Good Old Boys Sat Around the Table method. By including different stakeholders, you really get a richer idea of what is critical for the disease, not just from the point of view of medical personnel, but for the patients themselves who live with this every day.

**Michael:** I understand you've got a clip of Stephenson talking about that idea. Set us up where we'd like to hear.

**Anette:** This is Stephenson talking at a press conference last week where he presented this, both the prevalence study and the research definition and describing the GOBSAT method and how it differs from the Delphi method and how the Delphi method is superior.

**Stevenson:** Well in a sense it's the democratisation of decision making. When I was a young doctor there was a thing called GOBSAT. GOBSAT stood for, Good Old Boys Sat Around the Table - grey beards, usually white older men who would dominate proceedings and the views of one very light person might determine the outcome of that discussion. The Delphi process was developed initially by the RAND Corporation to try and remove that domineering influence to affect where every person involved has a single vote. My view counts for no more than anyone else.

**Michael:** Anette, that perspective brings us to another dimension to your story. You quoted a couple patient advocates who said that Long-COVID, "Has a strong claim to be the first illness created through patients finding one another on Twitter?"

**Anette:** Yes, that was an interesting, catchy thing that I found while I was doing the research for my story. That phrase came from Felicity Callard, and Elisa Perego, who are both researchers and themselves long COVID sufferers. The way that they described it in their paper is that early in 2020, the World Health Organization was really quite optimistic still, in its estimates.

They said that the median time from onset to clinical recovery was two weeks for mild cases and three to six weeks for moderate to severe cases. There were patients who were just not recovering along this timeline and they posted about their experiences on social media and really, from there, it got attention from the regular media and that is how it first came to the attention of the medical establishment and policymakers.

**Michael:** Very interesting and in-line with broader trends that we're seeing to give patients collectively a more active role in shaping the medical view of their illnesses.

**Anette:** Absolutely.

**Michael:** Was there anything that struck you about the definition?

**Anette:** On the one hand, it's somewhat alarming that many people seem to have multiple long COVID symptoms. The definitions only require one symptom but in the children and young people prevalence study, the cut off was three symptoms that they looked at. About half of the youngsters that had long COVID at all had five or more symptoms, so that's a lot of symptoms, right?

**Michael:** Yes.

**Anette:** On the other hand, and in a more optimistic vein, the definition of long COVID is pretty short term; symptoms after 12 weeks count as long COVID. Although people are now sounding the alarm, that after the acute crisis of COVID-19 we're going to have this longer crisis of what's called long COVID, or the post-acute sequelae of COVID. There's a bunch of names for it and that is definitely going to happen, but we still don't know how long that is going to be. That also means that there's hope that long COVID will not turn out to be a chronic condition for most people.

**Michael:** Hearing about the way that this emerged made me think a little bit about some of the definitions of the illness that arose around the first responders to 9/11 and veterans of the Gulf War, just this emergent understanding that comes onto the scene. It really was an interesting example to me. Do you think that there's precedent for the way that this definition has come into view, that it really says something about the way that we're going to recognize illness in the longer term?

**Anette:** I do think what Callard and Perego wrote about as really this being a definition or an illness that the patient's themselves noticed, and that they are more easily able to find each other via social media, that struck me as hopeful, in a sense, because I do think that in comparison to Gulf War illness, where I think people found themselves initially doubted and perhaps sometimes even belittled by the medical establishment, when groups can find each other sooner then, hopefully, help is on the way faster.

**Interviewer:** Yes, absolutely. With the definition really being so dynamic, and the way that's coming into focus, it's amazing to me that we actually have a huge number of drugs in development, trials underway to try to meet this challenge of long COVID, how does that even happen? Lee, tell us a little bit about that?

**Lee Landenberger:** Well, it's a worldwide race so there's a lot of competition and that's been looking at tests, clinical trials that are over and done with and they're looking at results and getting a much better idea of what's out there and what works or may not work but I think just the breadth of this list, this chart that we have in the

story, I find it fascinating. We found 41 studies that are either preparing to go on, most of them are prepping to go on out of this group, they still are recruiting for the most part. 41 studies around the world, there's studies being done in the US and Europe, of course, but also in other places: South America, Brazil in particular, Australia, New Zealand, and in Asia as well.

Out of these 41 studies that we're following of all these different drugs that they're trying in treating long COVID, we gathered the data from the BioWorld archives, and from Clarivate's database, Cortellis, and clinicaltrials.gov. The trials are being conducted around the world. There are some in South America and Australia as well as the United States and Europe. Some are on the road to completion and others haven't even begun recruiting. The symptoms that they're looking at are a wide range. Some of them are just brain fog, not being able to think clearly, what one research institute calls disturbed thinking. Then there's also headaches and poor sleep, and it goes all the way from there to organ failures.

**Michael:** Are the drugs that are being developed trying to hit the symptoms one by one, or are they trying to get at the multi-factorial nature of long COVID?

**Lee:** The primary endpoints for many of these studies include multiple symptoms. A lot of those symptoms are ones that fade away, as Annette mentioned, will fade away after a few months. The longer-term symptoms that may last out of it, we still don't know, that's what these tests are designed to measure.

**Michael:** Interesting. In terms of the way that people are approaching long COVID, are we talking mostly pills, IV treatments? Logistics I know has been just a big factor in COVID. In general, how are we getting treatments to people? How feasible is it to get them into a clinic for an IV infusion versus just giving them pills at the doctor's office and sending them home? Did you notice any trends in terms of delivery?

**Lee:** The only trend is that it's a wide range. There's no delivery system that's off the table. There are ones that are inhaled, there's intranasal, there's IVs, oral versions, and even rectal versions of the drugs that are being tested. These drugs, again, there's the antis, which are antivirals, and anti-inflammatories, antibiotics, antioxidants. There were also stem cells being tested, biologics, even statins, and remdesivir, it's here to stay. They're testing it a lot.

**Michael:** Interesting. I think that that diversity of delivery methods is maybe reflective of the diversity of locales in which trials are being conducted. You mentioned the global nature of that, and that's been something that's clearly come through in our coverage is just these trials and the research into all aspects of COVID, including long COVID, are really happening everywhere. It's like every nation's scientific Vanguard has brought their A-game to this. That's just amazed me from day one.

**Lee:** Yes, seemingly. It's not just the width of the geography that's interesting. Most of the studies that we're following in this BioWorld list are composed of adult participants. There are a lot fewer studies in teens than there are in adults, and then there's even fewer in children under the age of 11 than there are in teenagers.

**Michael:** Tell me about that age aspect of it. There are some of these studies that are looking at long COVID in those younger age groups?

**Lee:** There are some, but they're very few out of the 41. It's a small minority. Again, these are studies that are just getting underway.

**Michael:** I wonder if that research definition that Annette was talking about will help spark some of that research. Annette, do you think that having that definition in place is going to make trials more possible in younger people?

**Annette:** Possibly. Although what I'm thinking about is that perhaps the cell biology showing that a lot of the risk factors are present at the time of infection will spur trials for treating the acute infection with an eye to preventing long COVID, I could see that. The research definitions for now are more on an epidemiological level and certainly, they would make good standardized endpoints. That is also a possibility that that it'll show up in the drug discovery effort that way.

**Lee:** Anette, I have a question for you. I loved your story. I thought it really brought into focus a lot I had been wondering about. You wrote about acute COVID cases being replaced by long COVID cases. and that it'll be a drawn-out public health crisis. It becomes a crisis because why? There will be so many perhaps or how much money it takes to research into it and solve the problem? What makes this a crisis?

**Anette:** I think what will make it a crisis and people are most worried about low and middle-income countries, so anything that is chronic ends up being a strain on the healthcare system just for longer. In some ways we saw that with acute COVID because people were in the hospital for a long time when they had severe acute COVID even compared to something like the flu.

Then if you have 100 hospital beds, you have a bigger problem if the average stay in that hospital bed is 8 weeks than if it is 4 weeks. Likewise, if you suddenly have some number, whatever the number is, of chronically ill people more than you were preparing for, then your healthcare system, especially if it is already straining, has a problem. That's what that is really about.

**Lee:** Okay, thanks.

**Michael:** Well, it's certainly going to be interesting to see how that element and the other elements from trials and recognition of long COVID develops in the months and years to come. Annette, Lee, thank you so much for talking with me today. I'm going to pass it back to Lynn.

**Lynn:** Well, team, I think we better brace ourselves for the COVID news fatigue syndrome because it's going to continue, I think, for a long time and this is a really important topic and what is especially interesting to me is that it di start bubbling up on social media. I first started hearing from individual patients and patient groups who were really-- there's a lot of chatter about it that doctors and researchers weren't recognizing that, "Hey, the acute sickness is gone but I'm still sick, what is this?" So BioWorld will continue to cover this topic as long as need be.

Anette, Lee, Michael, we appreciate your work and I know we'll just keep tracking long COVID and the syndrome as we learn about it. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates. That's our show for today, if you need to track the development of drugs, turn to bioworld.com. Follow us on Twitter or email us at newsdesk@viralworld.com. Also, if you are enjoying the podcast, don't forget to subscribe. Thanks for joining us.

**Speaker 2:** BioWorld, published by Clarivate, is a subscription-based news service but all of our COVID-19 content, over 6,000 articles and data entries since the start of the pandemic are freely accessible.

**[00:23:53] [END OF AUDIO]**