This Week in Virology

TWiV 1092 Clinical Update

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Guest: Daniel Griffin

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Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick.

[theme music]

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1092, recorded on February 29, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: It's a leap day, so this episode will disappear next year, right?

[laughter]

DG: What will happen?

VR: What do you got on your tie now, Daniel?

DG: This is my biohazard bow tie.

VR: So those are little biohazard symbols?

DG: Yes, little biohazard, the sort of weird thing there.

VR: All right. Good.

DG: All right, let's jump into it. I try to keep these short, but then stuff happens and we need to talk about it. Let's start off with our quotation because it's maybe a tribute to all our listeners. "The highest activity a human being can attain is learning for understanding, because to understand is to be free." That's by Baruch Spinoza. I think a lot of people come here because they want to understand. They want education. They don't just want a little short little TikTok or a little soundbite. They actually want that understanding, so hopefully, we can keep providing it for everyone, and hopefully, some of that understanding is going to keep everyone safe so that they can be coming back for more.

We'll start off with RSV, an update on RSV. This is good news. It looks like things continue to drop with RSV. Really down from that high peak. This is also what we're seeing in the local area. Good news on the RSV front. This is interesting, right? We'll maybe get a little more into this is, this impacts some of our recommendations, right? We're getting near the end of when we're recommending that last trimester vaccination for pregnant individuals, because, by the time the child is born, we might be past it. We get sort of a little bit of regional nuance, but really, March is going to be where we start wrapping that up. March also is where we're wrapping up a lot of the Beyfortus, that passive immunization.

Now, RSV vaccinations, right, for older folks, that's actually something that has a durability. If you haven't got your RSV vaccine, think about getting it, but not quite as under the gun as you were in the past.

The flu going in the right direction, is still fairly high, though, still seeing a fair number of cases of influenza. Across the board, we are seeing that really starting to go in a positive direction from a judgment standpoint and a negative direction from a quantitative standpoint. Good stuff there. Again, it's regional, right? Right here in New York, where Vince and I are recording from, we're really getting down into the low levels. Still, we've got some hot spots. I don't know what they're doing out there in Ohio. Wyoming is going strong. New Mexico, Oklahoma, Arkansas, Texas, and Louisiana.

VR: Oh, you're good with your states, Daniel. I'm impressed.

DG: [chuckles] I feel like when I was in school, we had to memorize, and I don't know if people know, but Vincent, I have visited every single state except for one.

VR: Alaska?

DG: Never been to Alabama. No, I used to work up in Alaska doing hospital work.

VR: You've worked everywhere in the world.

DG: [chuckles] That might be true.

VR: I have been to most states, but not all of them. I think there are five or six I haven't been to.

DG: All right. Well, you got to get on that.

VR: Yes, I will.

DG: All right. Let's jump right into COVID.

VR: Wait, wait. Before you go, what countries have you been to? Rattle them off. I'm just curious.

DG: I always forget and I run through these, so I try to do it in a geographical spread. We'll start Canada, United States, where I live at the moment, Mexico, going down to Panama, the Dominican Republic, a little bit into Haiti. I won't quite mention that because it's a porous border so I'm not sure that was officially done. A lot of different areas in the Caribbean, Peru,

and then moving over to Ireland, Iceland, England, Scotland, right? I'm going to separate you guys there. France, Germany, the Czech Republic. Moving farther afield, Nepal, India, Thailand, Cambodia, Japan, a lot of visits to China, Zimbabwe, Zambia, Ghana, South Africa, Malawi. I'm forgetting stuff, but yes, just sort of a smattering. Lots of places.

VR: You've never been to Australia?

DG: I've never been to Australia.

VR: New Zealand?

DG: No, not yet.

VR: Your South American visitation is just Peru, basically.

DG: I know. I need to spend more time down there.

VR: All right. Thank you. I'm just curious because I know you travel a lot. It's more than I have.

DG: Yes, and I'm sure I've left stuff out, so I apologize for the countries that I didn't - Oh, Spain. I go to Spain a lot. Sorry about that. People probably who listen are like, but Dr. Griffin, you didn't mention Bonaire. You didn't mention the Dutch Antilles. I'm going to actually be in Denmark in April, so sorry, I left Denmark out. I've been there. Belgium. Yes, I'm sure I left lots out, so. OK.

VR: Not to Italy. I haven't been to Italy. Last one.

DG: Never been to Italy. Yes.

VR: Oh, my God. You have to go to Italy.

DG: Yes, that is on the list. [chuckles]

VR: OK.

DG: Oh, Kenya. I forgot Kenya. OK. Going into COVID, now that we've stopped my world travel update, a little bit of improvement. We are still, I just want to say is we are still at over - we are averaging over 200 deaths a day still. When we talk about different things like, OK, yes, that might be better than 2,000 deaths a day that we were seeing in the U.S. in the early days, just in New York alone. Still, 1,569 deaths last week average about 2,000 deaths a week from COVID, that's too many. We are, as we talked about with RSV and influenza, we're seeing from a wastewater surveillance, things are going in the right direction in most of the country and actually the country as an average, so moving in the right direction there.

VR: Daniel, flu, RSV, SARS-CoV-2, all trending downwards here at the end of February.

DG: Yes. Yes, and actually, dare I say, as anticipated. All right. This was a bit of news. We'll spend some time on the COVID active vaccination section. I will start this section with the news that yesterday, we're recording this Thursday, so Wednesday, February 28, 2024, the vaccine advisors to the Centers for Disease Control and Prevention recommended that people

ages 65 and older receive an additional dose of the current monovalent COVID-19 vaccine this spring. CDC Director Mandy Cohen endorsed the group's recommendation.

Here's a quotation from Dr. Cohen. "Today's recommendation allows older adults to receive an additional dose of this season's COVID-19 vaccine to provide added protection," said Mandy Cohen. "Most COVID-19 deaths and hospitalizations last year were among people 65 years and older. An additional vaccine dose can provide added protection that may have decreased over time for those at highest risk."

Now, I'm going to put in a link to the slides from this discussion as they give an insight into the science, but also its limitations. I'm not sure that what Dr. Cohen said is point-by-point right on. I'll discuss why I say that. A couple of things that they talked about. The first thing is, do people care? Are people 65 and older interested in COVID vaccines? They have a slide where they actually ask people what concerns about COVID-19 disease, confidence in COVID-19 vaccine safety, confidence that COVID-19 vaccine is somewhat or very important to protect me.

When you look at people 65 years of age, we actually see that the majority of them feel confident in the vaccine safety. The vast majority, 78% of them actually feel that the COVID-19 vaccine is an important thing to protect them.

VR: However, Daniel.

DG: Yes.

VR: The numbers of people they looked at is nothing. That's ridiculous. 65 people in one bar. I mean, this is no way a section of the U.S. Come on, at CDC.

[laughter]

DG: Yes, we should look at more people. The other which, and I think this is interesting, right? Because we're going to, we're going to talk a little bit about what do these extra doses do. I want to point out that this is on top of really broad immunity across the population. If you look in the different age groups, and they have a slide where they talk about this, only 1% to 2% of everyone in the United States is, I will say, unprotected from an immune point of view.

Talking about this population, the 65 years and older, we are seeing that the majority, 58%, have hybrid immunity. We are seeing that there's some infection-only seroprevalence. There's some vaccination, about a quarter of 65 and older have what they refer to as vaccination-only seroprevalence. The idea is actually, a quarter of these folks have not had a COVID infection, and that immunity is purely from vaccine.

As we always talk about, the ACIP and these different groups are trying to give recommendations about public health issues, where we often, when we're sitting face-to-face, we're talking about an individual. They phrase their discussion in the context of what are the public health problems that they're trying to address. As we talked about, COVID-19 hospitalization peaked in late December, early January. However, there still are approximately 20,000 new hospital admissions and 2,000 deaths each week due to COVID-19. Why are they targeting the greater than 65 years? These folks have the highest COVID-19

hospitalization rates and age is really a big issue when it comes to hospitalization. Also, mortality, particularly the 75 years of age and older.

They looked at some data. There is some science here that they're looking at. One of the things they looked at is something we've been talking about, is what is the durability of protection, right? We're not expecting these boosts to restore protection, restore high antibody levels for a year. We've talked about a three- to four-month expectation. When they looked at the – and I'm going to focus here on the greater than 65 folks – you see the best, the highest vaccine effectiveness. This is against hospitalization, right? It's not infections. It's against hospitalization. You see the most significant in the first two months. You still see solid protection out to 120 days. That's about four months. Once you get past there, you really start to see a drop in that calculated absolute vaccine efficacy against hospitalization. We see a similar pattern when we also bring in hospitalization and critical illness.

VR: Daniel, can I ask, in the hospitalization VE, the younger people do worse in some of the, in like the 60 to 119 days and the 120 to 179 days. They do worse than the older people. Why is that?

DG: [chuckles] Really interesting because they have a whole section where they talk about immunosurveillance and why it's so important to get the old people these updated vaccines. If you look at the data, you're starting to say, oh, and the young people need it even more often. Yes, big error bars, I'll give you that. Yes, clearly by the time you get out to 120 to 179, the young folks, right, the 18 to 64, that's like coming smack down at a vaccine effectiveness back down to zero, right?

VR: Remember, as you said, this is the original monovalent and bivalent booster. It is not the current Omicron formulation.

DG: Yes. That's, I think, part of the reality check, right? They acknowledge the reality check. People are looking at this and saying, oh, but if you get another booster, we might restore some degree of protection. Well, as they point out, no clinical trial immunogenicity data of this additional dose that they're talking about right now. They do say, but you know that initial dose does get a robust elicitation of neutralizing antibodies. It is providing protection against JN1 and other circulating variants. What are they going to recommend here?

Here's what it comes down to. The ACIP recommends that persons 65 years of age or older may receive an additional dose of 2023 to 2024. We're going to talk about "may" in a second here. They say that this should be informed by clinical judgment of a healthcare provider, personal preference, circumstances, considering the additional dose based upon the person's risk for severe COVID-19, the additional dose administered at least four months after that previous dose. Then there's this whole big discussion about the word “may.” Should we really say may, which is just sort of like, yes, you could do that, or should it actually be a recommendation?

Is this a should? Are they going to encourage people? Are they going to say in our expert opinion, based upon, as they acknowledge, very weak evidence, limited amount of evidence, but what they do know, does the discussion change that the recommendation is ACIP recommends that persons greater than 65 years of age should receive an additional dose?

They actually, an amendment gets introduced, they switch the voting measure to the stronger recommendation, and we end up with a final measure passed with 11 votes for yes, one vote no, one abstention.

VR: Let me get this correct. This is like an XBB version vaccine, basically, which was first launched in the fall. Is that correct?

DG: Yes. They're saying, if you got that shot in the fall, and you're 65 and older, this committee recommends, suggests that you should get an additional dose.

VR: OK. Why don't we have clinical data from that first dose in the fall? You had plenty of time, you had the respiratory virus season, you could have done a great study. Why don't we have anything, CDC?

DG: I think the biggest, I guess my biggest contention is, well, so again, we're sort of where this is, "expert opinion," what we call the Delphi consensus where you get a whole bunch of people in a room and say, we don't actually have data, but we're going to recommend you do this. Then, because the big data is, will this additional dose give us that extra? Will it restore, somehow, this protection that we--

VR: I understand that, but they didn't even look for the first dose to see if it is -[crosstalk]

DG: Yes, in this discussion, right, where's the slide with the data on - because we've talked about some data on the current, but where was that in the slide deck? Yes.

VR: I don't want to be anti-vaccine but I would like - I don't think if you make recommendations without scientific data supporting them, you're eroding confidence in vaccination and that's not good.

DG: Yes, I think, interesting, and I spent a little time, but I actually, when you talk about this “may” versus “should,” I like the “may,” but again, maybe this has a legalistic implication. If you look at it, you say, listen, you're over 65, you're interested in getting another vaccine, we think you're going to get a boost in antibodies for three to four months, it's been past four months, we've talked about individuals, they have a discussion with their provider, and then they try to go get the vaccine and the insurance company said, no, you're not eligible. Our system doesn't allow that to happen.

By giving a “should” recommendation, does it increase the access? I don't think we're going to get an onslaught, I think we're going to get a few percent of our population going for this extra dose. How much of this is opening up the public health access to these additional doses, versus how strong is this “should?” We probably need like a third word, this sort of a “soft should” versus a, “thou shall.”

VR: How about “must?”

[laughter]

DG: Must. That's it. That's a good one, too. I don't think we like shall and must in America, so.

VR: No.

DG: Yes, but I think, this is going to be out there, people are going to be discussing it. Yes, and there are certain patients that this makes sense, we think, and again, just putting it in the couch, but yes, this is always that challenge. We have to be careful when we make "should" vaccine recommendations, because after a while, it's the boy who cried wolf. They want to see the science, they want to see that this is really making a difference.

VR: Is there any negative of getting a booster in the spring?

DG: Yes, I think that's the great thing is they talked a lot about, is there is there a downside? Is there a risk? The overwhelming realization, the discussion was that these are incredibly safe vaccines, right? They're biologically impactful. It's not zero risk, but that risk is incredibly small, compared to the potential upside to boosting those antibodies, maybe even some kind of a T cell boost for some period of time. That's really was a risk-benefit discussion. If you're, let's say 22 years old, and you had a COVID infection, like so many people did during January, I think it makes sense to focus on a higher-risk group.

VR: One person voted no. Do we know who that is?

DG: I wanted to find out who was the no and who was the abstention. We may have to play back the tape to find out who that was. Then I thought about, well, I probably shouldn't find out and mention it. I'll look on my own time. [chuckles]

VR: No, it's always curious to know why someone voted a certain way, right?

DG: Yes. What's really nice, and I should go back and sort of, just spend a little time looking at that is that they give their reasoning. They say this is why I abstained. This is why I said no. Everyone votes and then they get their sort of, let me explain why I said that and that can be really informative.

The other, I should say at the same sort of context, in the slide deck was also this question that they asked, percentage who say they are taking each of the following precautions because of COVID-19 this fall and winter. It's actually a survey that was done back in the fall and there's this perception that no one cares about COVID anymore. Actually, if you look through some of the responses, a significant percent of people are avoiding large gatherings. Some people are still wearing a mask in crowded places. Some people are making decisions to avoid travel.

Some of us are still avoiding dining indoors at restaurants. There's still a percent of our population that are taking a COVID test before visiting with friends or family. If you say, are you doing anything, a solid percent of folks, though they're not necessarily publicizing this, but they're making decisions to try to keep themselves and their loved ones a little bit safer.

Now this is an interesting, I think this plays right into our discussion, is the brief report, "U.S. State Vaccine Mandates Did Not Influence COVID-19 Vaccination Rates but Reduced Uptake of COVID-19 Boosters and Flu Vaccines Compared to Bans on Vaccine Restrictions." That's all right in the title published in *PNAS.* Here the investigators use state-level data from the CDC to ask the question, they say, to test whether vaccine mandates predicted changes in COVID-

19 vaccine uptake as well as related voluntary behaviors involving COVID-19 boosters and seasonal influenza vaccines.

They suggest that the results show that COVID-19 vaccine adoption did not significantly change in the weeks before and after states implemented vaccine mandates, suggesting that mandates did not directly impact COVID-19 vaccination. I was a little surprised by that. Interesting. Compared to states that banned vaccine restrictions, we've discussed a few of those, states with mandates had lower levels of COVID-19 booster adoption. Say that again, states with mandates had lower levels of COVID-19 booster adoption as well as adult and child flu vaccination, especially when residents initially were less likely to vaccinate for COVID-19.

Just a little closer look at the findings. First, the investigators report: There was no statistically significant difference in weekly COVID-19 vaccination rates before and after the imposition of a mandate. They then go on to look at COVID-19 boosters and both adult and child flu vaccinations. There's a number of different, I guess I'll say, charts. You can look at COVID-19 booster proportions, and you've got states where the COVID-19 vaccination rate, they've got it with standard deviations. I have to say, a lot of potential confounders here, but it does raise this issue about when you start mandating things versus approaching vaccine decisions with an educational campaign, there's a potential risk of mandates having this negative response from the public. I don't know if you had any thoughts on this, Vincent.

VR: I think it's a backlash against mandates, but who's covered in these mandates? Is it just for school or is it a broader population?

DG: As we saw in New York, different populations. Initially, it was healthcare workers, but we also saw schools, we saw different occupations. Yes, really a lot of different situations where the vaccines were mandated.

VR: I think mandating for school entry is a great idea, but I think as this study shows, maybe in a broader population. Healthcare workers, the hospitals, the healthcare institutions should have their own flexibility, I think, right? When you go to a broader population, I think there's a backlash.

DG: Yes. I think we worry, right? We're seeing issues with measles vaccination rates. We're seeing this sort of spill over into other areas.

VR: In your place, Daniel, in your hospital, does your hospital mandate vaccination or does it come from the state?

DG: Early in the pandemic, that's interesting, it came from both, right? You had it mandated and then you had, dare I say it, enforced by the different healthcare facilities. Then interesting, there was this rebound after the fact where things got lifted and then a lot of people who were let go because they had not gotten vaccinated were then re-employed. Very interesting dynamic going on there.

Actually, I should mention this. We've been following the meetings. They're Wednesday, February 28, and then it'll be also the 29 today, there's meetings going on. There was a plan

to discuss novel OPV2 in the U.S. I don't know if you caught up on this. Dr. Sarah Kidd was going to be leading the discussion about the potential of using that here in the United States.

VR: This is dead in the water. It is not happening. If they think they're going to reintroduce OPV in the U.S., they're out of their minds. They don't know biology. They don't know public health. They don't know history. This is not happening. This virus causes paralysis in kids. You think that's going to work in the U.S. when we have IPV, which doesn't cause paralysis, it prevents it. I don't see any logic in talking about this and even putting it on the agenda. What is the purpose? You know what it is, Daniel, IPV doesn't prevent transmission of poliovirus, and they're thinking, well, nOPV2 might for a short period of time, but the negatives far outweigh that. I think IPV should be used globally, frankly. [crosstalk]

DG: I do, too. People say, oh, but it's so expensive. Come on. We're building aircraft carriers.

VR: Yes, indeed.

DG: All right. Moving to COVID early viral phase, number one, NIH treatment guidelines, et cetera., IDSA, Paxlovid. Another nice meta-analysis, effectiveness of nirmatrelvir/ritonavir on severe outcomes of COVID-19 in the era of vaccination and Omicron. An updated meta-analysis published in *Journal of Medical Virology*. I do want to point out, there are lots and lots of studies now. Don't let someone just cherry-pick one. Here, they're going to look at 32 studies included in this meta-analysis and they're going to do pooled risk ratios.

Basically, we are seeing nirmatrelvir with a mortality pooled risk ratio, 0.36. Hospitalization, 0.43. When you combine them together, 0.52. Progression to severe disease, 0.54. Then you see a subgroup analysis on vaccinated patients as well. You're seeing a lower effectiveness on mortality in that group, but similar effectiveness when you look at hospitalization, hospitalization and/or mortality, or progression to severe disease.

The authors' comment, and I'll agree with this, "This updated meta-analysis robustly confirms the protective effects of nirmatrelvir on severe COVID-19 outcomes." We're seeing, across the board, about a 50% reduction. When people start talking about, oh, maybe they're charging too much and we should get the price down. Yes, that's great. Even in vaccinated patients, as we see here, even in the time of Omicron, we're seeing that this is really an effective tool that we should be using. Number two, remdesivir, as we've discussed, not getting quite as much use.

Number three, molnupiravir. What about molnupiravir? The article, "Randomized Control Trial of Molnupiravir SARS-CoV-2 Viral and Antibody Response in At-risk Adult Outpatients," was published in *Nature Communications*. In this study, non-hospitalized participants within five days of SARS-CoV-2 symptoms were randomized to receive molnupiravir. We've got 253, or not, 324.

They studied viral and antibody dynamics, the effect of molnupiravir on viral whole genome sequence from 1,437 viral genomes. I'll applaud, not just PCRs, they actually collected swabs and viral transport medium and then cultured these on Calu-3 cells using a high-throughput culture method with screening over seven days for evidence of cytopathic effect and the presence of SARS-CoV-2 by lateral flow immunochromatography and PCR, they were able to recover viable virus.

Now, the positive culture rates for samples collected during the treatment, two through five, was 10.4% with molnupiravir versus 15.2% for the not getting. They say usual care but I'm going to say people that didn't get treatment. I hope that's not the usual care.

VR: It's azithromycin, Daniel.

DG: [chuckles] It's steroids. Don't forget.

VR: Horse paste.

DG: Oh my gosh. Post-treatment viability, days six through 20 dropped to 5.1% for molnupiravir and 2.5% for usual care. Now, they reported that molnupiravir was associated with lower anti-SARS-CoV-2 spike antibody titers. Serial sequencing revealed increased mutagenesis with molnupiravir treatment, dare I say, as expected. I think their conclusion is we should give more and more days of molnupiravir, but, yes.

VR: Isn't what we want to know the effect on progression to hospitalization, not positive cultures?

DG: I agree. I agree. We have good data that molnupiravir, though not as effective as Paxlovid, not as effective as remdesivir, is an effective treatment. It should be, if you're not on one or the other two, the usual care.

All right. Convalescent plasma, just so Arturo Casadevall remains my friend. I'll keep mentioning that. Isolation for the infected. We talked a little bit last week about rumors that the CDC might be coming out with updated guidance in, I think, April. So far, the CDC has not said anything, but a few states have actually started to change their guidance. Just echoing that the science has not changed, but some of the guidance has.

Second week, the cytokine storm week. Remember, steroids at the right time, in the right patient, at the right dose, and for the right duration. This is after the first week and in patients with oxidation saturations less than 94%. We discussed a meta-analysis where they suggested that six days was adequate. Just will nod that the ID Society NIH treatment guidelines still have 10 days in there.

Number two, anticoagulation guidelines from a number of organizations, including American Society of Hematology, pulmonary support, remdesivir still in the first 10 days, immune modulations in some cases. Yes, let's avoid those unnecessary antibiotics as listed by Vincent. Even though it tastes like chocolate. If you like the taste of chocolate, go get yourself some dark chocolate. You don't need to have the paste.

All right, COVID-19, the late phase, PASC/Long COVID. We have a fair number of things here. The article, “Spontaneous, Persistent, T-Cell Dependent Interferon Gamma Release in Patients Who Progressed to Long COVID,” was published in *Science Advances*. Not only did I run across, but this was sent to me by one of my patients as well, a fellow sailor. Let us start with the study design.

Unexposed donor samples, we've got 54, were recruited by the National Institute for Health Research BioResource Cambridge through the ARIA, so the Antiviral Responses in Aging. It's

a cool acronym. This cohort was recruited before October 2019. No participants were exposed to SARS-CoV-2 infections. The COVID-confirmed hospitalization patients, different group, right? This is N of 51, day 28, N of 20 for day 90, N of 40 for day 180, were enrolled following admission to Attenbrooke's Hospital, Royal Papworth and Cambridge and Peterborough Foundation Trust, where they confirmed diagnosis of COVID-19 via positive RT-qPCR. Then they enrolled Long COVID study patients. We've got N of 55 there.

Now, this cohort had symptoms that had persisted for at least five months after acute COVID-19 that could not be explained by an alternative diagnosis. As some patients were infected before routine testing began, a positive RT-PCR result, antibody seropositivity to nucleocapsid, or a positive IL-2 response to M and N peptides was required as proof of SARS-CoV-2 infection.

The investigators detected persistently high levels of interferon-gamma from peripheral blood mononuclear cells of patients with Long COVID using what they refer to as a highly sensitive FuoroSpot assays. These are not, I will comment, routinely available, but this interferon-gamma release was seen in the absence of ex vivo peptide stimulation. Explain what that means.

Normally, let's say you wanted to ask if, oh, has this patient been exposed to tuberculosis or something, and you're looking for memory cells. You would draw their blood, get those white cells. You're really focused on the memory T cells. You expose them to a peptide from the pathogen that triggers the interferon-gamma release. Here, we're seeing that this interferon-gamma release is occurring in these folks with Long COVID even without the peptide stimulation. We see that the interferon-gamma release was CD8-positive T cell-mediated and dependent on antigen presentation by CD14-positive cells.

Now, I mentioned a couple of things. One is that this is not commercially available. You do see separation with some degree of overlap, but you are starting to see some separation here between the unexposed and the folks with Long COVID. They followed the Long COVID cohort for up to 31 months after this acute infection. During follow-up period, I'm going to say this is what I found quite interesting, a considerable number of the patients experienced resolution of some, if not all, of their symptoms, either spontaneously or some folks are doing this after they get a SARS-CoV-2 vaccination.

They measured the unstimulated interferon-gamma release in patients with Long COVID before and after vaccination, and they found a significant decrease in the interferon-gamma after vaccination that actually correlated with symptom resolution. Interesting correlation, but the investigators point out in their discussion that at this stage, it's not clear whether the interferon-gamma is a mediator or a biomarker of Long COVID, but yes, it's interesting.

VR: As an immunologist, Daniel, what do you make of this?

DG: Normally, when you turn on your immune system to fight the pathogen, it's sort of a dangerous thing, right? You're unleashing the hordes and now you've got to somehow get them to stop. It's all over. Stop being turned on, stop being activated. You want your CD8 positives, your killer T cells, your cytotoxic T cells, you want them to turn off. You expect that interferon-gamma activation to settle down, and we're not seeing that.

From a mechanistic standpoint, it makes a certain amount of sense. Interesting that you vaccinate them, which we're hoping sort of helps steer the immune response in the right direction, maybe even clearing some remnant material that might be driving that stimulation. You see the T cells turn off like you're hoping, the people feel better. Mechanistically, this might make some degree of sense.

VR: Do you think that there's antigen present peptide or the T cells messed up in some way that just crank it out?

Daniel: I could buy either, and I don't know. I don't know which.

Vincent: All right.

Daniel: Imagine I said, I don't know. Even though I went to medical school, I still remember how to say that. All right. [chuckles] The article, "Blood-brain Barrier Disruption and Sustained Systemic Inflammation in Individuals with Long COVID-Associated Cognitive Impairment," was published in *Nature Neuroscience*. Maybe we have a theme here, like this ongoing systemic inflammation that should be shutting down in dozens.

Here, participants included patients who had recovered from COVID-19, male or female, aged 18 and above, with or without neurological symptoms. Patients with Long COVID with symptom persistence over 12 weeks from infection were also recruited. Here, they're going to use this dynamic contrast-enhanced magnetic residence imaging to assess blood-brain barrier disruption.

I think you guys may have even discussed a little bit of this on the deep dive recent COVID. They assess this. They then did transcriptomic analysis of peripheral blood mononuclear cells to look for dysregulation of the coagulation system and the adaptive immune response in individuals with brain fog. Sort of an interesting suggestion that there's some kind of ongoing systemic inflammation and maybe some ongoing blood barrier disruption.

All right. More to come. The article, "Prevalence of Persistent SARS-CoV-2 in a Large Community Surveillance Study," was recently published in *Nature*. Here, the investigators identified 381 individuals with SARS-CoV-2 RNA detected by PCR at low CT values, persisting for at least 30 days, of which 54 had viral RNA persisting for at least 60 days. In some individuals, they identified many viral amino acid substitutions, they say indicating, I'm going to change that to suggesting, periods of strong positive selection, whereas others had no consensus change in the sequence for prolonged periods consistent with weak selection. All PCR data, no viral culture, no plaque assays, no real ability to distinguish remnant RNA from replicating virus. What's exactly going on here? Does that persistent RNA drive any ongoing immune activation? Vincent, any thoughts?

VR: I heard Viviana Simon yesterday give a talk about her study at Mount Sinai, where they followed a population of immunosuppressed patients, and they see long-term production of virus in that patient population. I wonder in this one, how many of these are immunosuppressed? Because I do understand that immunosuppression, it can happen in many forms, leads to inability to clear virus, so it reproduces and it sustains changes, it evolves in the patient over time. This is only surprising that it's not in an immunocompromised population, or maybe they say it in the paper, I'm not sure.

DG: Maybe somehow, you're identifying individuals who have some type of immune issue, right?

VR: Maybe.

DG: Why is it persisting in them and not in other people? Again, we're sort of left with not really knowing if this is replicating virus or if this is just RNA that isn't being cleared.

VR: Well, in her study, they were able to culture virus from these individuals, right? They didn't quantify it, but they could do cell culture positivity. Many of them were treated with Paxlovid and five days was not sufficient. It could be that in this patient population, you need longer treatment, right?

DG: Yes, and in some immunosuppressed populations, it's a high RNA copy number, it's not this -[crosstalk]

VR: Yes, so her study was done in New York at Mount Sinai, and they see spike changes arising before they appear in the general population.

DG: Interesting. Interesting, yes. That's always been one of the concerns, right? That people are actually producing these changes, sort of giving the virus a fitness, a chance to improve fitness in the host, and then potentially, yes.

VR: Right, but you know what's interesting, some of these amino acid changes lead to immune evasion to antibodies, right?

DG: Yes.

VR: These patients do not make antibodies to the virus.

DG: There's still, yes, that's really interesting. That's fascinating.

VR: Maybe it's just fitness, and that happens to be similar changes that cause immune evasion.

DG: Yes, that would be the only sort of, the evolution. What would drive that evolution? It has to be some fitness advantage to be, but it is interesting because we normally would say, oh, obviously, it's immune evasive, it's being selected by the antibodies, but there's no antibodies there, so it's not.

VR: Yes.

DG: Fascinating. A small but encouraging study, “Long Term Outcomes of Hyperbaric Oxygen Therapy in Post Covid Condition: Longitudinal Follow-up of a Randomized Controlled Trial,” published in *Scientific Reports*. Now, context, back in July 2022, this group published the article, “Hyperbaric Oxygen Therapy Improves Neurocognitive Functions and Symptoms of Post-COVID Randomized Controlled Trial,” also *Scientific Reports*, where they reported improvements in a number of symptoms with hyperbaric oxygen therapy, which they attributed to increased brain perfusion, neuroplasticity.

Here, the authors perform follow-up on that cohort. The protocol involved, are you ready for this, 40 daily sessions, five sessions per week, in a two-month period. The protocol involved breathing 100% oxygen by mask at 2 atmospheric, 2ATA, for 90 minutes, with five-minute air breaks every 20 minutes, compression/decompression rates. Seventy-nine patients were randomized to either getting hyperbaric or a sham in the original study. Out of the 40 patients allocated to the hyperbaric arm, 37 completed the intervention, performed the short-term evaluation.

Of these, six declined their participation on any long-term evaluation. Accordingly, a total of 31 patients received the hyperbaric oxygen therapy, had both short-term and long-term post-treatment evaluations, and they're included in this current study analysis. A few limitations that before we look at the data, as point out, the sample size ends up becoming relatively small with 31 patients in total. Second, the primary endpoint in the original study, cognitive function, as well as brain imaging were not evaluated in this current longitudinal evaluation.

Since the original sham group after completing the study protocol were offered to be treated with hyperbaric oxygen, most of them received it, 69%, so they really couldn't serve as a proper control group. Now, they did, however, report that based on response to a short survey, there appeared to be encouraging long-term improvements in quality of life, quality of sleep, psychiatry, and pain symptoms. They're using this SF 36, this short form 36 questionnaire, and I'll leave a link to it so you can look at what they're asking. If you actually look at the data, a statistician will tell you that this is interesting, but you're not really seeing any huge difference. Really, when you compare short-term, long-term, really looks about the same. There's really no statistically significant difference between those two.

VR: Is this hyperbaric therapy really practical on a big scale, Daniel?

DG: I know patients are doing it, patients are desperate. Yes, is it really practical? Are we going to have the hundreds of thousands, millions of people with Long COVID end up in these hyperbaric oxygen chambers? It doesn't seem, and particularly when the impacts that we're seeing are as subtle as we're seeing on the SF 36. I'm not sure that this is really going to be a therapy for the masses, dare I say.

All right, I will close it out there with no one is safe until everyone is safe. We're in our American Society of Tropical Medicine and Hygiene fundraiser, where for February, March, and April, we'll double your donations up to a maximum donation of $20,000. This is mainly going to go to scholarships for women from low-middle income countries to go to the annual meeting and hopefully allow them to make some connections and further their careers. Go to parasiteswithoutborders.com and click ‘Donate.’

VR: It's time for your questions for Daniel. You can send them to Daniel@microbe.tv. Theodore writes, "I am a 46-year-old doctor taking biologics for plaque psoriasis and anti IL-17 monoclonal. As I am considered immunocompromised, automated system for COVID-19 appointments allowed me to do more than one shot per year. I've been doing two vaccines per year. My question is, do I really need more than one shot of the same vaccine each year?" "Does Cosentyx," which he's also taking, "make me so immunocompromised to need more than one or am I exaggerating? Colleagues that I've asked gave me a spectrum of answers from you don't really need it to be revaccinated if my antibody levels drop below 10 IUs."

DG: [chuckles] All right, so this is a great question and your timing is perfect. I know Vincent, you sort of knew the timing on the ACIP meeting this week, but this is in line with the current recommendations, as we've talked about, low level of certainty, not a lot of data to guide us here, so this is an expert opinion approach. The idea with the vaccines is you get this three- to four-month boost in antibody levels, T cell, basically boost in our inner immunity, some boost in protection. We have that data we discussed where it looks like you start to wane and lose that protection when you get to about 120 days.

This idea about spacing them four to six months apart makes a certain amount of sense, but as we're talking about, we don't have tremendous data. When someone gives you a, I'm going to say at this random antibody, I don't know where they make that stuff up. We certainly don't have that degree of understanding that we can look at antibody levels and really pick who should and when get a next booster.

VR: Jason writes, "My wife is pregnant and just entering her third trimester. It was my understanding that the recommendation was for pregnant people to get the RSV vaccine in their third trimester. We asked my wife's OBGYN about getting the vaccine and the doctor said they were no longer giving it to pregnant people now because it's beyond RSV season and no longer available. I looked on the CVS website and CVS will still give the vaccine to pregnant people, so I know it's available. I could make an appointment for later today. Thus, I'm confused about being advised that it's no longer available.

“My question is whether the advice not to get the vaccine in the third trimester is correct. Is there a downside to getting the vaccine? The only reason I could imagine not to get it is if immunity passed to the child was not expected to last until the next RSV season. That goes against my understanding that the vaccine is fairly durable, though perhaps that is not true for the baby. I'd appreciate any clarification. If there is a benefit, we could go back to the OBGYN and push back on the issue. Obviously, if there is a benefit, I want to make sure the baby is protected."

DG: Yes, this is great, and thanks for sending this in, and the timing is good, too, because of what we talked about. We're getting near the end. RSV is on the way down, but it's not gone, right? We're recording this on leap day. Is that what that's called? February 29, but this will be dropping right as we get into the beginning early days of March. We're getting right at the end depending upon different regions as far as by the time a person delivers, by the time the baby is born, will the RSV activity really be down? There isn't a downside, but you're sort of getting into this timing issue.

You can think about when's your due date. Maybe you're going to deliver early. What if you deliver early and you deliver in mid-March? We still have some RSV activity. We're still doing Beyfortus in certain regions. There isn't a big downside as you bring up. I'm not sure you even need to go back to your doctor, right? This vaccine is going to be available because it's not just for folks in their last trimester. It's also one of the two options for adults. It's going to be around. It's going to be an option. I think that you've got to just sort of look at risk-benefit. If you run out this afternoon, and maybe that'll be Saturday afternoon when this has dropped, I still think you're within that window, but yes, you're getting pretty close to the end of when RSV won't be a concern this season.

You bring up another, which is how long will those antibodies response? How long will that protection last? We have our studies in adults showing a durability of the vaccine out to two years, but what we're talking about here is protection for the newborn. Will whatever amount of immune protection you transfer to that child, will that still be viable next winter? Probably not. Your child is probably going to be a candidate for Beyfortus, nirsevimab, in the fall.

VR: Michelle writes, “My college-age son recently came down with mononucleosis while away at school. He's doing well after two weeks. My question is, how long is he contagious? I think I read that he could have virus in his saliva for up to 18 months. I'm currently on adalimumab, {Humira) for IBD/Crohn's disease. Since he graduates May 11, I obviously would like to go to his graduation and have him stay home with us for a week or so, but we wouldn't want to risk me catching the disease as I'm immunosuppressed. How easily can you catch mono? How contagious would he be three months out? Can the virus travel in air? I don't know if I've had mono myself before, but I would think that by 61 years old, I should have been exposed at some point. Is there a test to see if I have some immunity?"

DG: OK, these are great questions. Mono, in general, the most common cause of mono, is infection with Epstein-Barr virus, but that's not the only cause of the mono syndrome, the clinical syndrome like CMV. There's other triggers. That would be the first question is clarifying for yourself, is this an acute Epstein-Barr virus infection? If it is, we'll talk a little bit about that. If it is, it usually takes a few weeks from exposure to the onset of symptoms. By that time, a person is usually showing a positive IgM, a positive IgG.

During the acute mono symptom phase, people tend to be contagious. You can actually, even during that period of time, you can pick up the EBV DNA in a blood test. They have a viremic phase. Unlike some other pathogens, I should say like West Nile virus, we really got to look for antibodies because human beings do not get a tremendous amount of viremia unless they're immunocompromised.

Now, when that acute symptom phase declines, and maybe they develop that mono, right, people who are feeling crummy for a couple of months afterwards, that usually tends to move into a post-infectious sequelae. The serum EBV DNA will turn negative. The person is no longer contagious at that point. There are some individuals who are contagious for several weeks. There are rare individuals who remain contagious for months who maintain an elevated EBV DNA in the serum, in the saliva. A really easy thing to do here is clarify, is it EBV or not, or CMV, for instance, and do a serum viral DNA test. If it's negative, you're clear and can move forward.

VR: Louis writes, "I'm traveling to Argentina in April for two months. I got the flu vaccine in August. Should I get a second flu shot as I'm going to the Southern Hemisphere as flu season begins there, or should I get a flu shot there? Is it the same flu shot?"

DG: Yes, so it's the same flu shot, and you raise something that we have really good data on with influenza vaccination, is you get the initial protection, let's say two to three weeks after the shot is really when it tends to peak, and then you lose, I'm going to throw this number, about 10% per month. There was a recent study where it was 8%, so sort of a range there. Nowadays, you got it, let's say, August, so September, October, November, December, January, February. We're getting to the point where most of that protection, which does

correlate in the case of influenza with antibody levels, where most of that protection has waned.

No, I think it's reasonable to get another flu shot. It makes sense. You just figure out whether it's cheaper or easier for you to get it here or down there. Still using the same, but we do know that when there's a meeting this spring, coming up pretty soon, there's going to be recommendations for an update of the vaccines, and one of the influenza B will be removed. We're going to be down to a trivalent because that one has gone extinct like the dinosaurs.

VR: Jeff writes, "At the end of the last episode, with reference to the CDC guidance on five days of isolation following COVID infections, it sounded as if Daniel Griffin said, the science has not changed, the public guidance has, but it does not appear that the CDC has changed its recommendations on the website. Although I've heard a lot of speculation in the media, I have not heard any official announcements of a change. Can Dr. Griffin please clarify? As a clinician, I want to give patients the most up-to-date information I can. Recently, I've been saying that there's been discussion about changing the five-day rule, but that nothing has changed on the official guidance. Is this accurate or has the official guidance changed?"

DG: Yes, so you're right on. I'll just word that sentence. The official guidance from the CDC has not changed. When the people that broke those stories reached out, the CDC said, no comment. I can neither confirm nor deny. They plan to have an updated statement in April. It could be the same statement. It could be a different statement. As mentioned, the guidance has changed in certain places, certain states have said certain things. The science hasn't changed, and you are correct, this official CDC guidance has not changed.

VR: That's *TWiV weekly* clinical update with Dr. Daniel Griffin. Thank you, Daniel.

DG: Oh, thank you. Everyone, be safe.

[theme music]

VR: [chuckles] No comment.

[00:56:32] [END OF AUDIO]