This Week in Virology

TWiV 1088 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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pdf of this transcript available (link)

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

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1088, recorded on February 15, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today here at the incubator, New York City, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: I can see from here your bow tie today. It's very easy. Parasites Without Borders.

DG: Yes. What is that red little squirrely thing wrapped around the planet?

VR: It is a worm, but I don't remember which one.

DG: It's the giant intestinal worm, Ascaris.

VR: Oh, it's Ascaris, which comes to a point that I remember, when you were designing the logo, it wasn't pointed enough.

DG: There was a bit of a mutiny for it, "It doesn't look like ascaris. We can't do that." We spent a lot of money making sure it looked exactly like -

VR: A lot of money to get it pointed. OK. Very good.

DG: All right. Let's jump right in. I look for weather quotations this time of the year because it was just Groundhog Day, and that's my favorite day of the year, when we trust our weather forecasting to a little rodent. The fact that it's only right 30% of the time, we move right past that.

VR: That's right.

DG: The trouble with weather forecasting is that it's right too often for us to ignore it and wrong too often for us to rely on it. That's by Patrick Young.

VR: I'm not sure those numbers add up, but that's fine.

DG: All right. Let's jump right into RSV. We have the rapid communication published in *Eurosurveillance*, "Early Estimates of Nirsevimab Immunoprophylaxis Effectiveness Against Hospital Admission for Respiratory Syncytial Virus Lower Respiratory Tract Infections in infants, Spain, October 2023 to January 2024." So far, we have clinical trials showing 77.3% efficacy in preventing RSV, lower respiratory tract infection, hospital admission in healthy infants born at term or preterm. Nirsevimab passive immunization - I threw the word passive in there - also showed an 83% reduction in RSV-related hospitalization in infants in a real-world clinical trial setting. We also have data showing impact on the reduction of severity of RSV-related hospitalizations.

Here, late September, 2023, Spain introduced universal RSV prophylaxis into its national immunization program for all infants born after the first of April, 2023. Here we see the early estimates of the effectiveness of nirsevimab against hospital admission for RSV, lower respiratory tract infection in infants less than 9 months old in three autonomous regions of Spain. These results are from a multicenter hospital-based active surveillance program in nine hospitals in these three areas. You've got five hospitals in Valencia, three in Murcia, one in Valladolid, a province of Castilla y León in Spain.

The population during the data collection period consisted of all infants eligible for this passive immunization with nirsevimab during their first RSV season. They have this eligibility for that, and we have an N of 15,676, which represents 6.4% of the entire Spanish infant population eligible for immunization. The surveillance period lasted from 1 October 2023 to 31 December 2023, and then 10 January 2024, depending upon which hospital. All infants admitted with lower respiratory tract infection were included.

The effectiveness of nirsevimab immunoprophylaxis by region was assessed by the screening method in which they look at the infants immunized, the proportion immunized with nirsevimab among the RSV, lower respiratory tract infection hospitalized cases compared to the portion of immunized infants in the corresponding region hospital catchment area. They're doing this calculation. Based on this, they calculated that nirsevimab effectiveness against this endpoint was 69.3% in Valencia, 86.9% in Murcia, and 97% in Valladolid.

VR: Why is it such a big variation depending on the region? That's interesting.

DG: Actually, I have to say I found that interesting. I don't know, and this will be interesting, wide confidence margins. These are big numbers here.

VR: Ninety-seven percent is great, right?

DG: Beyond great, fantastic; 69.3% is still good. Actually, I should say, here's a good point. On my way in today, I'm getting texted by Jay Berger, the head of pediatrics for the Optum Tri-State, and it was this question of when do we stop doing nirsevimab. We'll talk about the numbers with RSV coming down. We have this general recommendation to think about doing this during the RSV season; October, November. We talked about regional differences going through March, and then the question was March 1st, March 15th, March 31st, when? At this point, as we'll talk about with the pattern, probably end of March, but I want to go a little longer because the RSV rates are still fairly high, and we're quickly approaching March.

VR: Is it possible that different parts of the country or the world would have different end dates?

DG: Like we have with flu, you can actually look at your regional incidence, and you could actually make an even more nuanced decision. I think that's reasonable because some parents are going to want more nuance, some people are going to want a general. The CDC here in the U.S. is making recommendations for the whole country, but actually, it would be reasonable to nuance those, particularly when we have shortage issues and say, "You folks out of Minnesota, you're through it. You folks in Georgia are still having high," and then adjust.

All right. Well, we have the announcement from GSK. GSK's RSV vaccine, "Arexvy, Accepted Under Priority Review in U.S. for the Prevention of RSV Disease in Adults Aged 50 to 59 at Increased risk." This is based on data from the NCT05590403. This is a phase 3, placebo-controlled, observer-blind, randomized, multi-country immunogenicity trial. Everyone has to remember those numbers. Basically, we're just asking, instead of it just being for those folks 60 and older, do we want to be also authorizing this for folks in the 50 to 59 if they have increased risk?

As mentioned, this is an immunogenicity trial. This study assessed the immune response in participants aged 50 to 59 with predefined stable chronic diseases leading to an increased risk of RSV disease. They're looking at 570 folks. Immune responses in a broader group of participants aged 50 to 59 without predefined chronic illnesses, same N=570, we're also evaluating. Then they're going to compare this immunogenicity data to adults aged 60 and older. The trial's primary endpoint is not going to be disease. It's going to be neutralization titers in groups, and we'll wait to hear the results of this review. We may be extending the RSV eligibility down to a younger age group, particularly if folks are at increased risk.

VR: All right. That's a different age group from the original trial, which was 60 and up?

DG: Exactly, yes. Where are we with RSV? It really looks like we're moving in the right direction. The peak this year was not as high as it was in the past. We sort of had that double peak, so probably the area under the curve looks pretty similar. We're really on the way down. We had a peak of about, what is it, 15,000 PCR detections. We've now dropped down, approaching about 6,000. We're down about two-thirds of the way, really moving in the right direction. Hopefully, this trend continues with RSV. As mentioned, this is national data. Like we cover with the flu, regionally, we see different issues.

Speaking of the flu, this is a topic we've covered before, the article, Redirecting Antibody Responses from Egg-adapted Epitopes Following Repeat Vaccination with Recombinant or Cell Culture-based versus Egg-based Influenza Vaccines," published in *Nature Communications*. This is actually getting a little bit of promotion from the CDC, I noticed. We've talked about this idea that when you grow up your vaccines and eggs, it attenuates them. We say egg attenuates. Not only does it attenuate, but it actually introduces certain egg-adapted epitopes, and you actually start targeting those.

There's some concern that if you keep getting these egg-based flu vaccines, that you keep boosting these egg-adapted epitopes, and then you're reducing your immunogenicity, as far as your targeting of what you really want to target. In this randomized trial, sera pre- and

post-vaccination with quadrivalent inactivated egg-based, cell culture-based, and recombinant influenza vaccines were collected from healthcare personnel, 18 to 64 years of age, during different years. We've got some from 2018, 2019, about 723; 2019 to 2020, 684. They report that vaccine egg-adapted changes had the most impact on our immunogenicity with regard to H3N2.

In year one, RIV4, so the recombinant - every time you hear R, think recombinant - induced higher neutralization and total HI, hemagglutinin, head-binding antibodies. Then you're going to compare them to the CC, so culture cell-based, so your CCs, think of your cell-based. They're going to look, in year two, among seven different repeat vaccination arms. Basically, we're going to find out the repeat vaccinations with either recombinant or cell-based continues to improve our antibody responses to circulating viruses with decreased neutralizing antibody egg cell ratios, where by giving these cell-based and recombinant, we're boosting away from this egg epitope targeting.

They're going to suggest, and I think the data is consistent with this, that multiple seasons of non-egg-based vaccination may be needed, but do accomplish, a redirection of the antibody responses to these egg-adapted epitopes and can refocus the immune response towards epitopes on the circulating virus to improve vaccine effectiveness.

VR: Normally, I would say, "Is this clinically relevant?" but we know that the egg adaptation does reduce human responses and leads to more disease. I think we should just stop growing the vaccines in eggs. They're suggesting for a few seasons. If you can make enough cell culture or recombinant vaccines to accomplish that, you might as well stay with them.

DG: I think it makes sense. One of the nice things we've talked about is we have good data for flu that there's a nice correlation between the antibody levels, neutralizing antibody levels. In a lot of ways, this is a nice bit of data to give us confidence moving in this direction. All right. When it comes to your vaccines next year, think about this. I will point out, this is 18 to 64. We have some internal data, I'll say, the UnitedHealthcare, UHG level, that it does look like there is a benefit of using the cell-based in this age group. Maybe this is moving in that direction.

Now, as far as people 65 and over, we'll have to see because, as we've mentioned previously, CDC gives certain recommendations. Now, perhaps I'm trying to make a point this week about how viral infections harm us, and not all the harm is in just the first one to two weeks. We have the article, “Risk of Cardiovascular Events After Influenza: A Population-based Self-controlled Case Series Study, Spain, 2011 through 2018.” This is this whole concept, and actually, I should say, the data I talked about before, most of the compelling data in this younger age group is not preventing people from ending up in the hospital with flu, not preventing deaths from flu, but actually targeting this cardiovascular issue that develops post-influenza.

Here, using a population-based self-controlled case series design, individual-level data from electronic registries, this is robust, 2,230,015, the risk of atherothrombotic events in subjects 50 years of age or older increased more than twofold during the 14 days after even the mildest influenza cases in patients with fewer risk factors, and then more than fourfold after

severe cases in our most vulnerable patients. Then, remaining in these vulnerable patients, more than twofold above baseline for the following two months after flu.

VR: Is this something you see?

DG: This is certainly something that we see. I don't think a lot of people necessarily recognize this. I know Mark Crislip used to always harp on this, and it's this idea, we think of the flu and, "Oh, I got the flu, and look, I was just fine," but then you had a heart attack three weeks later, or you had a stroke, and we don't always connect the dots. This data does connect the dots. I think one of the deep dives on *TWiV* talking about how you get a viral illness, and then you're not the same for a while. You may have something else happen, and maybe the clinician doesn't ask, "Have you had the flu in the last couple of months?" because if they did -

VR: We talked about measles exacerbating previous respiratory infections. You don't usually think, "I had flu three months ago, and now it's really bad. The measles is making it really bad." Clinicians need to - in that article we did, they said, "We have to get the history of people with unusually severe respiratory infections." For influenza, what is the frequency, roughly, of cardiovascular events? Do you know?

DG: As we see here, it's based on age and risk factors. It was enough in that under-64 age group that we looked at that this was actually a notable benefit to people getting a cell-based flu vaccine to prevent these cardiovascular issues.

VR: Do you have any idea what the mechanism might be?

DG: We're not sure. The thought, some of the evidence to date suggests that a prior influenza infection destabilizes the plaques. Remember, these are dynamic cholesterol foam macrophage cells in there. The thought is that, as we talked a lot with COVID, you're sick for the first week with the viral phase, but then you can have this post-acute inflammatory phase that continues for time.

VR: Is that what it's called, post-acute inflammatory phase?

DG: Yes.

VR: That's too long for headlines, Dan, and that's the problem.

DG: It is. We call it the immune rebound phase.

VR: No, I don't want the word rebound in there.

DG: OK. I just wanted to throw this in for context because I'm trying to harp on this issue that, when you get a viral illness, you can have problems afterwards. Again, to throw this in here, for context, I wanted to briefly mention the article, “Risk of Death Following Chikungunya Virus Disease in the 100 Million Brazilian Cohort, 2015-18: A Matched Cohort Study and Self-controlled Case Series,” published in *The Lancet*. In this investigation, they looked at 143,787 individuals that had “chik,” chikungunya, compared to matched controls. They looked at all-cause natural mortality up to 728 days after onset of chikungunya, this viral disease, and they're going to look at case-specific deaths.

We're going to be asking, is this just weird with flu, is this just weird with COVID, or is there maybe a common theme here about post-viral diseases, maybe your issue of ischemic heart disease, diabetes, renal vascular disease can go up. They go ahead and report in this population that the incidence rate ratio of death within seven days of chikungunya, if that makes sense, was 8.4. So it's 8.4 increase as compared to the unexposed. Then it's going to drop, but it's only going to drop to 2.26 following these folks out to almost three months.

Now, what's going on? You got over your chikungunya. You're all better now, supposedly, but what are these specific secondary outcomes? The deaths within the first 28 days after disease onset were almost double for cerebrovascular, having a stroke. We're seeing almost a fourfold increase in the risk of diabetes, and we're seeing a three- to fourfold increase in the risk of heart disease. Really sort of echoing what we were describing with flu, and also in line with some of the concerns we're seeing post-COVID.

VR: Again, you might not have the history taken, and you wouldn't know this, right?

DG: I think every doc needs to take an infectious disease history, "Where were you born? Where did you grow up? Tell me what's happened over the last year." I think that's a problem. You come in, I've got chest pain, it's radiating to my left arm, "All right. You're having acute MI." How many people say, "Have you had the flu? Have you had chikungunya in the last couple of months?"

VR: Yes, for sure. That needs to be part of the medical record also, right?

DG: Yes, and then, I wonder if AI will start flagging these connections like, "Did you know the risk that this presentation is actually due to ischemic heart disease is increased fourfold because of this recent viral illness?" Where are we with that influenza? Still actually sitting up pretty high here, still sitting about 16% positive, kind of sitting on a plateau with influenza. Maybe it's starting to go in the right direction, but time will tell, so still pretty high level, still seeing a lot of influenza out there.

Where are we seeing the influenza? I always like to look at the map. What are you doing down there in Texas? Georgia, South Carolina, a little call out to you for not doing a great job. Things look a little bit better in our immediate New York area. Minnesota, you guys just always do a great job. Maybe you don't test, I'm not sure. You can see that we have a lot of flu activity, but it's particularly high in certain areas. I'm heading down to Florida on Saturday. I'm seeing it's moderate to high.

VR: Not bad.

DG: Not bad though, yes.

VR: Some of these states probably don't vaccinate very much, like Texas.

DG: Texas, Georgia, you sort of worry about that as having a big impact on this.

VR: South Carolina.

DG: Yes. I just want to take a moment and just raise the issue. Have we forgotten about getting sick? Because you get all these comments about, "My son," and "He was sick," and then, "He was better, and now he's got a flu. What are they doing in those schools?" I think we got sort of spoiled for a few years with our kids not getting sick. Everyone was washing their hands. May not help that much with COVID, but helped with a lot of other things. People were being a little bit careful. They were testing. If you coughed in public, the dagger eyes looked at you. Everyone's now like, "Oh my gosh, everyone's getting everything."

I just want to point out, with influenza, we can look at prior seasons. We had a pretty high level this year, but not necessarily as high as it was going back to a prior season. We're maybe starting to come down, maybe starting to have another hub, but sometimes we see that. We saw that in 2019, 2020 season as we went into the beginning early days of COVID. There's just lots of stuff. Particularly, kids get sick during the winter. We mentioned the RSV peak, not even quite as high as the last big RSV peak we had. Kids get sick, kids get fevers.

All right. Now, COVID. Welcome to COVID. Still, unfortunately, sitting at about 200 deaths a day, so the average is 2,457. Bunch of people in the ICU, over 2,000 folks in the ICU, about 20,000 folks in hospital.

VR: Is this the weekly numbers?

DG: These are the weekly numbers, yes. Still from BNO, but wastewater. It actually looks like we've come off this hump. It looks like we're going to be moving in the right direction. Hopefully, we're headed in the right direction there. All right. A little bit of an update on COVID vaccines. We talked last week about whether you should be getting those vaccines all in the same arm or opposite arms. We also have an article looking at timing. When should you get that next dose? We have the article, “Comparative Effectiveness of Alternative Intervals Between First and Second Doses of mRNA COVID-19 Vaccines,” published in *Nature Communications*.

I want to point out, we have studies that we've talked about before where people have modeled, sort of said, "We think this," but here they're actually going to look at it. The methods are always critical in evaluating an investigation. Here, the investigators are using a target trial emulation approach. This is a way of looking at observational data, so this is observational data, but you adjust things to try to avoid many of the biases, such as this immortal time bias, other confounders.

This is still observational data. They didn't randomize people to different intervals. They looked at things happened and how did it go. The investigators used this study designed to compare the effectiveness of different inter-dose intervals among greater than six million mRNA vaccine recipients in Georgia from December 2020 to March 2022, so observational, but really a nice large N.

We're going to look at three different vaccine schedules. Number one, you listen to the FDA, you do what they said for Pfizer or Moderna, so about three weeks between doses for Pfizer, about four weeks for doses for Moderna with a little bit of a margin there. Then there's the late but allowable, so your Pfizer is going to go out to 26 to 42 days. Your Moderna is going to go out to 33 to 49 days. Then we have late, so greater than 43 days for the Pfizer, greater than

or equal to 50 for Moderna. Actually, the effectiveness endpoint here is SARS-CoV-2 infection for what that's worth.

They report that, in the short term, the risk of SARS-CoV-2 infection was lowest under the FDA-recommended protocol. Kind of thinking that makes sense because you can get that second booster in quick. The longer term, the late but allowable protocol actually resulted in the lowest risk. Looking at the figures, you can see how this spreads out. You see they're pretty close early on, but if we look at Pfizer-BioNTech, maybe the late but allowable is doing the best as far as the lowest cumulative risk. If we look at Moderna, again, you see this late but allowable, this 33 to 49 or the 26 to 42, just a little bit better, but not huge. Want to put this in context.

VR: It's interesting because we were always saying that the short interval was not a good idea, remember?

DG: We always had this idea in our head that three months was the sweet spot. Here, they're saying maybe two months is the sweet spot.

VR: I don't know about an infection though. That's pretty stringent. I would like to see disease and see if there's a difference.

DG: Because that's our goal. You've got sniffles, you tested positive, we're OK with that. The goal has always been, and we need to keep reinforcing, to prevent disease.

VR: You're not going to prevent infection forever, so that's an unrealistic goal to begin with. I'm not sure this is a good way to look at it. I think they should have looked at disease.

DG: Actually, you have. You have this database, you have over six million folks. The data's out there. By the way, this was *Nature,* so *Nature Communications*. The data is potentially analyzable. I'd love to see that. This is interesting. Not showing a huge difference in all honesty, but it would be great to see disease.

All right. The article, "Early Mortality After the First Dose of Coronavirus Disease 2019 Vaccination: A Target Trial Emulation," was published in *CID*. A problem that we encounter with COVID vaccinations was the hesitancy surrounding safety concerns. I'll take a sip of my water here. We still hear lots of anecdotes about how high-risk elderly patients they're too frail to vaccinate, they're going to die within the two months after getting a COVID vaccination. Now, is this because elderly people with lots of medical problems have an increased risk of death from an adverse vaccine side effect, or is this just a group with a high incidence of mortality to begin with? Are these people dying at a higher rate because they got vaccinated or are they actually dying at a lower rate because they got vaccinated?

Here, the investigators conducted a target trial emulation to estimate and compare risk of death up to 60 days after two COVID-19 vaccination strategies. Vaccination within seven days of enrollment versus no vaccination through follow-up. The study cohort included individuals aged 18 years of age or older enrolled in the VA administration system. We know that's lopsided to the elderly. Eligible to receive COVID-19 vaccination according to guideline recommendations. The outcomes of interest included deaths from any cause and excluding a COVID-19 diagnosis.

This is actually important distinction here because we do not get any credit for saving people from COVID. You just risk getting penalized if there's a safety issue with the vaccine. They included 3,158,570 veterans; 364,993 received the vaccination. At 60 days, there were 156 deaths per 100,000 veterans among those that were vaccinated versus 185 deaths in the group that did not get vaccinations. Remember, this is no credit for preventing the COVID, so this is pretty impressive.

VR: You prevent COVID, you prevent deaths from other things.

DG: Interesting enough.

VR: But there are not really other things that are related to sequelae of COVID, I presume.

DG: They go ahead and they exclude those with a COVID infection in the first 60 days, and we're going to calculate an absolute risk difference. We're going to look at a relative risk of 0.88. Interesting, if you get a 12% reduction from all causes, even when you just forget about COVID-19.

VR: By vaccinating.

DG: By vaccinating.

VR: That is preventing COVID and therefore has some effect on other diseases, other causes of death?

DG: Potentially, yes. As we've talked about, people don't just die from the acute COVID. Getting COVID can have other -. Interesting data. I think the big thing here is we have - remember these people out there are like, "I will guarantee you that in the next six months, 21% of the people that have COVID, they'll be dead," but they're not. They're not.

VR: They're full of it. They don't know what they're talking about.

DG: Vaccines are safe, vaccines are effective. As we see here again, vaccines are safe. All right. COVID early viral phase. Still number one, Paxlovid. We've talked a little bit about some of the challenges. The Paxlovid Paxcess program to help people get access there, work with your pharmacist, work with this program. Remdesivir, we don't use a lot of it, but individual the other day got on the horn, so to speak, with the ER doc. Spoke to a patient of one of my colleagues who was at the ER, issues with drug-drug interactions, and we went ahead and did a three-day course of remdesivir. Molnupiravir is another option, no renal adjustments, no drug-drug interactions. Still, in some settings, convalescent plasma can be an option.

Week two, the cytokine storm week, the early inflammatory phase, steroids at the right person, the right patient, right time, right dose. Remember, there's risk to steroids, so we don't just give this out willy-nilly. We also don't want to do it during the first week. We have some anticoagulation guidelines, pulmonary support, Remdesivir, if still in the first 10 days, immune modulation, perhaps tocilizumab, growing safety data on that, and let's avoid using antibacterial agents to treat our viruses. There are cases of co-infection. We've talked a little bit about the importance of identifying and treating those, but not just throwing antibiotics at viruses.

Today, I'm actually going to spend a lot of time on the late phase. This is going to be a primer, I think it's called. My plan is a special focus on the recognition and management of Long COVID, but let me start with the article, "Burnout, Compassion Fatigue, and the Long Haul of Caring for Long COVID." Now, in this article, the Family Health Center of San Diego shares their experience and efforts from clinicians who have participated in their CDC-funded three-year continuing professional development initiative.

We've talked previously about the issue of burnout in medicine, and they echo this by referencing that recent reports have found that 52% of nurses and 20% of physicians are planning to leave clinical practice. We have before us millions of Americans suffering from post-COVID conditions, and they point out that Long COVID is not the first, but part of a history of post-infectious debilitating conditions that we see after a number of infections. They suggest that part of the problem is that, after acknowledging the patient's suffering, clinicians are often left not knowing what to do for them.

This is going to be part of my initial educational efforts to target not only patients, because you can have a conversation, but also providers. Hopefully, this will be sharing a clinical approach to post-acute sequelae of COVID. I know I mentioned on - it was Monday of last week I had a discussion with David Putrino, and I'm going to be meeting with the education folks at Mount Sinai tomorrow morning, talking about creating an educational resource for a lot of clinicians that want to be able to interact with these patients, want to be able to not just acknowledge their suffering, but want to know how to approach diagnosis and want to know how to help these people. Part of my efforts is if you feel empowered, you're not going to want to leave, you're not going to feel burnt out, you're going to feel hopefully excited.

VR: Are you going to retire? Are you going to be one of those 20%?

DG: No. Every so often I joke with my family that I'm going to retire, and they just laugh.

VR: OK, good.

DG: While my focus here is post-COVID, or post-COVID conditions, PCC, much of what I'm going to talk about actually can be helpful, I suggest, for post-infectious sequelae in general. I call this PIS. That's my acronym.

VR: It's not a good one.

DG: It's not a good one, I know. The PIS Center of Excellence. Some of us are using pre-visit questionnaires. This could be a great way of getting lots of this information. Now, I personally like listening to the patient tell their story, so often, I listen, and then I try to extract critical information from the patient's narrative. I'm still one of those individuals that just enjoys that interaction and listening and hearing the story in that narrative form. I think I get a lot from that, maybe more than what a questionnaire will give me, but what information do I think is helpful? What am I trying to pull out of that story?

Usually, I try not to interrupt. I'll let them go for a while, but then a few directed questions. When was the first COVID infections? When were the other COVID infections? Because often, people have multiple ones. Then what happened with the infection or infections in terms of symptoms, severity, treatment? I want to know, did someone give you steroids? Did they

treat you with antibiotics? Did you get treated with an antiviral? Did you end up in the hospital? Then, and this ties really directly in, so what are the post-infectious concerns? This might be done by organ systems, but I like to leave this open and just listen.

As I point out, we are still learning a lot from our patients, and I think we should continue to do so. I might ask targeted issues, questions about how is this impacting your ability to perform activities of daily living? Are we seeing post-exertional malaise? Are you able to be active? If you're active, what happens during the activity? What happens after the activity? What happens on those times when you need to push yourself a little bit harder? As you'll see, I'm going to come back. I really want to detect whether or not post-exertional malaise is part of presentation.

Also, interesting enough, cognitive issues, you think people would just put that out. Sometimes it takes directed questioning, and you ask, "Are you having word-finding difficulties? Are you experiencing this brain fog?" Now, making the diagnosis, and I think this is important. We have our conversation, we get this narrative. Before I go past this point, I'll start to ask this question.

Does this sound like a post-infectious issue, or is maybe something else going on that this history and presentation has suggested? What was the timing in terms of symptom onset and timing in terms of the duration of symptoms? Are these ongoing symptoms? Are they fluctuating? Was there a period when you felt better before the symptoms returned? Did the symptoms start three to four weeks post-infection or just continue right from the start? Then, to make this distinction between acute, medium, and Long COVID, has it been 90 days since the infection?

I'm still hopeful during that less than 90 days, but I'm listening at this point. Does this sound like you were hiking in the woods and I'm worried about a tick-borne illness. Does this sound like it might be a thyroid or an adrenal issue. Visual disturbances. Are you actually having areas, describe that woman with the pituitary tumor. You don't want to miss other things just because the person had COVID.

Now, some people will use a formal scoring system to diagnose post-COVID conditions. I'll leave a link. There was a *JAMA* article. I tend not to. I feel like that might be helpful for certain research settings, I might do some cognitive testing, but I tend to think about the CDC definition as well as the WHO definition of Long COVID. Defined as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection with these symptoms lasting for at least two months with no other explanation.

I then might throw in some diagnostic testing. I think there are certain baseline tests that I suggest. Additional ones are often prompted by the initial evaluation. Talk about the basics first. Might do a complete blood count. Might do a comprehensive metabolic panel, a C-reactive protein, erythrocyte sedimentation rate, D-dimer, anti-nuclear antibodies, ANA, an EBV serology panel. We've talked about how there's this correlation with these very high EBV serology levels. CMV IgG. Again, those high levels we've seen. Serum serotonin, we've talked about seeing in low levels. Thyroid, so free T4 and TSH. Maybe testosterone in certain circumstances.

Sometimes, if I get a history or not, I might ask them to do the NASA Lean Testing, starting to look for dysautonomia. Maybe pulse oximetry testing at rest and with activity. Blood pressure testing with this. As I mentioned, sometimes targeted testing, someone who's maybe been in the ICU or who's had some significant pulmonary symptoms. There might be chest imaging. We might even, at this point, be getting a particular specialist involved. If someone has a lot of tachycardia, a lot of cardiac issues, I think I'll sort of say, at this point, "You don't need to do it alone."

A lot of times, this is going to take a multi-specialty approach. Maybe that can also help with the burnout and the isolation, "Let's find your colleagues that want to work with you, want to help your patients here," but then back to the diagnosis. The story makes sense, maybe there's some objective data that's consistent, which is helpful for the patients, also helpful for us. Then we actually have some options when it comes to diagnostic codes. We have COVID-19, U07.1. We have PASC, that's your post-COVID-19 condition unspecified, U09.9.

As I mentioned, we're not just talking about COVID, so we might be talking about sequelae of other specified infectious and parasitic diseases. That's our B94.8. Interesting enough, we might want to be thinking about symptoms. Is this a chronic fatigue presentation, an R53.82? Maybe it actually falls into this myalgic encephalitis chronic fatigue syndrome, which is a G93.32. This is an area where I know a lot of people struggle because you really have to have a conversation with your patient.

Patients are sensitive to being labeled, and a lot of times your diagnosis will be perceived as labeling, and patients have access to their records, so talk to your patient. Try to get a sense. This is going to have to be an honest discussion here because you're going to have to give them an honest diagnosis, but be sensitive. Have this discussion. Don't just have them surprised when they see something show up. A lot of times when it comes to disability and insurance, they look at PASC, they look at the COVID. They're like, "Yes, but what's the disability?" so you may be wanting to look for a diagnosis like a dysautonomia, an arrhythmia, a chronic fatigue.

All right, so now we feel comfortable with the diagnosis, what about treatment? This is where I have to say it gets even tougher. Part of this is going to go back to history where we'll ask, who have you seen for these issues? Usually, people have seen several providers. Have you gone to other centers? Have you gone to Long COVID centers? What have they tried? What have you tried? This is going to require you to create a certain amount of chemistry because people may not always be excited to share what they've done. They may be embarrassed. They may have had negative interactions with their healthcare system.

Then I'm going to move into what I'm going to call three different types of interventions. Number one, and limited here, evidence-based interventions. This is really where we want to be as much as possible. I want to point out, if a specific diagnosis is identified, such as POTS, dysautonomia, cardiac issues, sleep apnea, we have specific evidence-based therapeutics. We can address those issues. If POTS is identified, we might be talking about increased water and salt intake, certain exercise programs such as lower extremity strengthening to avoid venous pooling, maybe compression stockings, certain medications such as beta-blockers, midodrine, fludrocortisone.

Remember, as we go down this road, make sure you've identified that post-exertional malaise because the last thing we want to do is trigger something that we think is harmful. We've talked about biopsy studies where you might actually be inducing necrosis if you're not careful going down this road. The next, vaccination, post-infection as a therapeutic. This is going to reference our study that I was one of the authors on with Mount Sinai and Yale where we had people with Long COVID get vaccinated. Remember, the majority, but just the majority, 60% were better, 20% nothing, 20% were actually worse. In that study, we started to identify maybe certain serum levels of things that might predict your response to vaccination. Vaccination, maybe, but this is going to have to be a joint decision because one in five are going to get worse.

VR: That's a tough one.

DG: It is a tough one. Three out of five get better, but still, and just to harp on, really important to identify post-exertional malaise. One of our therapeutic things could be not triggering these episodes, not allowing a patient to continue to hurt themselves. If there's no evidence of post-exertional malaise, then physical therapy and real rehabilitation can be employed. We actually have some studies supporting that. If PEM is present, so post-exertional malaise is present, then no, we're not going down that road. We could actually harm them.

Another thing we've talked about, sort of surprising, but now a couple of studies, the bifidobacterium probiotics. Still trying to understand what's going on there, but 10 billion units, two times per day, but sometimes it requires a slow introduction, maybe 5 billion and then 5 billion twice a day, and then ratcheting our way up. Interesting enough, I have at least one patient that is getting the CYB-01, the probiotic-prebiotic formulation that was studied in Hong Kong. She has a friend that flies back and forth, smuggles it into the country. It's like the *Dallas Buyers Club*. I have no involvement.

Then we've talked a little bit about melatonin, 3 to 5 milligrams for bed, maybe helping with insomnia, but maybe actually having some impact upon cytokine levels. Again, some evidence there. Then we get into maybe the broader world. I'll say interventions extrapolated from evidence, but still not evidence-based. Still need to study this. Remember, 90% of our great ideas are ultimately not great ideas, so don't hang your hat. We need to fund these studies.

We've talked about folks with low serotonin. We've talked about how the SSRIs just really aren't giving us that bang that we hope, that response that we want. Sometimes we're actually working with our colleagues to use SSRIs at slightly higher doses. Listen, if you're not used to using these medicines, now is not the time to start on your Long COVID patients. Work with a colleague who's knowledgeable, flexible, and able to help patients here. Maybe using medicines that don't rely on just SSRI activity, so things like duloxetine, Wellbutrin, venlafaxine. Even we have folks using guanfacine before bed. There's some case reports of methylphenidate.

Remember, just a word of caution here. Don't just go using these medicines if you're not familiar and comfortable with using them. In patients with low cortisol, some folks are looking at glucocorticoid and mineral corticoid replacement. Again, evidence extrapolated. We don't have those studies evidence-based showing that this is actually associated with better outcomes.

What about nattokinase? This is something that a lot of the groups talk a bit about, this 2000 fibrillinic units BID used in patients with post-exertional malaise. This is based on the idea that maybe that post-exertional malaise is driven by mitochondrial dysfunction and maybe this nattokinase, so extrapolate it. And histamines. If we're seeing allergic or mast cell activation syndrome-like presentations, maybe even in those contexts using some therapies extrapolated from the MCAS. Box breathing.

VR: What's that?

DG: We're all going to practice box breathing together now. It's an interesting approach and a lot of the groups have fallen into doing this. Think of a box in your head. You breathe in for four seconds, hold it for four seconds, breathe out for four seconds, hold four seconds, and then repeat. It's this mindful breathing. Actually, it reminds me in a lot of ways of some of the yoga-based breathing, this mindful breathing. A lot of patients are reporting that it helps to settle them, particularly when they're feeling the buzzing, when they're feeling the rapid heart rates. Maybe we're getting some kind of a parasympathetic impact. Maybe we're extrapolating here from the evidence of the impacts upon the autonomic nervous system. This is all evidence extrapolated, but not evidence-based.

VR: This you do for a short period of time, right?

DG: You do it every day for just a few minutes of box breathing.

VR: It's boxed because it's one, two, three, four, I guess.

DG: I think it's like four, four, four, four, so you think of this box in your head. Unfortunately, we still have a number of anecdotal-based interventions. People have tried these. They've found a benefit. We're still waiting for more compelling evidence, but we have the NAC, N-acetyl cysteine, that's 600 milligrams twice a day. We have that low-dose naltrexone, the LDN, working with your compounding pharmacy and titrating up very slowly from 0.5 milligrams to 4.5 per day.

Some people are in low-dose aspirin. Sometimes we're actually stumbling across dietary changes that seem to correlate with improved outcomes, particularly when people avoid those high-sugar, those high-carb diets. Sometimes it'll be the nightshade vegetables. A lot of people will find their personal triggers. I'm hoping that is helpful, give people a little bit more direction, maybe a little less burnout. Hopefully, as we learn more, we're going to expand our evidence-based section.

I will conclude, as I have been doing for quite a while, no one is safe until everyone is safe. We are right now in the middle of our ASTMH fundraiser, where during the months of February, March, and April, we double your donations up to a potential maximum donation of $20,000.

VR: Thank you for the fundraiser from MicrobeTV, which just ended.

DG: Thank you.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Rachel writes, "A friend has their first known bout of COVID. They're mid-60s, healthy, vaccinated. Their friend took Paxlovid within five days of symptom onset and was in the ER later that day. After learning about that experience and being told by their MD that about 30% of people have some kind of reaction to Paxlovid, my friend is not taking Paxlovid. Is it true that 30% have a reaction? Wouldn't that be flagged in the safety research and what do you make of my friend's decision?"

DG: This is one of those, I like when this happens like in an academic center because then I could always say to that, "Is it really 35%? That seems really high. What study are you quoting?"

VR: That's right.

DG: Then you just see this blank bit of embarrassment. Maybe they would know I was in the hospital and not say that, but let's talk about that. The people that we're giving Paxlovid to, in general, we're talking about high-risk individuals, individuals who have COVID, the COVID might progress. We can actually look at the EPIC-HR data and ask a couple of questions. Really, how many people had any adverse event in the Paxlovid group? About 22%. What about the people that didn't get Paxlovid, it was 24%. People with COVID feel crummy. People with COVID often end up in the ER.

When you look at any adverse event, it's actually a little bit lower if you get the Paxlovid versus not, but still about a quarter of people are reporting some issue. Now, serious adverse events in the Paxlovid group, if we look at EPIC-HR, down about 1% or 2%. In the people that didn't get Paxlovid, 6% or 7%. Serious bad things. Even if we go back to like maximum grade three or four, not quite as bad, twice as high in placebo, but what about people ending up requiring hospitalization? This person went to the ER, that's not so bad, that's OK.

What about COVID-19-related hospitalization? If we looked at about an equal number, about five that got Paxlovid ended up getting hospitalized, 44, almost 10 times as many end up in the hospital. What about deaths? Nobody that got Paxlovid died. Nine people who didn't get Paxlovid died.

I have to say, it's irresponsible for that clinician to throw out this 35%. Physicians get all huffy if you ask, "Really? That seems high. What are you referencing? Where did you get that number?" Maybe they'll storm out and make you leave AMA or something. Please don't do that. Paxlovid is associated with better outcomes. People with COVID have issues. People with COVID end up going to the ER. Giving the Paxlovid, particularly someone who's sick enough and has risk factors that might end up in the ER, the Paxlovid is the right thing to do.

Don't stop it. Have a conversation, figure out what the adverse event is. Maybe you need to switch into molnupiravir. Maybe you need to do remdesivir because they are there in the ER where you can access IV therapy.

VR: Anne writes, "Can you comment? My patient got Paxlovid for free versus paying $1,000 by signing up for an account with Pfizer which allows them to share her information with advertisers. Recommended she do this by Wegmans pharmacist."

DG: We've talked about these different programs, so the Pax, the catchy Paxcess program, P-A-X-C-E-S-S. It is tough. Sharing your information, that's not great, so, yes.

VR: Also, Anne, who's an MD, writes, "Do you recommend booster pneumonia vaccine with Prevnar 20 in over 65-year-old patients as they do in up-to-date or not per ACIP, i.e., patients who already had a pneumovax and a Prevnar 13?"

DG: We're recommending the 20.

VR: Amanda writes, "Regarding seasonal administration of maternal RSV vaccination, per the CDC ACIP guidelines, pregnant persons 32 to 36 weeks should receive a dose of RSV vaccine using seasonal administration which they define as September through January for most of the U.S. Now that we are at the end of January, I'm wondering if the vaccine should still be offered to pregnant persons through February or even March since RSV season typically continues till the end of March and infants are still at risk of getting infected. CDC does say that local health departments may determine the best times to start and stop maternal RSV vaccination, but when I check the local health department sites, they just reiterate the CDC ACIP guidelines with no additional information specific to the reason."

DG: This is a great question. Thank you for asking this. There's the nuance we talked a little bit about. The RSV season is not always the same period of time. It's not always the same period of time in different regions, and people don't always stay put. I'm heading down to Florida on Saturday. You may decide to take a trip with your child. If the RSV season is continuing as it is right now, we're on our way down, but it's still going to probably continue into March, you want to nuance this a little bit. We may be past January. We probably still want to do a little bit more in the last trimester, the vaccinations, but we're probably getting near the end of that.

VR: Roberta writes, "I'm not sure I heard you correctly on Episode 1082 and another episode where an immunocompromised individual had a question about getting re-immunized after a three-month period from infection or previous vaccination. I thought I heard you suggest an additional COVID vaccine if immunosuppressed and three months out from previous vaccine or infection due to short duration of peak antibody response. I'm thinking of doing this as I am immunosuppressed, asplenic, diabetic, and one kidney. My last vaccine was Moderna in October, and 22 days later, it came down with COVID."

"First bout in 2021, I received monoclonal in '21, and once daily, Paxlovid in '23, and did well. I was thinking of obtaining the Novavax vaccine before I travel in March. I signed up at a local pharmacy for a vaccine today and got a message that it was canceled. I called them up and explained to them that I am immunocompromised, and they said their system would not allow them to fill the prescription. It blocks them unless greater than a year, and that insurance, Medicare, would not pay. I spoke to a pharmacist colleague of mine who works for a different chain, and he said they had no restrictions upon how many times they could administer every three months, but insurance might bounce it back. They don't carry Novavax. So frustrated. I carry Paxlovid with me when I travel, and I mask in airports, planes," and Roberta is an MD as well.

DG: Very frustrating, and so everything you're laying out here is true. As we've talked about, the antibody levels wane, so that benefit we're seeing is probably a three to four month. If you're immunocompromised, you're already probably dropping quite low. You probably haven't really gotten maybe the same level as someone else. You described a number of issues, so I think it makes sense. The science, it makes sense if you consider getting a second dose.

Again, the reality is insurance, Medicare, they may not cover it. They don't necessarily cover everything that makes sense scientifically. They've got their programs. It's a bit frustrating because you wanted to get Novavax, and now the place where you can get it has this policy. You may want to ask and return the call and say, "If I'm willing to pay for it, if I'm willing to shell out the $120, whatever it is, would you then allow me to do it?" That may be ultimately what it takes.

VR: You're saying we are beholden to the insurance companies basically for our health.

DG: We're beholden to the insurance companies to have them pay for stuff, and this actually unfortunately goes back to a Bush. I actually liked the second Bush. He did tremendous things in Sub-Saharan Africa, tremendous things with global health, but there was this ruling where the insurance companies are protected. If you have a bad outcome and end up in the hospital and you then say, "Hey, I wanted to get this COVID shot and I couldn't," basically you can sue the health insurance for the cost of the COVID shot.

VR: One more from Gail. "Would you recommend that people who are over 65 and immunocompromised get a second booster of the latest COVID vaccine 2023, and if so, how long after getting it last year?"

DG: Yes. We talked a little bit echoing that last question. You get this boost probably three to four months. If you jumped in early in September and here we are in February, you're far out. I do have a few patients that are opting to do a second boost and that's reasonable. Certainly, you don't want to mandate that everyone has to get two boosts, but there's certain individuals that tolerate the vaccines quite well and they want that extra degree of protection.

VR: If you're willing to pay for it yourself, you can get boosts every three months if you want, right?

DG: Yes.

VR: As long as your doctor -

DG: They're licensed vaccines. Talk to your doctor.

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

DG: Oh, thank you, and everyone, be safe.

[music]

[00:59:02] [END OF AUDIO]