This Week in Virology

TWiV 1052 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.

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From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1052, recorded on October 12, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today here in Boston, Massachusetts, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Daniel, what are we doing in Boston?

DG: We are recording at IDWeek, Infectious Disease Week, where hundreds of infectious disease specialists, aficionados, people from industry are gathered to learn about the latest and greatest in infectious disease.

VR: It's quite a meeting, really interesting, and a good place to do a podcast, like a weekly clinical update.

DG: I think that would be great.

[laughter

DG: All right. I'm going to start off with my Boston-appropriate quotation. Those who are familiar with Boston, "I guess no true Bostonian would trust a place that was sunny and pleasant all the time. But a gritty, perpetually cold and gloomy neighborhood? Throw in a couple of Dunkin' Donuts locations, and I'm right at home." That's Rick Riordan.

VR: Who is Rick Riordan?

DG: Anyone know?

VR: I don't know.

DG: He's a writer. He writes the *Percy Jackson* books. There are a lot of teenage books. Actually, I have to say, they're great, Vincent. His son, Rick Riordan's son, both hated history

and suffered from dyslexia. That was his inspiration to write these books, where the heroes, the protagonists of the stories, suffer from dyslexia. It's a great way to learn about mythology. Great stuff. Plug for the books.

VR: The only thing I disagree with is Dunkin' Donuts. I'm not a big fan of Dunkin' Donuts.

[laughter]

DG: That's how I know I was in Boston this morning, when someone grabbed me coffee, and they said, "Oh, the line was too long at Starbucks, so I went to Dunkin' Donuts, where there's one on every corner."

VR: There's a really good place not far from here. I don't remember the name of it. Not a chain, it's good. Sometimes it's best not to look for the chains.

DG: All right. Let's start off with a little bit of good news. Malaria. Our listeners may be aware that there are now vaccines for malaria. The first approved and widely distributed was RTS,S, which is sold under the name Mosquirix, and produced by GSK, a pharmaceutical company located in London. I think they put that in there. This vaccine has been given to nearly 1.7 million children in Ghana, Kenya, and Malawi since 2019. There's supply issues, so the vaccine can't meet the demand.

Now, we have another vaccine, R21, which met the WHO's target of 75% efficacy of preventing the disease in a trial of 4,800 children, who each received three doses, that seems like a theme, before a seasonal malaria peak. A booster dose after 12 months maintained protection. Just to give you a sense, that old vaccine, $9.80 per dose. This new vaccine, $2 to $4 per dose.

VR: That's great.

DG: Actually, much easier to produce. We should meet our supply issues, and it should be available in mid-2024.

VR: These are delivered intramuscularly?

DG: Yes.

VR: Great. That amount of protection is great. 75%, right?

DG: It's tremendous, actually. Protection against clinical disease and RSV. I'm going to say, everyone pay attention to this, because I think this is really important. Why are we talking about RSV all the time? *MMWR, "*Disease Severity of Respiratory Syncytial Virus Compared with COVID-19 and Influenza Among Hospitalized Adults Aged Greater Than or Equal to 60 Years, IVY Network, 20 U.S. states, February 2022 through May 2023," posted on October 6.

The big takeaway from this report was that during February 2022 through May 2023, while hospitalizations for RSV were less frequent, they were associated with more severe disease than were hospitalizations for COVID-19 or influenza, including receipt of standard oxygen, high-flow nasal cannula, ending up on a vent, ending up in the ICU. Just to go through, to

characterize this severity, they looked at 5,784 adults, 60 years of age or older hospitalized with an acute respiratory illness, and either a laboratory confirmed RSV, SARS-CoV-2, or influenza.

They prospectively enrolled from 25 hospitals in 20 U.S. states. They're going to go ahead and they're going to compare RSV disease severity to COVID in our immune world here and influenza. They're going to look at folks that require standard-flow, that's less than 30 liters of oxygen per minute, high-flow nasal cannula, and other forms of non-invasive ventilation, such as your CPAP, your BiPAP, ICU admission, and ending up on a ventilator or death.

Now, they do point out that less people end up in the hospital with RSV compared to COVID, compared to flu. If you actually compare the outcomes of those folks hospitalized with RSV, they're more likely to require oxygen therapy, more likely to end up with high-flow nasal cannula, more likely to end up in the ICU. I think this is the big one. They are twice as likely to end up on a ventilator or to die if you compare that directly to influenza.

VR: Why do you think they're less likely to be hospitalized?

DG: I think one thing is just a prevalence. There's less RSV out there. I think that's one of the issues. If we had the same amount of RSV, you'd say, "Oh, well, it's less likely to get you to the hospital." If you look at RSV infections, we see less of them, but when we do see them, if a patient ends up in the hospital, and this is a big change, if they end up in the hospital with COVID, they end up in the hospital with flu, if they end up in the hospital with RSV, RSV is twice as likely for them to end up on a ventilator, end up not surviving.

VR: How do COVID and flu compare in this study?

DG: Let's see in this study, because we have the table. [chuckles] They actually look at about 4,734 patients with COVID-19, 58.2 are requiring oxygen. Flu patients, they have 746, 65.8, sort of similar, standard. High-flow versus non-invasive, similar, about 12%, 14%. ICU admission, pretty similar. Then you get a little bit of a difference. 10% of the COVID patients die, 7% of the flu patients die, 13.5% of the RSV patients die.

VR: Because people are always asking, how does COVID compare to flu? There you go. It's very similar.

DG: It's similar. I think this is telling because everyone keeps saying, "It's over. No one's dying of COVID anymore." We're going to get into numbers in a minute, but as you see in the study, 10% of these individuals who ended up in the hospital with COVID did not survive. They either ended up on a ventilator or they died. A lot of times, as people probably know, we're making the decision ahead of time, should we even go ahead and put this person on a ventilator? Because the chance of getting off a ventilator is single digits, very small for most people.

Yes, I feel like you preempted this. What is going on with COVID? What are the numbers like? Actually, now I've started - I was talking this morning about, I used to wake up in the morning and look at my Johns Hopkins, or maybe my Worldometer and compare the two, what's going on with COVID? Now, I look at *BNO* on X or Twitter, whatever it's called these days. Once a week, we get a nice update on what's going on. New cases still, about 250,000 new cases here in the U.S. last week. States report again, 50 out of 50. In hospital, we have 15,655. In the ICU,

we have about 2,000. That's actually up about 10% from last week. New deaths, we're seeing 1,466. We're still seeing over 200 deaths a day in the U.S.

VR: These individuals who are dying, what distinguishes them from others?

DG: The majority of deaths are in individuals over the age of 65.

VR: They are vaccinated?

DG: At this point, the differentiator is not immunity or not. People have been infected. They've been vaccinated. Very hard to find someone who's not been infected or vaccinated. What's the big difference? They're older individuals. They have medical problems which put them at increased risk. Then what's the biggest one, not given early antiviral therapy.

VR: We can't repeat that too much. Can we? [chuckles]

DG: We keep saying that. That's the big thing. Everyone's got immunity. There's only so much we can do at this point with vaccines because we've got that immunity. We get a little bit of a boost. What's a big? Like 80%, 90% reduction for these folks who are ending up in the hospital. Look at these numbers. 1,466 deaths. That should be reduced. Two-thousand people in the ICU. Over 15,000 in hospital. Those numbers should be reduced if we can.

VR: Someone at this meeting told me that 90% of those deaths, those people never got an antiviral.

DG: Not only is that true, but what's really disturbing is if a patient goes to their doctor and says, "Hey, I've got COVID. I understand there's this medicine, this Paxlovid," majority of those providers are not actually giving their patients access to the medicine. We have a tremendous educational challenge there.

What about the future? We can go into wastewater. I have to say, everyone else is doing really well except the Northeast. I'm blaming it on you Italians and the Columbus Day celebration. Just to say that there, we were going in the right direction, but in the last week, we're actually seeing the country as a whole moving upward. It's all thanks to those Northeasterners.

VR: You're a Northeasterner, too.

[laughter]

DG: I celebrated Native American Day, so I did not contribute to this.

[laughter]

DG: We are going to move right into the early viral phase. We sort of hit on this. We talked about this a lot last time. We'll go through this in detail because there's really a nice article that came out. The article, “Nirmatrelvir-Ritonavir and COVID-19 Mortality and Hospitalization Among Patients with Vulnerability to COVID-19 Complications,” published in *JAMA Network Open*.

This article got a bit of media attention because it seems to feed into this idea that the virus has changed, it's no longer working against the new variants. I'm just going to go through this a little bit and then give some context. These are results of a cohort study of adult patients in British Columbia, Canada, between February 1st, 2022, February 3rd, 2023. Patients were eligible if they belonged to one of four higher risk groups. They break these down into CEV, so clinically extremely vulnerable 1, clinically extremely vulnerable 2. Then they look at these different groups.

Patients with COVID-19 who received Paxlovid, so the nirmatrelvir/ritonavir, were matched to patients in the same vulnerability group, same sex, same age, same propensity scores. The primary outcome, I think this is important, was death from any because or emergency hospitalization with COVID-19 within 28 days. That's something I think we've harped on repeatedly. When someone talks about an outcome, we just have to ask, what outcome? What efficacy are we talking about?

Anyone who ends up, I need to go to the hospital, remember, this is Canada, think about what may or may not make someone do that, they go ahead and they look at 6,866 individuals included in the study. The mean age was 70. We have a range, 57 to 80 for the interquartile range. Compared with unexposed controls, treatment with nirmatrelvir and ritonavir was associated with statistically significant reductions in the primary outcome in the CEV1 group, so that's severely immunocompromised. We have 560 folks there. In the CEV2 group, that's a moderately immunocompromised group. That was a large, 2,628.

The CEV3 group, there was also a reduction, but in these 2,100 patients, it did not reach statistical significance. A couple things for us to look at. It was nice to get a chance to speak to some of my Canadian colleagues this morning. Nirmatrelvir/ritonavir-exposed individuals did not require a positive PCR test. They just assumed that, well, if they got the drug, that was why they got it. Prescribing physicians were required to make sure their patient tested positive within five days prior to prescribing the drug. Not five days from symptom onset, but five days from a positive test.

We can walk through the timing here. The big thing is to put this in context. We have patients here who may have had a positive test. They may have had symptoms past the window for Paxlovid benefit, but we're still seeing it. I think a big thing here really is that timing. One of the things I do want to point out is we now have over 449 studies looking at real-world effectiveness of Paxlovid, but which ones hit the media? It's the ones where the sky is falling. In one of the subgroups, they did not reach statistical significance. It doesn't work, but that's not the appropriate or right conclusion.

We're in that first week. This is acute viral infection. We're going to go through the different treatments. Number one, Paxlovid. We talked a lot last week about studies looking at, is there really any a rebound? Should we worry about it? The simple answer is no. Paxlovid is the number one recommended treatment by the NIH, by the CDC, by all the guidelines across. Number one, Paxlovid. Number two, we have remdesivir. Number three, we have Thor's Hammer, molnupiravir. Four, convalescent plasma, just a treatment option for the immunocompromised with no other options.

Then let's avoid doing harmful and useless things. This one was so painful for me to read, Vincent. Can you imagine? “Antibiotic use among hospitalized patients with COVID-19 in the United States, March 2020 through June 2022,” published in *Open Forum Infectious Diseases*. These are the results of a retrospective study to describe antibiotic use among U.S. adults hospitalized with a COVID-19 diagnosis.

I understand to some degree that a patient shows up in the ER, the ER doc sees pneumonia, they don't yet know that it's a COVID-19 pneumonia. Maybe they get that first dose of the antibiotics, but what happens once they're hospitalized? Once an ID doc can get involved, once an internist can get involved, once the admitting hospitalist takes over? Despite a decrease in overall antibiotic use, most patients hospitalized with COVID-19 received antibiotics on admission, 88.1%, regardless of their critical care status.

VR: Do they continue to get antibiotics or is it just one dose?

DG: No, so that's the problem. It isn't just one dose. This isn't just getting a dose in the ER. This is they get admitted, they're not necessarily, I understand too, the other is they end up in the ICU. They're in the ICU, they're super sick, you're not sure, you're erring on the side of antibiotics because you don't want to miss that septic patient. These are general floor patients, 70%, 80% plus getting a course of antibiotics for a viral illness.

VR: Presumably they should have received an antiviral before getting in the hospital.

DG: I think that's the big thing, is that they shouldn't end up getting these antibiotics. They should get antivirals. Then they don't end up in the hospital, and then we don't end up with these problems. Now, there's another, and I think this is worth bringing to people's attention if they've been following this, and this is the article, “One Week of Oral Camostat Versus Placebo in Nonhospitalized Adults With Mild-to-Moderate Coronavirus Disease 2019: A Randomized Controlled Phase 2 Trial,” recently published in *CID*.

VR: Daniel, can we tell folks what camostat does?

DG: I'm going to let you do that. I was hoping you'd - Let's talk about viral entry and the different paths.

VR: When the SARS-CoV-2 virus binds the plasma membrane in a respiratory tract cell. Also, on the surface of that cell is a second protein called TMPRSS2. It's actually a nice name, TMPRSS2.

DG: It is, yes.

VR: That is a protease that cleaves the spike of SARS-CoV-2 particle. Then the virus fuses with the cell membrane and the RNA goes in. Entry occurs at the surface via this TMPRSS2. Camostat is an inhibitor of TMPRSS2. That's how it works. Those cells in the respiratory tract have TMPRSS on the surface and that's where you're inhibiting entry. I'm glad to see this because a long time ago, camostat was going to be trialed and then the hydroxychloroquine thing happened and people got scared of looking at inhibitors of entry. This is good. Tell us what happened.

DG: Not good.

[laughter]

DG: No, this was interesting, too, because there was a lot of ideas that maybe as we had different variants, this TMPRSS pathway was becoming more important. Some of the people thought, OK, maybe even early on, if there was evidence that it didn't work, maybe now we have a variant that's going to be more susceptible, so let's go ahead, let's do the trial. They do the trial, phase 2 trial, 216 participants, 109 randomized to camostat, 107 to placebo. Forty-five percent reported less than five days of symptoms at study entry. We kind of want that early. Twenty-six percent met the protocol definition of higher risk of progression of severe COVID-19. Younger, median age was 37.

Unfortunately, no significant differences in the levels of SARS-CoV-2 RNA on days three, seven, and 14. Through day 28, 5.6 participants in the camostat arm and 4.7 participants in the placebo arm were hospitalized. One participant in the camostat arm died. No one in the placebo arm died. Phase 2 study, non-hospitalized patients, mild to moderate COVID-19 oral camostat did not accelerate viral clearance or time to symptom onset or result in reduced hospitalization.

VR: I have an explanation or potential explanation.

DG: Go for it.

VR: The problem is that if you inhibit entry at the plasma membrane, the virus can be taken up by endocytosis and enter from an endosome because there's a protease in the endosome, it's called cathepsin L, which will cleave the spike. That's probably why this didn't work. If you wanted to inhibit entry, you need to inhibit both TMPRSS2 and cathepsin L. There are drugs that will inhibit, and one of them is hydroxychloroquine, but we don't want to use that because it has -

DG: That was one of the challenges, I think, early on, is people were saying, "Maybe you need to use the two drugs together." The challenge, and I think it's important to remind everyone this, is that if we look at the hydroxychloroquine data, we probably increased mortality by about 10%. Actually, it made things worse. We don't really at this point want to like, "Oh, maybe we just need to do that trial."

VR: I think that's why the camostat wasn't trialed with the hydroxychloroquine, because the HCQ has bad side effects. You don't want to use that.

Dr. Daniel: Yes, it does.

VR: You need something else.

DG: Not only the trials, I remember in the hospital, nurses would come to me, "Mr. Jones, vomiting in his face mask because of the GI side effects of hydroxychloroquine," but we didn't know early on. We've got through that first week. Hopefully, our patients have gotten their early antiviral therapy. Hopefully, they're not going to show up during the second week. Hopefully, we're not treating viruses with antibiotics, but here we are with the article,

“Assessment of the Available Therapeutic Approaches for Severe COVID-19: A Meta-analysis of Randomized Controlled Trials,” published in *Scientific Reports*.

This is going to really go through what are all these different treatments out there and what do we know about them from the different trials. The authors conducted a meta-analysis of randomized controlled trials compared with standard of care. Database searching was performed separately for each severe COVID-19 treatment, such as anakinra, remdesivir, baricitinib, ivermectin, ritonavir, tocilizumab, sarilumab, sotrovimab, casi/imdevimab.

They present the results in a risk ratio. We've got confidence intervals and other analysis. There's a lot here. Nice analysis of risk of bias in the different included studies. They start with that. I think that's really key. You've got to really ask, "Before we look at the studies, are they reliable? Is there a lot of bias?" Then what I really love, lots of forest plots. We can actually look at the individual studies and see how they factor into the analysis. Let's walk through. I do, this is open access. We'll leave a link in the show notes. Take a look at each one and the forest plots.

Anakinra, remember that? Maybe a trend toward more death. Remdesivir was favored over standard of care. Baricitinib was favored over standard of care. Ivermectin, apparently, if we only include studies that were actually done and not the fraudulent ones, ivermectin is not helpful. Cue up the hate mail. Then, yes, if you wait too long and try those monoclonal antibodies once a person already has severe disease, not so helpful. What about tocilizumab?

They put this right up in the abstract, and this was interesting. Let me read. "We obtained the most statistically significant outcomes favorable tocilizumab compared to standard of care for death incidents. We have a relative risk of 0.87. Need for mechanical ventilation, relative risk of 0.78, number of patients discharged from the hospital, 1.13.” The authors conclude this meta-analysis has revealed that a considerable amount of research characterized by a very diverse methodology is available. Despite the limited data that met the criteria for inclusion in the meta-analysis, we show that the available treatment options for severe COVID-19 are effective.

VR: Toci is the IL-6 antibody, correct?

DG: Exactly, IL-6 receptor.

VR: These are people coming in later in infection and inflammatory phase, it's not surprising that was helpful, right?

DG: Yes. I think this is our paradigm that we've been talking about for a while, which drugs we'll include, which we don't. Patient ends up in the hospital. They've got oxygen saturation lower than 94%. We should probably say we are seeing patients in the first week, too. This is that second week classic cytokine storm, early inflammatory phase. Number one, steroids, 6 milligrams a day for six days. We've talked about the meta-analysis, reining that in from 10. No real benefit once you get to day six, past day six.

Anticoagulation, we've got a bunch of guidelines. Pulmonary support, remdesivir if we're still in the first 10 days. Then immune modulation, and yes, tocilizumab was the winner there. Avoiding those unnecessary antibiotics and antiparasitics. An area we've been spending a lot

of time on lately, fortunately, is late phase Long COVID. Let me start with the article, “Effect of Monovalent COVID-19 Vaccines on Viral Interference between SARS-CoV-2 and Several DNA Viruses in Patients with Long-COVID Syndrome,” recently published in *NPJ Vaccines*.

For those following this story, there's been a lot of evidence now that Epstein-Barr virus, so EBV reactivation, other DNA viruses may be involved in Long COVID symptoms. There's also evidence that vaccination can both prevent and be an evidence-based treatment for Long COVID. Here the investigators evaluated the reactivation of several members of the Herpesviridae family, so EBV, CMV, HSV, and parvovirus B19, another adenovirus that can reactivate in patients with Long COVID syndrome.

Clinical and laboratory data for 252 consecutive patients with PCR-verified past SARS-CoV-2 infection and Long COVID syndrome, 155 vaccinated, 97 non-vaccinated, were recorded during April 2021 through May 2022, so we're about 200 median, 243 days post-COVID-19 infection. DNA virus related IgG and IgM titers were compared between vaccinated and non-vaccinated Long COVID patients with age and sex matched, non-infected, unvaccinated controls.

Vaccination with monovalent COVID-19 vaccinations was associated with significantly less frequent fatigue and multi-organ symptoms, significantly less cumulative DNA virus related IgM positivity, significantly lower levels of plasma IgG subfractions 2 and 4 for EBV, and significantly lower quantitative CMV IgG, IgM, and EBV IgM titers.

VR: What we're saying here is if you're not vaccinated, you're infected with SARS-CoV-2, it reactivates these other latent viruses, EBV and CMV, and that can be a problem. If you're vaccinated, that incidence goes down?

DG: Yes, that seems to be part of this growing story that people who develop Long COVID, part of the syndrome may be that they get this reactivation and vaccination may be one of the mechanisms for why vaccines can be protective.

VR: If you remember the Iwasaki paper we talked about here, reactivation of these DNA viruses was associated with Long COVID, one of the associated factors, right?

DG: Yes. More bad news, the article, “Local Budesonide Therapy in the Management of Persistent Hyposmia in Suspected Non-severe COVID-19 Patients: Results of a Randomized Controlled Trial,” recently published in the *International Journal of Infectious Disease*. These people, they can't smell. We're hoping that some steroids squirted up the nose might do the trick. We talked last week about another trial looking at this. These are the results of a multicentric randomized superiority trial.

The experimental group received budesonide, a steroid, and physiological saline nasal irrigations administered via three syringes of 20 milliliters in each nasal cavity in the morning and evening for 30 days. The control group, similar protocol, except no steroid in the squirts. Patients were included if they were 18 years old with a SARS-CoV-2 infection and presenting an isolated hyposmia persisting 30 days after symptom onset. Unfortunately, they report that local budesonide efficacy was not demonstrated for persistent hyposmia related to COVID-19.

VR: I'm not surprised because I think by then the inflammation is finished. I think the damage to the olfactory epithelium was done long before, and this is not going to make a difference.

DG: It's a good study to read because in the discussion they talk a little bit about that there may be different things going on at different times. Early on, if you do MRIs of people who have loss of smell with COVID, you actually can see a lot of inflammation in the olfactory region, in the area where the olfactory cells come through the cribriform plate. As time goes by, that inflammation starts to go down, and what they're postulating is you may be missing your window. At this point, you may actually have permanent damage.

VR: This is, I don't remember, 30 days after symptom onset or loss of smell, so it's too late. Yes, I don't remember.

DG: Persisting 30 days after symptom onset.

VR: It's too late. The problem you run into is you don't want to give steroids too early because then you -

DG: I wonder maybe the timing here, let's say we have people, so it's week two, you're outside that first week, where maybe it's going to be OK. They say, "I can't smell." If we jump in then -

VR: Then, yes.

DG: - Could it be a timing, and we get the inflammation shut down early, could we then - More research that needs to be done. I will then, before we get to our emails, close with, as I have for about four years now, if you can believe that, "No one is safe until everyone is safe." We're still in the middle of our Floating Doctors fundraiser, August, September, and October. This is our last month, trying to get up to a total donation of $10,000 that we can double to give Floating Doctors $20,000 to continue to do the great work that they're doing down in Panama.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Owen writes, "I'm a regular listener to your show. I'm a C3-4 quadriplegic, 62 years old. I'm at an elevated risk of respiratory issues because of my age and paralysis. Early on in the pandemic, there were plenty of places to monitor the amount of infection in local communities, but much of it has gone away. For the average Joes, such as myself, can you suggest a good strategy for monitoring levels? Maybe something similar to influenza monitoring."

Also, on today's show, you had a question asking about the location of the injection. Remember the deltoid versus lower down, right?

DG: Yes, down on the trapezius.

VR: "Since my muscles are atrophied and my shoulders are subluxed, would you suggest a better muscle for COVID injections? Are the influenza vaccines in need of a similar muscle?"

DG: A couple of questions there. We always leave links in our notes, places where you can go and see what's going on. We're doing some questions this morning asking different people like, "What are they following?" Are they following hospitalization levels? Are they following

test positivity? Are they following wastewater? Are they seeing what appears in the mainstream media? No, it's not what I'm recommending. It's almost counter-cyclic. You never really know what the mainstream media wants to cover that week.

You can, if you go through our links, you can see from the CDC pretty reliable data on hospitalizations. That's a reliable metric. Tells us what's going on right now, but it's going to tell us what happened with infections a week and a half earlier. You can look at wastewater. That tells you what's really happening in real time, which is going to translate 10 to 14 days later in hospitalization. Yes, follow the links on our pages. That'll give you a sense of what's happening.

We're starting to see SARS-CoV-2 fall into somewhat of a respiratory pattern. We've seen spikes now, basically, December, January for the last few years. We expect to see that again. It's a respiratory spread pathogen. Then the other, I guess, is where to get those shots. The nice thing is in the FDA approval for the shots. It's deltoid or lateral thigh. The lateral thigh is sort of underutilized. Sometimes it can be a challenge. You go to a lot of pharmacies that are doing it. They don't have people trained to inject in lateral thigh, so that can be a challenge.

It's a great route for someone who maybe doesn't have the muscle mass in other places, or actually a group has reached out to me because they do a lot of breast reconstructions, maybe a person is struggling with breast cancer, they're shedding the lymph node enlargement up in that region. Sometimes there's medical reasons why that lateral thigh is a good option.

VR: This is the lateral thigh, here?

DG: Just lateral thigh. We moved away from the butt shots. There's nerves and blood vessels there. I don't know why we were ever doing that. You had to drop your pants.

VR: You still have to drop for a lateral thigh, don't you?

DG: I tell people to wear shorts, short shorts. The kind of shorts that my girls are not allowed out of the house wearing.

VR: In the middle of winter.

[laughter]

VR: How far up or down the lateral? Right in the middle?

DG: Yes, right in the middle, right in the meaty lateral thigh.

VR: Very good.

DG: Lori writes, "I have a question regarding measuring of cortisol levels, specifically related to Long COVID. Does the time of day when blood is taken make a big difference in cortisol level? Also, if an individual who experiences fatigue has blood taken on a day when they're able to get out of bed feeling relatively good, how might their cortisol level differ from a day when they cannot make it to the clinic to get blood drawn as they can't get out of bed?" Let's take those two first.

DG: No, these are great questions because this has now come up. The study with Akiko and David Petrino, that was their big thing. You draw a line. You could say, "These people with Long COVID have significantly lower cortisol than people without Long COVID." A lot of people now are asking, like, "Is this another? It's a biomarker. Maybe I can start checking things on my patients. Maybe I check a cortisol, maybe I check serology for EBV and CMV and other things like that."

The challenge is exactly what you're bringing up is that cortisol definitely varies based on time of the day. The labs will actually have for you cortisol drawn between 7:00 and 9.30. This is our range because that's usually when you see the elevation. In the afternoon, they have a different - Then this is great because this came up just this week.

I was talking to a patient about, hey, based on this, they had read about this, well, versions of it in the mainstream. They wanted to know, should I get a cortisol? I explained the importance of getting an AM cortisol. She just said, "I'm just trash in the morning. How am I supposed to go out and get an AM cortisol?" It's going to be interesting. The day that she goes is going to be the day that she feels well. Yes, that's going to be a challenge.

VR: You have to have home [crosstalk]--

DG: You almost need home cortisol where they could just, at what, nine o'clock in the morning, 8.30 in the morning, they roll over and the blood gets drawn. That would be a question. I should probably reach out to Akiko and ask her, "How did you get these AM cortisols in these people with Long COVID? Particularly if they had to travel to Mount Sinai or Yale, where they go into a local lab, were they home draws? How did you get them at the same time?"

VR: How much blood did you need for that?

DG: Not really a lot, just a small amount.

VR: It would be like a glucose test, also? Just a drop?

DG: They're still doing it as you're drawing one of those -

VR: Yes, sure, vacutainers. Then Lori goes on, "When having routine blood work done, would non-classical monocytes be measured?" I think that's one of the groups in the Akiko study.

DG: Yes, the non-classical monocytes.

VR: "A member of my family had COVID in the spring of 2020. Over the next year, she had tests done to try and explain her hypersomnia, fatigue, and brain fog. Of course, this was before Long COVID was being widely recognized. She is presently being treated with drugs for narcolepsy, which along with altering her daily activities has helped a bit. At this point, I don't think there's any benefit for her to try and have any tests done to diagnose Long COVID as it would not change her medication. Do you agree?"

DG: Yes, this is a challenge. At this point, validating doing these tests, we're not really sure how that translates into different therapeutics, but hopefully, that will come. Some people

though, it is nice for them to be able to say, "Hey, you have a profile that is consistent with what we're seeing in Long COVID." The danger and what a lot of people are worried about is the reverse might happen. They might say, "Oh, your profile, you don't have the elevated EBV serology. Your AM cortisol is not decreased," so they're worried they'll be excluded somehow.

VR: Non-classical monocytes, that wouldn't be [crosstalk]--

DG: That would not be part of a normal blood test, yes.

VR: Lisa writes, "I'm wondering if I should get vaccinated for shingles. I'm 44 and I had shingles 11 years ago." Let's take that.

DG: We'll start with that. The recommendation for the shingle shot is over the age of 50. We hit 50, I did that, hit 50, boom, went ahead, got my shingle shot. Waited three months, got my second one. You could do it one to six months. There's a range, three months is reasonable. For people that have shingles, there is evidence that it can prevent someone from having a recurrence, so perfectly reasonable in someone who had shingles in their 30s to consider getting the vaccine.

VR: She wants to know if having shingles counts as being immunocompromised, especially at that young age.

DG: It would raise some sort of a, what's going on? Why did you have it in your 30s? Is there a good explanation? Is there something in your genetics? Fifty percent of us will get shingles at some time in our life.

VR: I had a student years ago at Columbia in her 20s and she was on immunosuppressive therapy. She got shingles.

DG: Your class was way too stressful, you see.

VR: [chuckles] Lisa continues, "I know this doesn't work for COVID, but is there a shingles antibody test that can tell me whether I need to get vaccinated?"

DG: There is an antibody. This is the chicken pox titer, but we don't really do that. We don't really check your titers and decide, it's just a blanket, you hit 50 years old.

VR: "PS., I don't know if this is relevant since I don't think it counts as immunocompromised in regards to vaccines, but I have ME/CFS, POTS, mast cell activation syndrome, fibromyalgia, and von Willebrand type 1. Does that count for being immunosuppressed, any of those?

DG: Run through the list again. That was a lot.

VR: ME/CFS, POTS, You know what that is, right?

DG: Autonomic dysfunction, postural orthostatic tachycardia syndrome.

VR: Mast cell activation syndrome, fibromyalgia, and von Willebrand type 1.

DG: None of those fall into like a classic immunocompromised category, but they certainly would raise concerns for different things.

VR: Final one is from Jen. "Let's suppose someone has the very bad luck of testing positive for COVID a day or two after they received the 2023-24 formulation COVID vaccine." Of course, not due to the vaccine as that's impossible. If this person takes -

DG: Maybe due to go into the vaccine center, but no, that's also pretty quick too.

VR: It's too quick, right?

DG: Yes, it's too quick.

VR: "If this person takes Paxlovid, will it blunt both the virus replication, (yay), and also any helpful immune response to the vaccine, (bummer)? Are there any reasons Paxlovid should be avoided right after vaccination in a COVID positive patient who otherwise would be recommended to receive that treatment?"

It's a really good question.

DG: It is a really good question. Let's go through it. Let's first think about the infection. Some people used to worry about this with the monoclonal antibodies. If you got a monoclonal antibody, if you get Paxlovid, if you shut down viral replication, you're not going to get as robust an antibody response. You may not even get as robust a T cell response. That's our goal.

Our recommendations are, if you've been infected, wait three months before you get your next boost. That's still there. That's the goal. The goal is we do not want the virus to replicate. We don't want a big immune response. I don't think we've considered that to be enough of a reduction that it doesn't give you the boost in memory. Now, let's think about how those mRNA, I'm assuming it's an mRNA or it could be a Novavax. Novavax protein, it's already there. Immune system's going to see it. I don't see any interaction with Paxlovid there.

Let's think about the mRNA. The mRNA is going to go through.

VR: No problem with Paxlovid.

DG: Again, no problems.

VR: No, you don't need a protease to do any of that.

DG: No protease for any of this. I don't see any problems.

VR: No, I would say you should take the Paxlovid to avoid getting very sick, right?

DG: Yes.

VR: Even if for some reason it interfered with the vaccination, which it doesn't, I would say take it anyway and then get vaccinated again later if you needed to.

DG: Three months later. Yes, that's fine.

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

DG: Thank you, Vincent. Everyone, be safe.

[clapping]

[music]

[00:43:01] [END OF AUDIO]