This Week in Virology

TWiV 1027 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.

[music]

VR: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1,027, recorded on July 20, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Not too long ago, Daniel, there were rumblings about perhaps having Mpox outbreaks. Has that ever materialized?

DG: Just a few here or there. We haven't seen any major outbreaks yet, so keep an eye on that.

VR: The models all said we were going to have a big outbreak.

DG: You can't trust the models. [chuckles]

VR: OK, OK.

DG: Actually, I would worry about August just to let everyone - Just speaking about what I know about behavior, we'll see what happens next month. We're almost there. I don't know if you noticed, so we just recorded *This Week in Parasitism*. I'm wearing my Giardia bow tie.

VR: That figured in part of the episode, didn't it?

DG: Maybe it was appropriate. Let us get right into it with my quotation. "It's when we start working together that the real healing takes place. It's when we start spilling our sweat and not our blood." That's David Hume, actually, one of my favorite philosophers when I was coming up through the ranks, studying philosophy out at University of Colorado, Boulder. I will just give people a little background here. Actually, we're still seeing a trickle of norovirus cases. I guess we can call it winter vomiting. It's now going to be summer vomiting disease. A number of Babesia cases.

COVID? COVID is just sort of this low rumble in the outpatient. We've got a few patients here or there that are getting admitted. We are starting to see maybe a little more in our urgent care, a little more reports in our camp environment, just to give people a heads up there. Malaria, oh, my gosh, we are now up to eight cases. Another case was just diagnosed on Tuesday in Florida. RSV, I wanted to share the news here. Really a lot going on in RSV.

The FDA approved a new drug to treat RSV in babies and toddlers. On January 17, the FDA approved Beyfortus or nirsevimab. I like that, nirsevimab, right? For the prevention of RSV, lower respiratory tract disease in neonates and infants born during or entering their first RSV season and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. A lot of ideas that this is going to be for everyone under 2, a thought of maybe we'll charge a little bit less and get it out to more folks.

Nirsevimab binds to the pre-fusion confirmation of the RSV fusion protein, i.e., it binds to the site at which the virus would attach to a cell, effectively neutralizing the virus. It has a modified Fc region extending the half-life of the drugs. It's going to last for the season. One dose of Beyfortus administered as a single intramuscular injection prior to or during RSV season may provide protection during that season. The data suggests the reduced risk of medically attended RSV, lower respiratory tract infection, about 70% to 75% relative to placebo.

We'll mention this is the second monoclonal after palivizumab for preventing RSV in young children. As I mentioned, what about the cost? We did mention that palivizumab is not used a lot because it's thousands of dollars a dose. Well, the price per course is estimated to be $600 in the U.S. and $300 in Europe versus those thousands of dollars for palivizumab.

VR: Do you think maybe the maker of palivizumab could lower the price?

DG: You know, one of the interesting issues might be the indications, right? This is a very broad indication and so, yes, I'm curious what's going to happen with the palivizumab.

VR: Can they also be used therapeutically?

DG: You know, the approval was for prevention. That's an interesting question.

VR: Same with palivizumab, it's also preventative?

DG: Yes, they're both preventive but - Yes, it'd be interesting to look at trials. What if you jump in? Can you jump in quick enough and make a difference here?

VR: If an infant has RSV, what do you do then? How do you treat it?

DG: In most cases, it's really supportive care. Give them oxygen. You raise an interesting point. From a mechanism point of view, it seems like this could potentially have an impact if you can get it in there early enough.

VR: Well, you'd have to do a trial to see how many days you have, right?

DG: I think that's it. You got to do the science. I know that's - [laughs]

VR: Yes.

DG: You really, really do because does it work, when does it work, and whom does it work? You need to know.

VR: Remind us where we are with vaccines for RSV.

DG: RSV, we've got the two vaccines. We've got the vaccination option for those 16 and over. Remember, that's the high-risk people, shared decision-making if you're just there by age. We also have the vaccination in the last trimester of a pregnant individual so that then the newborn is protected.

VR: Got it. OK.

DG: Moving into COVID, we got a lot of questions about this. Actually, people were asking about this issue on the last live stream that I was on. The article, "Transmission of SARS-CoV-2 in Free-Ranging Whitetail Deer in the United States," was published in *Nature Communications*. It got a little social media and regular media attention and suggested that here in the U.S., SARS-CoV-2 was transmitted from humans to deer more than 100 times, mutated, and then was potentially transmitted back to humans in three cases.

VR: People like their deer, don't they?

DG: They do. You got to stop playing with the deer so much. All right. Once something is tucked away as truth, it's pretty hard to correct it, even when you have actually a lot of data to correct it. The paper, "Omicron Subvariant BA.5 Efficiently Infects Lung Cells," was recently published in *Nature Communications*. Need I bother? Is anyone going to listen, Vincent? Have everyone decided? Well, we -

VR: Yes, go ahead.

DG: [laughs] - discussed some work suggesting that the SARS-CoV-2 Omicron subvariants BA.1 and BA.2 exhibit reduced lung cell infection relative to previously circulating SARS-CoV-2 variants, but here, the investigators show that the spike protein of BA.5, that's an Omicron, exhibits increased cleavage at the S1/S2 site, and they suggest that this drives cell-cell fusion and lung cell entry with higher efficiency than its counterparts from BA.1, BA.2. They argue that increased lung cell entry depends on a particular mutation, ΔH69/ΔV70, and is associated with efficient replication of BA.5 in cultured lung cells similar to their early variants. Further, BA.5 replicates in the lungs of female Balb/c mice, and the nasal cavity of female ferrets with higher efficiency than BA.1.

VR: Dan, do you remember, very recently you talked about a study in Hong Kong on pathogenicity of Omicron. Do you remember which variant they were looking at there?

DG: That's actually, I have to say, when I was talking about this, it made me think about, do we need to sort of tease out? We have enough data to say, because people just broadly say, "Oh, Omicron, it's mild." Then we've said, "Actually, if you look at -" You're not seeing that. I guess now we might be asking, which Omicron are you talking about when you say it's mild?

Which Omicron are we talking about when you point out that it's not mild? I think the one consistent thing is, what makes Omicron mild? Immunity, early treatment.

VR: Yes, clearly.

DG: All right. As clearly as we say that, I'm not sure, but, OK, [laughs] I'm not sure people are getting the message.

VR: Well, interestingly, I'm sorry to interrupt, but -

DG: No, please do.

VR: - in that paper that you just referenced - Let me - I think I have it here. Hang on. Yes. It's *Nature Communication*. Omicron subvariant BA.5 efficiently infects lung cells. The subvariants BA.1 and BA.2 exhibit reduced lung cell infection, which may account for their reduced pathogenicity.

DG: Yes, do you see that? That's crazy, even right there in their intro.

VR: Right.

DG: Yes, yes. OK. All right. The article, "COVID-19 Scent Dog Research Highlights and Synthesis During the Pandemic of December 2019-April 2023," was published in the *Journal of Osteopathic Medicine*. They reported, they looked at a bunch of studies that analyzed how dogs might detect COVID in asymptomatic people. It's interesting. I'm going to say COVID because we've tried to point out, they're not sniffing the virus. There's something about the people. They were able to detect asymptomatic people. They were able to detect folks with Long COVID. I like that. They're even able to detect folks with some of the new COVID due to variants.

Among the 29 studies they looked at in the field studies, the dogs performed comparable to PCR tests with, are you ready for this, sensitivity ranging from 68.6% to 95.9%, with three of the six ranging between 92% and 95.9%. The specificities ranged from 75% to 99.9%, with three of the six ranging between 95.1% and 99.9%. Different dogs, but all the dog sniffing results occurred, are you ready for this, in a matter of seconds to no more than 15 minutes. Not four days, not "Have I gotten that test result? I got it done on Monday. It's Saturday," no, minutes to 15 minutes at most. Much faster than other forms of testing, and yes, if you look up this article, lots of cute dog pictures.

VR: The bottom line is that technology is for the dogs.

DG: The dogs win.

VR: I saw this title, COVID-19 scent, I thought it was $0.19 that it meant it was a cheap -

[laughter]

DG: How much is that? That'll be COVID-19 cents.

VR: Right. [chuckles]

DG: All right. I wanted to throw this out here because this is something that I think has been bouncing around. Hopefully, I'm trying to generate some angry emails. Here's a question I've got. Ventilation, transmission, is SARS-CoV-2 airborne or enhanced droplet? Different medical centers use different terminology. I'll have to say, at one medical center where I do some clinical time, they actually have introduced something called enhanced droplet. They put a sticker on the door. The door stays shut. The person is not in a negative pressure room, all the people that are going to take care of the individual, they gown, they glove, they put on an N95. This question, does every admitted patient need a negative pressure room or can we just close the room, close the door, and wear N95s?

Other places where I work, I think this is funny, they've got these red isolation airborne precautions but they're doing the same thing. They're just shutting the door. They're not putting them all in negative pressure rooms. I'm just curious. I'm hoping this triggers some emotional email responses. One is, I think you've got to be honest, right? If you're doing enhanced droplet and you're just shutting a door, that is not a negative pressure room with 15 air changes per hour and negative pressure relative to the hallway with particularly an antechamber, so pointing that out, folks.

VR: What's an enhanced droplet, Daniel?

DG: [laughs] It's actually this new approach where they basically have said, "OK, we're going to shut the door. Everyone taking care of the patient is going to wear an N95 but we're not going to require that every single COVID patient be in an individual negative pressure chamber."

VR: I see. They're all in the same area.

DG: You can put them on a regular floor. You can put them in a regular room. You just keep them either cohorted by themselves and you keep that door shut, and everyone going in and out is practicing this enhanced hygiene.

VR: OK.

DG: All right, COVID active vaccination immunity, perhaps a little controversy. You're going to like this one, Vincent. I tell you ahead of time. “T-cell Immunity Against Severe Acute Respiratory Syndrome Coronavirus 2 Measured by an Interferon Gamma Release Assay is Strongly Associated with Patient Outcomes in Vaccinated Persons Hospitalized with Delta or Omicron Variants,” published in *JID*. These are the results of a prospective, longitudinal study including vaccinated patients hospitalized with Delta and Omicron SARS-CoV-2 variants. TrimericS-IgG antibodies and SARS-CoV-2 T-cell responses were measured using a specific quantitative interferon gamma release assay. Primary outcomes were all-cause 28-day mortality or need for ICU admission.

I should talk a little bit about how you do this kind of an assay. Basically, you're going to draw an individual's blood. You're going to actually spin it so you've got that buffy coat with your white cells. They're going to be your T-cells. Then you're actually going to go ahead and do a stimulation to see how much interferon gamma is released from those T-cells. The whole idea of a quantitative interferon gamma release assay for looking at SARS-CoV-2 T-cell response doesn't seem quite as hard as people seem to think assessing T-cell responses need be.

OK, so here they are. Bets are in. What did they find? Is it the T-cells? Is it the B-cells? Is it both? Well, of 181 individuals, remember these are vaccinated folks, 87.3% had detectable SARS-CoV-2 antibodies, 50.8% showed SARS-CoV-2 specific T-cell responses, and 48% had both responses. Patients who died within 28 days or admitted to ICU were less likely to have both unspecific and specific T-cell responses in the IGRA. In the adjusted analysis for the entire cohort, having both T-cell and antibody responses at admission, 0.16, so an 84% reduced hazard of 28-day mortality or ICU admission.

VR: Daniel, when are they taking the bloods here? Do you know offhand?

DG: At admission.

VR: I'm surprised that -

DG: The person shows up at the door, and they do it.

VR: They're being admitted for COVID, obviously, right?

DG: Yes.

VR: It's interesting that only half of them had both responses. I'm very surprised at that. What about you?

DG: There's an interesting idea here. Maybe this is an immune deep dive. We've always talked about, OK, so antibodies take a certain amount of time, T-cells take three or four days, but let's go into the nuance. Adaptive immune cells actually undergo evolutionary pressure. One person's T-cell repertoire might be a little bit different than another person's T-cell repertoire. The idea here when you go into some of this stuff, is the idea that certain people, and don't worry, I've got a cool study coming up on this, might actually have a significant amount, we'll call it, a public T-cell pre-population, ready to respond to SARS-CoV-2 and other coronaviruses.

The idea here is maybe what we're seeing is maybe certain people, when they get that proper vaccination, are getting this sustained T-cell memory and response or, as we'll talk about a little bit later, maybe certain people with the right HLA subtype, MHC molecules might be primed.

VR: Yes, it's a possibility. Are they using a mix of peptides here, covering, whatever, the whole spike or something like that? Do you know?

DG: That I don't.

VR: I'm sure they're not just using a single peptide because that could be a problem.

DG: That could skew. Yes, that could skew things. I thought it was interesting. I mean, we're starting to see, well, in this paper, we're seeing just having the antibodies alone, that's not enough if you've got that T-cell. Here, we're saying, it's admission. Most people getting admitted for COVID, it's during the second week, they should have had enough time to have a T-cell response. It's the people who, and half the people, 50.8%, have a specific T-cell

response, 49.2% don't. Half the folks, you're in the second week, and the T-cells are not kicking in.

VR: Yes, I would be interested to know if you waited a bit longer, if they would, right?

DG: Yes, yes. Again, is it timing? Is it a binary?

VR: Yes.

DG: They do a nice figure, too, it's a really nice probability of event-free survival, and they follow that over time. You really see this separate out over time. Boy, the folks that have the IGRA positive, as well as the immune B-cell IgG response really doing much better.

VR: Well, this is good to see, data that support what we've been suggesting and others. I mean, Alessandro Sette, Shane Crotty, saying that T-cells are, John Wherry, the T-cells are important. Now we see that some data starting to support that, right?

DG: I like the way you word that because that's science. Science is we're waiting for the data, we're willing to modify our ideas. This has been a big discussion for a long time. How important are the neutralizing antibodies? How important are the non-neutralizing antibodies? How important are the memory B-cells? How important are the T-cells? Here, we're really seeing a huge impact of having an appropriate T-cell response.

All right, moving into COVID, the early viral upper respiratory non-hypoxic phase. This is, for some, the first week of viral symptoms, but what about those people who have no symptoms? Is that fair? [laughs] Well, it may not be fair but there might be an explanation. The article, "A Common Allele of *HLA* is Associated with Asymptomatic SARS-CoV-2 Infection," recently published in *Nature*. This study enrolled 29,947 individuals for whom high-resolution *HLA* genotyping data was available in a smartphone-based study designed to track COVID-19 symptoms and outcomes. Their discovery cohort (n=1,428) comprised unvaccinated individuals who reported a positive test result for SARS-CoV-2. They tested for association of five *HLA* loci, that's human leukocyte antigen, with disease course, and identified a strong association between *HLA-B**15:01 and having an asymptomatic infection observed in two independent cohorts, suggesting that this genetic association is due to pre-existing T-cell immunity.

They show that T-cells from pre-pandemic samples from individuals carrying *HLA-B**15:01 were reactive to the immunodominant SARS-CoV-2 S-derived peptide, NQKLIANQF. The majority of the reactive T-cells displayed a memory phenotype, that's important to think about, were highly polyfunctional, and were cross-reactive to a peptide derived from seasonal coronaviruses.

The crystalline structure, and they've got some great figures, so you've got to go look at this, the crystalline structure of *HLA-B**15:01 peptide complexes demonstrates that these peptides, NQKLIANQF and another one from OC43- and HKU1-CoV, share a similar ability to be stabilized and presented by *HLA-B**15:01. Finally, they show that the structural similarity of the peptide underpins T-cell cross-reactivity of high-affinity public T-cell receptors, providing the molecular basis for this *HLA-B**15:01 mediated pre-existing immunity.

I'm going to put this in a little bit of context because there's a lot of immunology here. A significant association of *HLA-B**15:01 with asymptomatic infection, so you're basically genotyping people, and if you've got this *HLA-B**15:01, you have an association with asymptomatic infection. After they adjust for a bunch of variables, odds ratio of 2.4, so about 2.5 times, but then there are strong additive effects for associated genotypes. Individuals that have two copies were more than eight times as likely to remain asymptomatic than individuals carrying other genotypes. We see an odds ratio of 8.58. Overall, about 20% of individuals, so one in five of the individuals who remained asymptomatic after infection, carry the *HLA-B**15:01 compared with 9% among patients reporting symptoms.

VR: The *HLA*s present on the surface of the infected cell, the viral peptides, and then the T-cells recognize that and kill that cell. That's the basis for *HLA*, right? What we're saying is if you have a particular *HLA*, it's really good at presenting a particular peptide that's recognized by the T-cells that these people have, but not everybody has those T-cells, right?

DG: Exactly, or the MHC. This is the MHC on the T-cells but, yes.

VR: This is MHC.

DG: Really interesting. It's this whole evolutionary impact. I'm just trying to tease this out. There's an evolutionary impact on adaptive immunity, but since these also have a memory phenotype, there may also be a priming from OC43 or HKU1 or, now, as we'll probably see in the future, there may be a priming from prior infection and vaccination.

VR: Sure.

DG: Interesting stuff.

VR: No, I think this is very - We're actually going to do this on *TWiV* tomorrow. It's a really good study. I like it very much.

DG: Oh, this is great. Well, I will be listening, and what do we do? Well, whether you have this or not, if you are symptomatic and high-risk, number one, Paxlovid, number two, remdesivir, number three, molnupiravir, convalescent plasma in certain situations, avoid doing those harmful and useful things. Just a reminder on the small print in the CDC isolation recommendations, as I mentioned, we are seeing folks that are testing positive, that are symptomatic and the question comes up, what am I supposed to do? Can I just go to work? It's just COVID. Well, what is the CDC that updated the recommendations in May? What is May 2023 recommendations? Here, just to run through them.

If you test positive for COVID-19, stay home for at least five days, and isolate from others in your home. You are likely most infectious during those first five days. That's really the science. I mean, 85%, 90% transmission is happening in those first five days. Recommending that you wear a high-quality mask if you must be around others at home or in public. Some folks have to. Do not go to places where you can't wear that mask. Try to separate from others as much as possible, using a separate bathroom. Take steps to improve the ventilation. Keep those fans on. Open those windows. I'm sure how exciting that is in 95-degree heat. Don't share personal household items like cup, towels, and utensils. You shouldn't do that anyway. Then,

if you have no symptoms, you may end isolation after day five. That's where everyone stops reading.

Then, the small print. What is the small print? [chuckles] Regardless of when you end isolation, until at least day 11, avoid being around people who are more likely to get very sick from COVID-19. Remember to wear a high-quality mask when indoors, around others at home, and in public, and do not go places where you're unable to wear a mask until you're able to discontinue masking. Then, there's actually a few other things that are thrown in.

All right. Let's move on to the second week. Some people feel better, and then, about probably 10%, 20%, particularly, of our high-risk individuals, will start having a tough time that second week, the early inflammatory or cytokine storm phase, steroids in the right person, anticoagulation. What about anticoagulation? There's some guidelines out there, but what are people doing? We've talked repeatedly about the guidelines to help with decisions around anticoagulation in patients hospitalized with moderate to severe COVID during this early inflammatory phase. What are people actually doing?

The article, "National Trends in Anticoagulation Therapy for COVID-19 Hospitalized Adults in the United States: Analyses of the National COVID Cohort Collaborative," was recently published in *JID*. Here, the authors use the National COVID Cohort Collaborative, conducted a retrospective cohort study to assess anticoagulation use patterns and identify factors associated with therapeutic anticoagulation. In a nutshell, among 162,842 hospitalized COVID-19 patients, 64% received anticoagulation, 24% received therapeutic anticoagulation. Therapeutic anticoagulation use declined from 32% in 2020 to 12% in 2022, especially after December 2021.

What are the current ASH guidelines and what are we seeing here? Well, early in the pandemic, the advice out of China was not to use anticoagulation at all. Well, this guidance rapidly changed and we moved to low-quality evidence suggesting to use full-dose anticoagulation for floor patients, therapeutic dose for critical patients with concerns about bleeding risks, outweighing benefits. All of this was couched in the low-quality evidence we were working with and recommendations to assess each individual patient for their risk of benefit.

Now, in this study, a few things stood out. Two-thirds were getting anticoagulation, and, actually, surprisingly, one-third got no anticoagulation. I have to say, that's sort of interesting because this was the COVID wars. It was a great *New York Times* piece where really a lot of us in the trenches quickly realized that not using anticoagulation, the majority of our patients were having significant thrombotic embolic complications. It's surprising that still about a third of patients are not getting anticoagulation at all.

The other was that in contrast to the ASH guidance, where you're saying the risk of bleeding would suggest using a lower dose, sicker, critically ill patients were the ones more likely to get therapeutic anticoagulation, going against what evidence we did have. Also, the association with not using full-dose anticoagulation with Omicron and in patients that have been vaccinated.

All right. Remdesivir, remember, we've talked a little bit about that. Actually, we have an update on remdesivir. I wasn't sure where to put this, but they have updated the approval. This approval is now for use in patients with severe renal impairment based upon results from a Phase 1 study, as well as results from the Phase 3 REDPINE trial that demonstrated the pharmacokinetics and safety profile of VEKLURY or remdesivir. Basically, for a while, we've been talking about using remdesivir in individuals with severe renal impairment, including those on dialysis. Here, it is now approved. No longer stepping outside of the product insert, the directions, you can use remdesivir independent of renal function, also no drug-drug interaction. Again, really a great option when we have access.

All right, let us move into COVID, the late phase, PASC, Long COVID. I'm going to suggest people spend a little time. I was going to say those interested, but everyone should be interested in Long COVID. The review article, “The Immunology of Long COVID,” was recently published in *Nature Review*s *Immunology*. Really, in many ways, this is the greatest hits of theories behind the cause of Long COVID. In table one, they lay them out. I have to say, just to qualify, people tweet this out, "Look, they finally admitted." I'm like, "They're just listing the theories," so, yes, take a deep breath there.

OK, what are the hypothetical mechanisms underlying Long COVID pathogenesis? One, and I think we definitely see this, organ damage in targeted tissue. There are folks who have loss of pulmonary function, really, people who have cardiac damage that occurs. There certainly can be damage in targeted tissues. Another hypothetical mechanism is persistent virus or antigen reservoirs. Another is reactivation of Epstein-Barr or other latent viruses, maybe even activation of endogenous viruses, changes in inflammatory activation, systemic immunity, immune subsets, and their transcription profiles.

The theory of vascular endothelial activation or dysfunction, the hypothesis around a role for mast cell activation, hypothesis around an autoimmune basis, and that might be autoantibodies or T-cells, and a hypothesis around a microbiota dysbiosis. Now, there are 166 references so it's really a great way to look through and see what all the different research are on the different theories. There's a really nice Table 3 with a list of different trials, with their rationale, and where they're being conducted. I should just point out, for everyone who's been tweeting this out there, this is a list of theories.

VR: I was going to say a lot of hypotheses there, Daniel.

DG: Yes. That's what they are. We do need hypotheses but, remember, there's a big difference between a hypothesis and what we actually know.

VR: Absolutely.

DG: All right, low and middle-income countries. I want people not to just be thinking about the wealthier, resource-rich areas. As I continue to say, no one is safe until everyone is safe. Here we are, getting near the end of July, finishing our May, June, and July Foundation for International Medical Relief of Children fundraiser, trying to get up to that donation of $20,000 from Parasites Without Borders to FIMRC. Pause your recording, go to parasiteswithoutborders.com, click on that Donate button.

VR: Time for your questions for Daniel. You can send them to daniel@microbe.tv. Alice writes, "I am 79, reasonably healthy with SVT. I had a bivalent booster in October '22, which I think was my fifth shot, and wonder whether I should have another bivalent now or wait until the fall for the potentially new booster." Related question, "Do you think we have some protection now, even though the last booster was in October? I think you told someone that if they had three shots, they are pretty well protected, but not sure."

DG: OK, no, this is great and repetition is important here. Vince and I have been talking for a while about what are we trying to achieve with these vaccines? What do we try to achieve with vaccines in general? It's protection against disease. We've talked of polio is the great model, right? That injected polio vaccine does not protect you against infection. It certainly does a great job of protecting folks against disease, the disease polio with the paralysis. We are continuing to see durable protection against disease with those three shots.

Then the question comes is, can we get some sort of enhancement above that, some kind of boost? There's a lot of studies trying to look at monovalent versus bivalent. I have to say, there was one that I just recently was looking at, didn't end up including, because I think it was flawed by a time bias issue because as time goes by. Also, there's an issue, as we've talked about, with if you're going to get those boosted mucosal antibodies, neutralizing antibodies, reduce your risk of infection for maybe three or four months. That study was looking at, really, the peak was two to four weeks. That really quickly dropped off after that boost.

In a situation like you're describing, at this point, most of us are saying if you've already gotten your primary series, which would be three shots in most people's mind, then wait till October, November. If you're in a higher-risk group, it probably makes sense to get that three- to four-month boost extra protection. It's probably not going to be something everyone needs to do but, yes, I would recommend waiting at this point.

VR: Have a plan, right, Daniel?

DG: Well, that's probably the most important. You've already really gotten that 90% out of your vaccine. Well, let's get another 90% out of appropriate early treatment.

VR: Susan writes, "A man who is physically fit, just turning 70, went to the hospital at the end of last week with atrial fibrillation after having exerted himself riding a bicycle in the heat and humidity. There's a family history of heart problems. He was treated with Cardizem, a beta block, and a beta blocker, put on Eliquis. After scans, et cetera, finally treated with electric shock therapy on Monday, went home Tuesday, tested positive for COVID-19, called the cardiologist, was told to continue existing medicines and not add Paxlovid. In view of the fact that the electric shock treatment can be followed by blood clots being thrown out of the heart, is that the right path?"

DG: You know, I think the interesting thing there is, OK, so you call the cardiologist and he told you what to do about your cardiac problems but COVID is not a cardiology issue. Call your infectious disease doctor, call your primary doctor who might then reach out to an infectious disease doctor. Yes, don't call me for management of your Afib and don't call the cardiologist for management of your COVID-19.

VR: Amy writes, "My dad is still experiencing brain fog and fatigue after acquiring his second COVID infection about three-plus months ago. I encouraged him to go to a clinic that specializes in Long COVID in his area. He wasn't satisfied that they just told him his blood work indicated that he has a lot of inflammation in his body. He wants to do this commercial long-haulers test that seems pretty sketchy to me, covidlonghaulers.com. I'm not aware of a validated Long COVID test and I have a feeling they just want to sell them on the treatment, which I don't fully understand, even after perusing their website. What do you think of these types of tests? Are they legit?"

DG: Yes, they're not. You know, it is tough. Maybe that'll generate some hate mail there, but come on. There's a lot of snake oil salesmen out there, people that are willing to take your money. We actually had an issue when we were trying to identify which are the centers of excellence for Long COVID. We asked a really simple question, is just show us some metric by which you're making people better above just the natural history of people that recover over time? Couldn't really see that. Yes, this is tough when they want to take your money and do some panel and then, hopefully, they're not going to take more of your money, but that is often what that leads to.

VR: Separately, a neighbor takes hyaluronic acid for inflammation reduction. Is that something that could be effective for Long COVID?

DG: Yes, if anything, there's so many questions. Anyone who knows the answer to that they probably are just making it up. We don't know. There's a lot of different things that people are trying, but we really need the science. We really need the controlled trials. If I say it works, you might get a placebo effect, but that's not what we're after. We want stuff that actually works.

VR: All right, we'll end up with a polio question. Frances writes, "I received the original polio vaccine, three injections back in the '50s." Wow, that would be IPV. “Since I am a registered nurse, over the years I received boosters with the oral vaccine. Last booster was over 10 years ago. Now I am 76 years old, work per diem infusing home care patients. Should I receive another booster? If yes, the injection or oral vaccine?

DG: [chuckles] I think you're set. I think you're done. Vincent, any thoughts?

VR: No, she's done and she can only get the injected in the U.S. We don't give the OPV anymore, but no, no, don't need any more. You're absolutely right.

DG: Yes.

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

DG: Oh, thank you. Everyone, be safe

[music]

[silence]

[00:39:33] [END OF AUDIO]