This Week in Virology

TWiV 1160 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. From *MicrobeTV,* this is *TWiV, This Week in Virology*, Episode 1160, recorded on October 24, 2024. I'm Vincent Racaniello, and you're listening to the podcast about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: You got a bow tie with red blotches, that's all I can tell you.

DG: Yes, it's apparently higher quality once it gets posted, but there's little RNA segments, maybe there's about eight of them.

VR: That must be influenza.

DG: Yes, yes, that was too easy. [chuckles] We got a lot to cover. I was actually thinking about, at the end of next month when I head to Africa, I'm hoping that we have some actual shorter ones, so I'm not sitting out there.

VR: It's always a challenge from Africa.

DG: It is, right? Let's jump into it. First, I have a quotation. I'll start off with this one. I think I'm going to use a quotation from my daughter later. "A public-opinion poll is no substitute for thought."

VR: It's great.

DG: Interesting enough, that's Warren Buffett. We will get into why I picked that this week. We'll start off with mpox. Over the past week, Africa's surge of new mpox cases has continued. The region passed a grim marker with fatal cases passing 1,000 for the year. I think it's actually over 1,100. Also, Germany detected its first case of the mpox clade 1b. This was in Cologne.

A 33-year-old man was isolated after being admitted to the hospital for treatment on the 12th. The case was detected, as mentioned, in Cologne. I actually have a friend of mine who Vincent, Kay Schaefer. He lives in Cologne. He's visiting me. He's the head of Tropmedex. He presented a Corsica schistosomiasis case on *TWiP* at one point.

VR: Cool.

DG: The results of more detailed testing on this individual showed on October 18 that the patient had the clade 1b variant. This is the new form - the clade that's linked to the global health emergency declared by the WHO just back in August. Now, reminders. The current outbreak originated in the DRC. It spread to neighboring countries. Actually, the thought is that this German patient picked it up in an East African country and brought it back.

VR: Daniel, why do we have so many cases? Are we not getting enough vaccine there?

DG: I think that's a lot of it. A lot of it is logistics. A lot of it's getting people vaccinated. We have a call. We have all this money. This ongoing effort. It's really not happening. Now, there are some features of this, which maybe people don't realize. We're going to talk about an article in a second. The vaccine is approved for adults. It's approved down for adolescents. Who does this current mpox clade 1b outbreak impact?

We have the article, "Epidemiological Analysis of Confirmed Mpox Cases, Burundi, 3 July to 9 September 2024." This was a rapid communication in *Eurosurveillance.* From January 2023 to present, broad geographic expansion of the clade 1 monkeypox virus, the Democratic Republic of the Congo, has resulted in what is the largest mpox outbreak thus far recorded. This national outbreak has included the expansion of mpox to all provinces in the DRC. As well as what we're talking a lot about is this clade 1b, which is associated with sustained human-to-human transmission. Now, the first reported case was in South Kivu province.

Really, this is spread, as mentioned, all throughout the DRC. It's also spread to a number of neighboring countries in East Africa. Here are a few takeaways that maybe answers your question, Vincent. We are not seeing a disease impacting gay men. A lot of people seem to miss that, it got stuck in their head. Mpox, that's gay men. The tough thing here, it sort of has me a little bit torn, is that there's a percent of our population that, "Oh, it's gay men, it's them, it's not a problem for me." This does not trigger the same sympathy as describing a horrible viral disease that's infecting children.

In this case, as we're going to see, particularly little girls, young girls. The study results indicate that the average age of girls who were infected was 6 years old. This is not gay men. This is little girls, little children. This subvariant called clade 1b appears to spread more rapidly than the clade 2 that we're familiar with. Hundreds of children have died of the disease in eastern Congo. There's really Figure 2 in this paper, I will leave a link, but you can really look at Figure 2 and see the majority of the affected individuals are really young, single-digit age children, predominantly girls.

VR: How are they getting it, Daniel, from their parents, right, most likely?

DG: It actually looks like a lot of this because there just aren't that many parents that are affected is children-children. We're also concerned that it may be getting onto the pets. The pets may be acting as fomites, which is really kind of tough. I'm looking at my two dogs, the one that I really like and the other one.

VR: Oh, I'm sure you like them both.

DG: I like them both. It's really tough. What do we do for these youngest kids? We don't actually have an approved vaccine for, t3, 4-year-old little kids.

VR: We got caught shorthanded here.

DG: Yes, we needed to be ready for this. We need to finish these trials. We need to really be able to reach out with the vaccine because this is just horrible. Over a thousand people have died. Hundreds of children have died. It is a horrible disease.

VR: I was thinking today, a lot of people in the U.S. say, "Should we be worried?" I say, "Yes, you should, because people are dying over there. You should worry about that." We're all in this together.

DG: No one is safe until everyone is safe.

VR: It's a good saying. You should use it.

DG: [laughs] I think it's funny. I think Paul often uses it in his book. Someone was like, "Oh, he should attribute that to Dr. Griffin." I'm like, "Paul and I are friends. Don't worry. It's all good." I'm pleased that he uses that expression. Let's jump into Marburg. I was all excited to just share nothing but good news. Then I just became aware of the fact that after eight days with no new cases, Rwanda's health ministry just reported one new case. After sitting at 62 for eight days, we now bumped up to 63.

This is interesting. The man tested positive. He's doing well. He actually doesn't have the usual Marburg symptoms. He was vaccinated against Marburg a few days ago. It's not clear if he was exposed to the virus before or after the vaccination. Keep following this number of deaths still steady at 15. No new deaths. There are two patients in treatment, 46 have recovered. I'll leave a link there. Hopefully, this is a testament to the health care system there in Rwanda and their ability to really contain this before it spreads.

RSV, we're still holding steady. We haven't really seen a rise in RSV yet, but we did get some news when it comes to vaccines. "FDA Approves Pfizer's RSV Vaccine ABRYSVO for Adults aged 18 to 59 at Increased Risk for Disease." What's going on here? The FDA's decision is based on the Phase 3 clinical trial. This is the MONeT trial. Sort of interesting the way they create the MONeT acronym there, which is investigating the safety, tolerability, immunogenicity of this vaccine. This is the prefusion F vaccine.

The company is going to - eventually we'll get to see these results in a peer-reviewed scientific journal. That'll be great. We'll discuss that when that's available. What's the story here? They're moving this down into younger folks,18 to 59, that's pretty young. Who are these people? Oh, it's only for people that are at increased risk. Well, what are those underlying chronic conditions that would make someone eligible for RSV vaccination?

Obesity, diabetes, chronic obstructive pulmonary disease, heart failure, chronic kidney disease, asthma. There actually are a number of folks that are going to be going to be considered for this. If you look at that age group, almost 10% of Americans have one of those qualifiers. Then once you bump up to the 50 to 64, about a quarter of Americans have the qualifier. Then once you get to 75, just everyone across the board.

VR: I was surprised to learn that 10% for 18 to 49. That means those people are all at risk for severe any infection.

DG: It's really true, yes. We starting to realize that these are our neighbors, these are our children, these are our friends.

VR: Daniel, when the CDC says you don't need a vaccine if you're under 50, let's say COVID.

DG: Unless there's always that caveat.

VR: Unless you have -

DG: An increased risk, yes.

VR: Some people don't even know they have an increased risk, right?

DG: I think a lot of people also are not comfortable admitting that they actually have obesity. We'll follow that. Another update, I thought this was very timely. Pneumococcal disease. "CDC Recommends Lowering the Age for Pneumococcal Vaccination from 65 to," oh my gosh, "50 years old." That sort of gets me in there. The ACIP voted to expand its recommendation for the use of certain pneumococcal vaccines, including - we could talk about which ones they included.

First, just the comment that lowered the vaccination recommendation from 65 down to 50. That makes sense. We have a couple of choices here. What vaccines are we predominantly using? We've moved a lot away from the polysaccharide to the conjugate vaccine. We're basically talking about two products, a Pfizer product and a Merck product. Don't worry, they had their news press releases ready to go. For Pfizer, that's the Prevnar 20. For Merck, that's the CAPVAXINE, which is a PCV21.

Then they're already battling it out. Merck is telling us that their vaccine, which was just approved in June, covers 85% of the invasive pneumococcal disease versus the 51% for their competitor Pfizer with the PCV20. Now I actually, Vincent, so I went to go get my Novavax. It was a funny thing. First I go online. I'm going to schedule my Novavax and I find out there's a local Rite Aid that I'm going to go to. I put in that I want my Novavax.

Hey, while I'm there, I also want my flu shot, get them both at the same time. Then they've got good marketing. They're like, "Hey, while you're here, it might be time for you to update your tetanus, diphtheria, and acellular pertussis." Sure, I'm pro-vaccine, I check that box. They also say, "By the way, would you like to get your pneumococcal vaccine?" I'm thinking, "Well, what's that all about? I'm not over 65."

VR: There you go. They're up to date, that's good.

DG: Yes, I'm up to date.

VR: You get four vaccines at once.

DG: Yes, so I did. It was absolutely fine. I think there was Saturday, like for an hour, I was feeling a little tired, but it's all right. Then I felt all better. All right, so we'll follow. Flu hasn't really quite increased. We're still waiting for that. We'll keep an eye on that. Usually starts

taking off down in the South. Now is the time to get those flu shots, reduce your risk of severe disease.

COVID, this is going to be interesting this time. No more yellow, no more orange, no more people at that 8% of total deaths. Things seem like they've settled down a little bit. We've got Colorado and Illinois, which are in that 2-to-4% of all the deaths are due to COVID. The rest of the country is 2% or lower. Our wastewater is still going in the right direction. We're actually getting to that spring low, and we'll see what happens next. What I think is interesting, and someone reached out, made me aware of this, is what's going on in the UK. I just want to talk a little bit about the pattern in the U.S. relative to the UK. I care, because my son Barnaby is over there in London, breathing, which is risky activity when it comes to COVID.

Riding in the tube with all those Brits who are also breathing. You can see, and we'll leave in a link to the UKHSA dashboard. You can see, influenza comes up, and then we have a nice flat period. RSV, very similar. It has this nice seasonality, and then it goes down, and we're starting to see a little bit of RSV coming up in the UK. COVID, we actually have a fall surge. It really did not - it rose, it went down a little, it came back up again. Really not in much of a seasonal pattern there.

VR: Yes, now it seems to be coming down off that little peak.

DG: Yes. We'll see what happens there.

VR: Yes, that's why we left the UK,

DG: Is that why we left? Why we wanted our own country?

VR: We have our own epidemiological patterns.

DG: Yes, but we kept all the really good stuff, like inches and feet and wonderful measuring system. I put up the variants. Because we have these new variants, XEC. I don't know what that means to you, Vincent, but what it means in common mythology is that we're going to have a winter surge. Is that what it means?

VR: Not necessarily.

DG: You mean it might have something to do with behavior and not the fact that there's -

VR: The problem is, what do people do during the winter? They stay indoors with each other. That would cause the surge with any variant.

DG: Yes, I think that's the thing. There's always a new variant. All right, so you mentioned the indoors and that moves us right into ventilation transmission. The article, " The Risk of SARS-CoV-2 Transmission in Community Indoor Settings: A Systematic Review and Meta-analysis," published in *JID*. Here the authors conducted a systematic review to estimate the secondary attack rates of SARS-CoV-2 and the factors modifying transmission risk in community indoor settings.

I have to say, I really like this way of looking at transmission. Although vaccines are the most effective preventive measures for severe illness, they don't really substantially reduce the SARS-CoV-2 transmission in these crowded settings. We talked about that. Vaccines prevent severe disease, but what can we do relative to these indoor settings? This sort of updates us.

Early on, there was a focus on how are things transmitted and the close contact, but very clearly you get in an indoor setting with poor ventilation, that six feet away is just not far enough. Here the authors included 34 studies with data on 577 index cases, 898 secondary cases, and 9,173 contacts. The setting-specific SARS, what a horrible word, secondary attack rates were the worst. What was the worst? Can you guess? Where's Rich Condit and Kathy? I think they do -

VR: Oh, singing events.

DG: Singing events. Singing events were the worst, followed by indoor meetings and entertainment venues. Then also in the top three, fitness centers. Now here's what's actually interesting. They found no difference in the secondary attack rates looking at particular index case characteristics, viral setting specific characteristics. I'm going to go through Table 2 because I want to talk a little bit about what people have - the myths out there.

One of the myths out there is that, oh, well, you see the different variants have more transmissibility. They have higher secondary attack rates. Let's look at that. Is that really true? They've got a whole bunch of studies here. We've got studies looking at wild type, Delta/Omicron. What did we see? Did we find any statistically significant difference in secondary?

VR: No difference.

DG: No.

VR: In fact, these settings are good settings to measure this because there are a lot of people in one place. These entertainment events, singing events, indoor meetings, et cetera, those are always good to capture this information. Yes, there's no difference in transmission. It's what we've been saying all along. It's people's behavior.

DG: Isn't this kind of crazy because everyone is certain? No one believes this is true because they decided and then they said it often enough. I think you only have to say something like five times -

VR: Unless you're a cardiologist, then you think it's true.

DG: Yes, then you're sure it's true. Here's the science. We're looking at the science. We're looking at all these studies, 34 studies and the secondary attack rate for the wild type, for the Delta, for the Omicron, no difference. No difference.

VR: Happy to see this.

DG: That's special.

VR: What does make a difference, Daniel?

DG: What's interesting here, and maybe this is a little concerning, is what if we look at the symptom status of the index case? Let's say you've got someone who's symptomatic, they're coughing, they're sneezing. I'm keeping 10 or 20 feet away from them versus someone who's asymptomatic. The symptomatic people, the secondary attack rate, we only have 17, but the asymptomatic person, they're right in your face, you don't even know they're breathing the virus so you don't bother to back away, it is 54. It's like, three times as high.

VR: Yes, that's the killer about asymptomatic shedding. You don't know. That's why you have to wear a mask all the time.

DG: It's a problem. if you're at high risk and you're going to be in one of these indoor like poorly ventilated situations, it's really tough. The other which was age, right?

VR: Logically, we shouldn't think that you could look at someone and say, "Oh, I can take my mask off."

DG: We do. We tend to believe that. There's this whole idea, "I feel better. I can't be contagious anymore. I feel fine. I certainly couldn't be the one who infected that person." Yes, we have a common sense that just is resistant to the truth, to the facts. We also saw like, more transmission in the pre-symptomatic than the symptomatic, so sort of a hierarchy.

Asymptomatic, the worst, followed by pre-symptomatic. Really the people to worry about the least are the symptomatic people because we just don't hang out with them. Then interesting enough, the age actually, you saw transmission under 40, you saw transmission over 40. Actually, it was the older folks that were spreading it more. Interesting stuff here.

VR: I wonder why the older folks are spreading it more. They think they know everything?

DG: Maybe because the hearing, they can't hear so well, so they get really, "What? What did you say?" I'm speculating. I don't know. We'll have to follow that up. Kids do spread, by the way, walking biohazards.

Let's move into vaccine. We've got a couple of interesting things here. The first, the article, "Relative Effectiveness of the Novavax, the NVX-CoV-2373 Vaccine, Compared with the BNT-162b2," so the Pfizer-BioNTech," Vaccine in Adolescents," published in the *Pediatric Infectious Disease Journal*.

This is a retrospective matched cohort study that evaluated the efficacy of two doses of Novavax compared with that of the Pfizer-BioNTech vaccines in preventing severe acute respiratory syndrome, COVID-2, infection in adolescents. They analyzed 13-week risk differences and ratios between the two vaccines. They end up with 465 folks in each group. Let's give everyone just a little chance to get those bets in.

We're just looking at infection rates, so all right there. I wish we were looking at something else, but they're adolescents. Throughout the follow-up period, 4% of the Novavax recipients and about 3% of the Pfizer-BioNTech recipients contracted SARS-CoV-2 infection, really basically overlapping confidence intervals. The findings suggest that really pretty similar between the two vaccines, but then let's look at the data.

Let's follow it out over time because that's what I'm thinking, "If we just follow it long enough, there's this idea that the Novavax has more durability because we're not going to have those long-lived plasma cells in the bone marrow." We're actually starting to see a little separation going in the wrong way for Novavax at about 13 weeks, but still overlapping confidence intervals, so I don't want to make it too obvious.

VR: Would have been nice if they went longer, right?

DG: That's what they need to do, and they can, right, just keep following those folks and see what happens over time. I think this makes life a little bit easier. We've been talking about this. Let's just sort of put it out there. The CDC Vaccine Advisory Group recommended and the CDC Director Mandy Cohen endorsed a second 2024/2025 COVID-19 vaccine dose, basically saying, "Hey, listen, if you're 65 and older, or maybe you're younger, but you have risk factors, just get a vaccine every six months." Why did they say this?

Well, the CDC makes a couple comments. Data continue to confirm the importance of vaccination to protect those most at risk for severe outcomes of COVID-19. Receiving recommended COVID-19 vaccines can restore and enhance protection. Then, interesting, COVID-19 vaccination also reduces the chance of suffering the effects of Long COVID, which can develop during or following acute infection and last for an extended duration. I like that they're mentioning Long COVID as an endpoint. I like the fact that they acknowledge it. This really can last for an extended duration.

All right, the early viral phase we have our guidelines. Apparently, now they're going to talk about rebound with monoclonal antibodies. No one's immune, shall I use that term. We have the article, "Viral and Symptom Rebound Following anti-SARS-CoV-2 Monoclonal Antibody Therapy in a Randomized Placebo-controlled Trial." Let's see where this one was published, *JID.* In this study, the authors explored viral and symptom rebound after COVID-19 monoclonal antibody cocktail therapy. They're going to compare that to placebo in the ACTIV-2 trial.

The participants underwent these nasal PCRs at study days three, seven, 14, and 28. Now they're going to be smart. They're going to define the rebound as RNA greater than or equal to 3 and greater than or equal to 0.4 log increases from day three to seven. You've got to have symptom rebound, hospitalization, moderate to severe symptoms. They've got to last for greater than two days after your symptoms initially got better. What do they find, Vincent?

VR: There's no rebound.

DG: There's no rebound.

VR: I'm happy because now we would have had monoclonal rebound, right?

DG: No. Then no one would want to ever treat anything. Oh my gosh. All right. What do we still recommend? Number one, Paxlovid. Number two, remdesivir. Number three, molnupiravir. Number four, convalescent plasma. We're really not doing a lot of monoclonal, so this is just maybe comments for the next time around. Early inflammatory week. Number one, steroids at the right time in the right patient at the right dose and for the right duration. We have some updates from the American Society of Hematology, guidelines for anticoagulation.

There are about 30 authors there. I see my name somewhere in the mix, about the eighth author in of the 30. I think it's random, the order. I don't know. I certainly don't feel like I did more work than the 22 people after my name. Really, it's a group effort. We've been continuing to work on updating these. "ASH Living Guidelines on Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Executive Summary." Published in *Blood Advances*.

Really just to sum this up, no big game-changers here. In most situations, based on the available evidence, recommending prophylactic intensity over therapeutic intensity anticoagulation, with some exception if you freed through. Then the other, just to highlight, the ASH guideline panel continues to suggest against using post-discharge outpatient anticoagulant thromboprophylaxis in patients with COVID-19. Unless you have another reason, unless they have confirmed clotting, or maybe they have another indication for anticoagulation.

As always, an individual assessment of the patient's risk of thrombosis and bleeding and shared decision-making are important when deciding on whether to use post-discharge thromboprophylaxis. We say that for every - we always make a caveat there. Pulmonary support, remdesivir, and then immunomodulation in some cases.

Just a couple to finish us off here for COVID, the late phase. I really like this first. It's really a call to action. It's the article, " The Importance of Including Long COVID Outcomes When Developing Novel Treatments for Acute COVID-19," also published in *JID.*

The abstract really hits what they're sharing with us. Amid efforts to develop effective treatments for acute COVID-19, there's growing recognition of the need to address Long COVID as a key outcome measure. They argue there are seven compelling reasons to include Long COVID. One, Long COVID is not rare. Two, Long COVID is debilitating to individuals and it has a high societal cost. Three, those at high risk of severe COVID-19 are also at higher risk of developing Long COVID. Four, treatments for acute COVID may actually reduce the risk of Long COVID.

Five, measures exist to track Long COVID. Six, Long COVID considerations are potentially important for making those acute COVID-19 treatment decisions. I'm driving my friends to the airport and my wife is calling me, "Is it still true? Do we still think that early antivirals might decrease the risk of Long COVID?" Seven, deaths and hospitalizations due to COVID-19, are, they say, increasingly rare. I'm just going to say are decreased. It's worthwhile to include assessments where possible to facilitate the uptake of acute COVID-19 treatments that lessen the societal burden of Long COVID.

Actually, in Figure 2, they show that really in almost 70% of the clinical trials out there, the registered clinical trials, don't even look at Long COVID. There's only about 5% that have explicit data collection on Long COVID. I agree with them, that really needs to change. For most people, this is much more common than dying, than ending up in the hospital, is ending up with Long COVID. I'll wrap us up with the last article, “The Persistence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME-CFS) after SARS-CoV-2 Infection: A Systematic Review and Meta-analysis," published in *Journal of Infection.*

These results of a systematic review and meta-analysis to determine the proportion of Long COVID patients that actually satisfy the ME-CFS diagnostic criteria. They find 13 eligible studies, a total of 1,973 Long COVID patients, and they actually find that about half, over half, 51% of Long COVID patients actually satisfy ME-CFS diagnostic criteria with fatigue, sleep disruption, and muscle joint pain being the most common symptoms. Importantly, Long COVID patients also experience the ME-CFS hallmark symptom, post-exertional malaise.

VR: Let me understand this. ME-CFS and Long COVID are different, yet there are some symptoms that overlap. We think for ME-CFS, it's a post-acute disease, but it could be many, many different kinds of viruses. SARS-CoV-2 is just another one that could lead to ME-CFS, right?

DG: I actually think that's a perfect way to sum it up, yes. Some people after COVID end up with ME-CFS. They meet the diagnostic criteria, that non-restorative sleep, the cognitive issue, the post-exertional malaise, yes.

VR: In a way, it's a validation of ME-CFS because previously, it was always hard to know what the trigger was, and many didn't believe the patients. Now you have a clear temporal association, so there's no question.

DG: I hope that's the way this is taken. There was this concern with ME-CFS and Long COVID, and, "Hey, you're stealing our spotlight." It was never a spotlight. Maybe now they're generating a spotlight. I think that's the way to view this. I think this is a validation. Hopefully, this is going to lead to less dismissiveness, a recognition ME-CFS, it's a thing. Long COVID, it's a thing, and these are people suffering that we can help.

I'll finish it off with no one is safe until everyone is safe. We're finishing this off - I think this is the last one that will drop when people have time to go on to parasiteswithoutborders.com to help us with our Floating Doctors fundraiser. We're hoping to get up to a maximum donation of $20,000 to help support Floating Doctors and the great work they do down in Panama.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Chuck writes, "Received an mRNA boost on September 20th. Exposed to COVID on the 22nd. A friend visited with a slight cough. He had just returned from Europe, unmasked on planes and terminals. Positive tests on the 26th. Paxlovid the 27th." Question one, "How does getting COVID so soon after the shot affect my immunity? This is my first bout of COVID."

DG: Basically, you're getting that presentation to your immune system. I would not feel like it's going to do anything untoward to the vaccine, particularly kind of got the timing right on

this here. I'm hoping at the end of the day, you're going to get some degree of immunity. I'm also hoping that you're going to get through this and do well.

VR: Question two, "I'm a 74-year-old aerobic athlete. How should I approach return to activity? Writing on day 26 after positive test. Still a bit tired with cold symptoms. Have not missed a show in two and a half years."

DG: Well, Chuck, I'm sorry that you ended up with COVID. Great, though, that you're a 74-year-old aerobic athlete. You've been training for this. You're ready for this. You'll notice that your heart rate variability probably get a little bit more of a heart rate increase just with what before would not do it. Slow down your pace a little bit. It's OK to exercise, but just don't overdo it. Keep that heart rate down, in a safe, maybe a 60% of maximum. Let's see, you're 74. That's going to be 150. We're going to say, keep your heart rate down about 100, 110 or so. Just take it easy for a little while as you recover.

VR: Lori writes, "In your October 17 episode, you mentioned a result from a study finding that multiple boosters significantly reduce long-term symptoms by 30-70%. I'm assuming it means that multiple boosters before Long COVID symptoms will reduce Long COVID. Not that getting boosters once you have it will reduce it. Please clarify."

DG: We actually got another paper. It's, hopefully, this is like the final submission to *Nature Communications*. Looking at really the issue of vaccines as therapeutic. One of the first things that we notice, and this is your 30-70%, is that people who had Long COVID, and this is when vaccines just came about. If they got vaccinated, they got one dose, two dose, three doses, we saw about this 50, 60% reduction in people ending up, 50, 60% reduction in people still having Long COVID.

Fifty, 60% of people got their three doses of vaccine, and the Long COVID went away. We did a prospective study that was published, and it was a collaboration with Akiko up at Yale, and I think Mount Sinai was involved as well. Smaller subset of patients confirmed that was really it. Sixty percent got better, which is great. Unfortunately, 20% just didn't get any better. Twenty percent actually said they felt a little bit worse.

We were trying to understand why that happened. The vaccines can actually be a therapeutic. The other side, as we've seen repeatedly, is like why do we no longer see 20% of the population getting Long COVID? It really looks like there's a correlation that vaccines before infection reduce your risk of Long COVID. Vaccinations after may actually have a therapeutic benefit.

VR: Robert writes, "A longtime listener and advocate for science. Please tell me how a clinician, ‘Midwestern Doctor,‘ gets to this point. It's quite frightening to see this type of rhetoric. Thanks for all you do." He sent a Substack by a person named A Midwestern Doctor from the Forgotten Side of Medicine who writes, "Basically, COVID-19 vaccines cause cognitive impairment. This is making doctors make mistakes."

DG: Oh, my gosh. It is crazy. I was at a talk this morning, and then people were talking about pancreatic cancer. The whole anecdotal like, "Oh, we seem to be seeing more of this." There's this weird anecdotal thing. If anything the mortality from cancer is actually going down. There was all these ideas that, "Oh, no, COVID-19 vaccines are going to because all

these people to die from cancer." Actually, the data is not supporting any of this. This whole idea that COVID-19 vaccines are associated with cognitive impairment. If anything, COVID-19 and Long COVID can manifest as cognitive impairment. It's really tough.

VR: David writes, "In late August, I did suffer COVID, was quickly treated with Paxlovid, and quick resolution of symptoms. I'll be traveling to Chicago for Thanksgiving. I was wondering if I should still get my next dose of vaccine two weeks prior to the trip, or should I wait till December? Thanks for your advice." David is an MD asking for your advice. That's great.

DG: Thanks, David. Actually, your timing is like right on the edge there. It was interesting I saw something on social media where it was like, if you get infected in June, then they have the three months and you get your next. Right here, you got infected in late August. We're thinking you should get your shot in late November. You're still in that three-month window. If you did it two weeks early, so it had that peak as you go into the holiday season. I think that's reasonable.

VR: Connor writes, "I'm a nurse in the emergency department at a community hospital connected to a large academic institution in the South. I'm coming up on finishing my first year as an RN, and I have been rather disheartened by the overwhelming reluctance of providers to prescribe Paxlovid for COVID patients. There's always some sort of rationale from the provider when asked about it. The patient's not at high risk. Oh, it's too expensive.

Rebound is not worth it. I've tried before to suggest that the data actually suggests that these drawbacks to Paxlovid are overblown, especially with providers who know that prior to being a nurse, I worked as a master's trained chemist. I'm always told that Paxlovid is really just not good. Do you have any recommendations for advocating for a change in practice, especially for a new nurse interacting with seasoned providers?"

DG: Connor, this is challenging. As you probably realize, physician student might not like to be challenged by their patients or their nurses. It is really a difficult line to walk to. I suspect that at your community hospital, there are maybe a few physicians in the same camp who feel exactly the way you feel, who are aware that there are NIH and Infectious Disease Society of America guidelines that are evidence-based.

As you're probably seeing, you're seeing patients end up in the hospital because they were not given Paxlovid. What was my advice? Find those evidence-based providers. They're there. Then, sort of work as much as you can. It is a challenge. I certainly appreciate how tough this is. I find this tough as a physician interacting with physicians who are not evidence-based.

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

DG: Oh, thank you. Everyone be safe.

[END OF AUDIO]