This Week in Virology

TWiV 1082 Clinical Update

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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

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VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1082, recorded on January 25, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today here in New York at the Incubator, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: All right, Daniel, what's with the tuxedo? We said we were going to be casual here.

DG: You didn't get the memo. Tonight is Burns Night. For any of the Scots in the audience, this is a celebration of Rabbie Burns, famous for “Auld Lang Syne,” the Nobel laureate poet of Scotland. After I record, I will be going with my daughter, Daisy, to celebrate Burns Night. We will be enjoying some wee drafts of Scotch. We'll be reciting poems, singing Rabbie Burns' songs, and I will be enjoying some haggis.

VR: You have to wear a tux to this?

DG: This particular event, this is a very formal occasion.

VR: How many people are going to this event?

DG: I think it'll be about 100 or so.

VR: How do these people get selected?

DG: You just sign up. It'll be a mix of - You can wear a standard Western tuxedo, which Tuxedo Park, New York City, we're the home of the tuxedo, or you're allowed to wear a kilt.

VR: What you have is a standard Western tuxedo. You tied the bow tie yourself, I see.

DG: Yes, I just learned to do that.

VR: OK, very good. All right, well, we're here to do a clinical update.

DG: All right. Let's start off with our quotation. "Good advice is always certain to be ignored, but that's no reason not to give it."

VR: That's pretty sad that it's always certain to be ignored, right?

DG: I think people need to, unfortunately, learn their own lessons. No, that's a quote from Agatha Christie. Sure, we have a lot of fans in the audience. I particularly enjoy her Poirot stories with the Belgian detective. Let's get right into RSV. We warned a little bit about this, that things were starting to come down. Sometimes, we see that double hump. It looks like we saw that double hump. RSV is still up there. We're still seeing a significant amount of RSV activity.

Just a reminder, we're going to actually talk next week about all the updated safety information. We've really moved from this shared decision-making. Most of us are just saying, "If you haven't gotten your RSV vaccine and you're 60 or over, go ahead and get it. If you're pregnant last trimester, go ahead and get it. Let's really reduce these numbers."

VR: Now, Daniel, I can't read the X-axis on either of these. On the right, you have a big peak. When was that, two years ago?

DG: Actually, I should pull out my glasses because the numbers are tiny on the X-axis. The Y-axis is huge. Let me just get this close so I can see it. Yes, that was actually November of 2022.

VR: Do you remember this big outbreak back then?

DG: Yes. One of the tough things, and I was listening to a *TWiV,* two back. Actually, I missed one of the deep dives. One of the challenges we've had over time with data is if you don't test for something, you're not going to see it. When we went into early days of 2020, all of our resources went into SARS-CoV-2 viral testing. We weren't testing for flu. We weren't testing for RSV. It was a bit of a data vacuum.

Actually, it got people confused because they were saying things like, "Oh, you can't get two things at the same time." You can't diagnose two things at the same time if you're only testing for one of them. Yes, we had quite a lot of RSV last year. You can see the peak's a little bit lower this year if you look at the data that we'll leave links in.

VR: 2022, big peak, right? Then, it looks to me like not a lot throughout '23. Now, at the end of '23, and now it's gone up again.

DG: The 2022, that's end of November going into December. The peak was a little bit earlier. In a lot of ways, that is good from an epidemiological standpoint. Because when you have your peak going into the December holiday, that peak can start to stretch. People return to school. You get this little resurgence that we're seeing. I'm hoping next year, we can compare this and see a nice drop, a much lower level. OK, let's move into influenza. Levels are still high here. We're still above the 10% positive. We're still seeing lots and lots of cases.

VR: What I find interesting there, Daniel, is you see a peak and we're declining. You said last time, "We'll see if it goes up again." It's still declining, but it could still go up. Because if you look at previous years, it does go up in middle to late January, early February.

DG: Yes, sometimes we see this sort of double peak. You can see it went down, but we're sitting on a plateau the last little bit here. We'll see, does it drop? Does it rise back up with people returning to schools? A lot of the kids, they're back in the elementary and all those schools. Universities, some of those are firing back up. We will see. It's mostly H1N1. It's over 80%, it's H1N1. Reassuring, the cases that we're seeing that are actually influenza B, it's about 17.5%. It is all Victoria lineage.

Remember, we had that confusion where someone dumped some Yamagata lineage sequences in from a few years back. No, we may be done with Yamagata lineage influenza B. All right. Across the country, we're still seeing a lot of activity. We're starting to see a little bit of sunlight, or should I say, green, a little bit of a few areas where the activity is starting to drop down. New York, it's getting a little bit better. Minnesota, I'm still not sure why they do such a great job out there.

VR: Someone asked me last night on the stream why some states are higher than others before the other states. It seems like it doesn't make sense epidemiologically that a border would do that, right? Is it a matter of testing sometimes?

DG: Part of it's testing, but part of it actually is the way the respiratory viruses come into the country and the way they spread. RSV, influenza, it's not like there's a border between Georgia and Florida. What happens is we often see the increased respiratory activity in the southeast, and then we see it spread through the country. It doesn't respect state borderlines.

VR: Because you see that Texas is very high. Just above it, Oklahoma is moderate.

DG: It's an average. If you're right on the border, it's not like you can move north 10 miles and be safe.

VR: Yes, but I also think that Texas reports it, and that's Texas, and then Oklahoma reports their own, and that's Oklahoma. They're separate entities.

DG: That's why you end up with the - You see the distinct borders. It's a reporting artifact. All right. Moving into COVID, can you believe we're still talking about COVID in 2024?

VR: Oh, we will forever, Daniel, right?

DG: It is here to stay. I think because it's here to stay, it's the big winter. It's a big respiratory pathogen. It's important that clinicians, that those of us that are not clinicians, potential patients, even clinicians, are up to date. Where are we? Deaths, we're still up at 2,381 new deaths just this last week. I mentioned I get this data from BNO. That's up 149 higher than it was a week before. Deaths are still on the way up.

We are starting to see a little bit of a decline in hospital numbers, a little bit of a decline in the ICU. If you look at wastewater, things look like they're on the way down. We're probably going

to see a drop in RSV, probably going to see a drop in influenza, probably going to see a decline in COVID cases.

VR: Daniel, the 2,381 deaths, why are those people dying?

DG: We're going to talk a little bit more about this next week. At this point, immunity is a fairly universal phenomenon. People have had repeated infections. People have been vaccinated. The biggest thing is we have individuals who are at high risk of progression, and they're not being offered early treatment. We'll talk a little bit about a veteran study that just came across my desk today.

What's happening is people are saying, "Oh, I think you'll be OK," waiting until it's too late. "Oh, it seems mild. Let's wait and see if you get sick." By the time people get sick and go from mild to moderate, it's too late. They end up in the hospital. Unfortunately, we still see these deaths.

VR: Most of these are elderly, you would say?

DG: They really are. The majority are elderly. Majority are people with medical problems. Some of the medical problems, to be honest, hypertension, obesity, high cholesterol, maybe a heart problem.

VR: We have a lot of that in the US.

DG: We certainly do. We certainly do. I'm going to move right into an article which I think hopefully will get a lot of thinking from our listeners. How is SARS-CoV-2 transmitted? How is this virus transmitted? What can we do to decrease the amount of SARS-CoV-2 transmission in healthcare settings? This is an article, "Integrated Genomic and Social Network Analyses of Severe Acute Respiratory Syndrome Coronavirus 2 Transmission in the Healthcare Setting," recently published in *CID, Clinical Infectious Diseases.*

These are the results of a retrospective cross-sectional analysis of viral genomics from all available SARS-CoV-2 viral samples collected at UC San Diego Health and social network analysis using the electronic medical record to derive temporospatial overlap, so that's time and space, overlap of infections among related viromes, and supplemented with contact tracing data.

We've got all these viral samples from UC San Diego Health, and we're going to look at who was where, who was where when. We're going to look at the genomes. We're going to follow transmission, and we're going to try to figure out what was going on. Were we doing things to mitigate transmission? Were we doing things that resulted in transmission? The outcome measure for any instance of healthcare transmission defined as cases with closely related viral genomes and epidemiological connection within the healthcare setting during this infection period between November 2020 and January 2022.

We're going to look at 12,933 viral genomes obtained from 35,666 patients and healthcare workers. A big thing about this study, which actually is really, I think, helpful, is UC San Diego Health has two campuses. There's the older Hillcrest Campus. This was established back in 1966, a 381-bed hospital with multiple shared patient rooms, and they're going to compare

this to the newer 418-bed La Jolla Campus built between 1993 and 2016, where they have a majority of modern single occupancy rooms, better ventilation systems.

During the study period, November 2020 through January 2022, there were, well, 15,333 adult admissions at the Hillcrest Campus, 20,765 at the La Jolla Campus. Where do you think most of the transmissions occurred? Can you guess?

VR: I would guess at the older facility.

DG: The older facility with poor ventilation.

VR: Poor ventilation, multi-patient rooms.

DG: All the people stuck in the rooms. Yes, actually, 79% during the second and third, 75% during Omicron. Yes, the majority of the transmission was actually happening at Hillcrest, where only about 21% were at the La Jolla Campus. The rate of SARS-CoV-2 transmissions per 1,000 admissions was 2.54 at Hillcrest compared to 0.63 at the La Jolla Campus. That's quite a -

VR: Basically, they can use the genomic data to imply transmission, right?

DG: Yes, we can say, "Here's your index, we've got the genetics. Here's who gets it. It's the same." Six-fold higher transmission when you stick a whole bunch of people together in crowded rooms with poor ventilation. We're not surprised, but there are some more interesting things. Most patients who either acquired or transmitted SARS-CoV-2 in the hospital were in a shared room during part of their stay.

Now, this is interesting. They did not identify a single transmission event from exposures via open doors of COVID-19 patients or from patients being placed in non-negative pressure rooms. Unless you're in the same room with a person, and this is a big thing because there's this whole terminology around airborne. Recently, there's these measles issues where they're like, "Were you even in the building?" Measles is like if you're even in the building, 90% of people are getting measles.

There's really this - People love to use that like, "OK, how can it be transmitted through the air but not be airborne?" This is one of the things that we're seeing from this study. This is not measles, this is not tuberculosis. If you have an individual in a well-ventilated room, it's a private room, even if the door is open, it's not like it's coming out and just filling the hallways.

VR: A long time ago, you could have sat in the hallway of the hospital and done *TWiV* clinical updates.

DG: I didn't need to worry as much as I did.

VR: You went to your car because you were -

DG: Yes, I wasn't sure. Is it going to sneak under the crack, under the door when I was - Actually, that's also, I think, interesting. There were no transmissions from COVID-19 patients to healthcare workers in the ICU. That makes sense, too, because we've talked about timing.

First five, seven days, that's when we see all the transmission. Second week, that's when you get the inflammatory, the cytokine storm. That's when people end up in the ICU.

Most of those folks who end up in the ICU, even though they're PCR positive, they're no longer contagious. It sort of was safer for me to be in the ICU.

VR: ICU, the beds are all open to each other, essentially, right?

DG: Depends on the unit. A lot of them, they're separated. What we had done during the height of it, there was such a large volume that we reversed things. We made the entire ICU at negative pressure. You would enter with an N95 and everything was open because it was just the ability to give each person a protected space. To summarize, the majority of healthcare-associated transmission events happened either between healthcare workers when there were breaks in masking protocol or in the setting of shared patient rooms in a hospital with older infrastructure.

They suggest that airborne infectious isolation rooms with negative pressure differentials are not indispensable to safely managing patients infected with SARS-CoV-2. They found that masking for source control was effective in the study. However, given that there are inevitable lapses in adherence to infection prevention protocols, healthcare facilities could further benefit by expanding mitigation measures, including enhancing ventilation and air exchanges, particularly in those older facilities, in all spaces.

VR: Making more single occupancy rooms, but that's tough, right?

DG: Financially, it's tough because you lose capacity. We're already having issues now, particularly this time of year with capacity. What do you do?

VR: This one hospital, the new one, is 416 beds. You're limited to 416 patients. It's not a lot during an outbreak, right?

DG: No, it's not.

VR: ICU capacity is even lower, typically?

DG: Yes. Most hospitals, it's 10% or less of the total beds are ICU beds.

VR: That total includes ICU?

DG: Yes.

VR: OK.

DG: All right. Vaccines. This week, Peter Hotez is perhaps celebrating as Corbevax, the COVID-19 vaccine developed by Children's Hospital down there in Texas. It's developed by BioE, India-based, on the RBD protein antigen technology from this Texas Children's Hospital Center for Vaccine Development. They received WHO Emergency Use Listing approval. This is where they use the recombinant Pichia pastoris yeast strain that expresses the RBD protein of SARS-CoV-2. Then, they formulate this with optimized adjuvants to develop this vaccine.

VR: This is like an EUA in the U.S.?

DG: It's kind of like that. The one thing I have to say, and Peter, I don't know how many of you are listening to our updates all the time, I would love to see some peer-reviewed data on the efficacy of this vaccine.

VR: I was just going to ask you that. Do we have any such thing?

DG: I don't. I was looking through this because I've got to figure the WHO has got to have some kind of data if they're going to give this Emergency Use Listing. I don't know. I was reading a little bit through. There's modifications. This is not just the original RBD protein, there's modified updates. I'd love to see the actual efficacy data.

VR: The other vaccines are not RBD only?

DG: No. That was actually a decision early on. Do we do just RBD? Do we do the whole spike protein?

VR: I remember Pfizer was doing RBD and whole spike and they decided on whole spike, right?

DG: Yes. I don't know. I'd love to see the data. Poor Peter, he always gets this - What is it? Industry shawl and you're just, "He's giving this stuff out for free." All right.

VR: Hopefully, it works. That's the thing.

DG: We want it if it works. You give it out for free. All right. COVID early viral phase. Maybe Peter will write in.

VR: I don't think Peter ever listens.

DG: OK. All right. COVID early viral phase. This is interesting. I ran across this article several times because it seems to have made a splash in the press. Then, it keeps bringing me back to this article. I'm like, "Oh, OK. It's that article." The article, *"*Oral Simnotrelvir for Adult Patients with Mild-to-Moderate COVID-19," was published in *The New England Journal of Medicine*. Simnotrelvir is an oral 3-chymotrypsin-like protease inhibitor that's been found to have in vitro activity against SARS-CoV-2.

Vincent: In vitro means in cells and culture, right?

Daniel: You got it, you got it, in cells, in culture. Now, just to give people a little background. In vitro, in cells and culture. In vivos, you can actually put it in living systems. We mentioned this protease. There's two viral proteases. There's the main protease, and that's the chymotrypsin-like protease, or the Mpro, the main protease. The other is the papain-like protease. Really similar to Paxlovid. We've got a protease inhibitor here.

These are the results of a phase 2-3 double-blind, randomized, placebo-controlled trial where they assigned patients with mild to moderate COVID-19 onset of symptoms within the past three days in a one-to-one ratio to get the simnotrelvir, so it's 750 milligrams, plus 100 milligrams of ritonavir or placebo.

VR: You need ritonavir for this one also.

DG: Yes, to keep those levels up and causes all those drug-drug interactions. The primary efficacy endpoint was time to sustained resolution of symptoms, defined as the absence of 11 COVID-19-related symptoms for two consecutive days. Then, we stopped looking. Safety and changes in viral load were also assessed. Here, they look at a total of 1,208 patients enrolled at 35 sites in China: 603 get the Simnotrelvir, 605 get placebo.

Among patients in the modified intent-to-treat population who received the drug or placebo within 72 hours after symptom onset, the time to sustained resolution of symptoms was significantly shorter in the treatment group than in placebo, so 180 hours versus 216 hours. I was sort of trying to do the math, about 36 hours sooner, about a day and a half sooner, you feel better. Median difference, they say, at 35.8, so about a day and a half. On day five, the decrease in viral load from baseline was greater in treated than placebo. Now, the incidence of adverse events during treatment was a little higher in treated, so 29% versus 21.6%, but most of the adverse events were mild or moderate.

VR: How would this compare to Paxlovid? Did they trial it in a similar way, time to resolution?

DG: It's not head-to-head. There was the EPIC Standard-Risk, which was trying to find this kind of a difference. I suspect it's pretty similar as far as the impact on symptoms.

VR: They only look for two days.

DG: They look for two days and they don't ask, "What about day eight, nine?" They don't follow it a little bit longer, which would be helpful. I think one of the big arguments that they've talked about here is most people, when they're making a decision about the medicine, they're like, "I'm not going to end up in the hospital. I'm not going to die."

To have that conversation, this medicine will make you feel better more quickly. You'll feel better a day and a half sooner. A lot of people, that's going to be what motivates them to want to go ahead and take the medicine, maybe clinicians to go ahead and actually prescribe the medicine.

VR: I presume this is not going to be licensed in the U.S.

DG: You wonder where it would fit in when you've already got Paxlovid.

VR: It's very interesting. It's for patients with mild to moderate COVID, whereas Paxlovid is for people who might have serious.

DG: Yes, for mild to moderate, but with a risk of progression. Paxlovid isn't really FDA approved for make you feel better quicker. It's FDA approved for keep you from progressing to severe disease.

VR: Is it just for people, Paxlovid, who are potentially going to have severe disease with comorbidities or older and so forth?

DG: That's really the FDA approval, but we're starting to see a little bit of a slide. We'll talk a little bit about some of the discussion about Long COVID and is that really an evidence-based place for Paxlovid.

All right, last week, I promised I would talk about this preprint, "Persistence of an Infectious Form of SARS-CoV-2 Post Protease Inhibitor Treatment of Permissive Cells in Vitro," posted on *bioRxiv*. You're going to recognize some of these authors there. The authors are Manoj S. Nair, Maria Luck, Yaoxing Huang, Yosef Sabo, and David D. Ho. All working up at Columbia University in the Hammer Science Building.

VR: I know it well, and so do you.

DG: Yes, very well, actually. This was posted on December 21, 2023. Since I've been getting a lot of questions, and there's good science here, I wanted to spend some time going over the results and what are the actual implications. In this investigation, the authors look at persistence of infectious SARS-CoV-2 in several permissive cell lines after treatment with high doses of nirmatrelvir or ensitrelvir. They're also going to look at remdesivir, by the way, in vitro.

As everyone knows, nirmatrelvir, that's that protease inhibitor in Paxlovid. Ensitrelvir, that's the Japanese protease inhibitor known as Xocova. They're also going to, as I mentioned, be throwing remdesivir in these assays. That's Veklury, I guess, the Viking drug. The three different permissive cell lines are going to be an HuH7 ACE2, an A549 ACE2, and a vero TMPRSS2. We'll go through the figures a little bit. Jump in, Vincent, at any point.

To start with Figure 1, they examine the persistence of, they say, infectious virus in HuH7 ACE2 for three consecutive days after treatment with each of these drugs, so nirmatrelvir, ensitrelvir, or remdesivir. The decay, half-lives of the infectivity were measured to be 23.9 for nirmatrelvir, 26.7 for ensitrelvir. Now, in distinct contrast, remdesivir-treated cells had no measurable infectivity at all the time points assessed. They say that this initial finding suggested that while nirmatrelvir or ensitrelvir could block the main viral protease, a replication-competent form of the virus can actually persist post-treatment intracellularly. Similar results with other cell types, more time points, and even with a different variant.

VR: What's the protocol? They infect and then add the drug?

DG: Yes, they infect.

VR: How many hours later?

DG: I want to say it was about eight hours or something, a pretty short period of time. Infect, jump in. We've got -

VR: I just remember, we did the paper on Paxlovid a long time ago on *TWiV.* There was a substantial inhibition of virus reproduction. This is slightly different. I don't know what accounts for that.

DG: This is a log scale and you're still seeing this pretty significant reduction.

VR: It's interesting there, remdesivir, really, on the graph, there's nothing. There's no infectivity.

DG: Yes, it's pretty impressive actually, right?

VR: Yes, one only wonders if remdesivir had been orally available, what it would have done.

DG: Even if there'd been better access. Right now, we still do it, but it's 0.5% of treatment courses out there are remdesivir. Really, oral is just such an easier lift than telling somebody who's sick, "You've got to go somewhere and get an IV infusion for three days in a row."

VR: Despite the non-zero effect of nirmatrelvir, it's still very effective in patients.

DG: I think that's an interesting thing, even before we get onto the next figure. This is interesting. This is great. If you look at the pine tree data, which is getting it in the first seven days, you look at the EPIC High-Risk data, getting Paxlovid in the first five days, you got about equivalent clinical outcomes, about an 88% reduction in progression. How meaningful is this? We'll come back to that. How clinically relevant is this?

VR: It's a cell culture also.

DG: It's also a cell culture, so you don't have the whole -

VR: Very different from a whole animal, whether it's a non-human or human.

DG: Then, we'll go on to Figure 2. There, we're going to look further into this phenomenon by examining levels of SARS-CoV-2 genomic RNA, nucleocapsid protein in infected cells, again, treated with nirmatrelvir or remdesivir. Here, we've got the HuH7 ACE2 infected with SARS-CoV-2. Here, actually, it says six hours. It's infected at 0.5 MOI for six hours, after which the virus was removed and replaced with growth media, supplemented with either the nirmatrelvir or the remdesivir. Then, we've got the infectivity decay post-removal of the nirmatrelvir or remdesivir. Again, I've been on remdesivir. It seems a little bit better here.

VR: In terms of genomic RNA, yes. I don't know what that means because this is a PCR assay, so it doesn't necessarily mean infectivity. I think the previous experiment is more useful.

DG: I think what they're trying to go here is with the idea that maybe this is what's going to persist and allow for - I was going to say, they use the inflammatory thing of reinitiating, or flaring back up, or something like that. That's what a lot of it is, what they're suggesting here. They're suggesting that our studies on SARS-CoV-2 infected cells in vitro suggest there is an intermediary form of the virus that is blocked at the stage of polypeptide cleavage by the protease inhibitors, nirmatrelvir or ensitrelvir.

The nature of this viral intermediate is yet unclear, but it decays slowly with a half-life of approximately one day. Maybe it can allow for a reigniting of viral replication once you stop the drug, once you have this intermediate form still at some level.

VR: There's no evidence for that, is there?

DG: Unfortunately, no. That was it, reigniting.

VR: I think you have to be careful in cell culture. There's no immune response to take care of things in addition. What's interesting to me here is that even with all these drugs, the nucleocapsid protein still remains high at all time points after treatment. That protein is quite stable. Even though you're inhibiting a lot of viral replication, the protein - That may be why the antigen tests remain positive for a long time.

DG: I think that's actually really important and insightful. How can you test positive and no longer transmit? As we're seeing here, you've got the stable protein. It's in cells. That secondary phase of the disease, that inflammatory phase kicks in. You're shedding these epithelial, these mucosal cells. They're full of the protein. They don't necessarily have a virus that can infect or get anyone sick. That is the amazing thing. It's been all this time. Everyone talks about rebound and they publish papers left and right. Are we seeing transmission after day 10?

VR: No, there's no evidence. In fact, some of the papers where we discussed, they said there's no evidence that this is a transmission issue. This is a very interesting figure because even with remdesivir, there's persistence of nucleocapsid protein up to 72 hours in the presence of the drug. That is really important.

DG: The protein sticks around. People keep asking, but I'm not sure it's really clinically relevant. I don't want people to like quote this article and be like, "Oh, see, rebound really is a thing. Now, I understand the mechanism." We've been over this many times. As per the CDC, not a thing. Number one, person gets infected. They're at high risk of progression, Paxlovid. Get it within the first five days.

I'm not sure there's a cliff here. The FDA is out to five days, but if it's right past day five and we were still seeing, 88% in the first three, 86% in the first five. If it's day six, have you really suddenly zero efficacy in a high-risk person? You do better erring on the side of treating rather than withholding.

VR: As you have said many times, what people are calling rebound is in fact the inflammatory phase.

DG: Yes. You get a little bit of a reprieve. You feel better because you took this, and then you get hit with the early inflammatory cytokine storm. You feel crummy for a few days, not quite as crummy as you would have felt if you had not gotten that reprieve and that quick shutdown of the viral replication.

VR: People are having positive RATs again and they say, "See, the virus has come back." No, actually it hasn't. It's just been persisting.

DG: Yes. It's just got this persistent stable protein in the cells in your nose.

VR: I got an email from someone who said, "Why are you guys so against rebound? It clearly is a thing." We're not against it. We just don't see the evidence that there's something called rebound.

DG: Yes. I always show this link to this article, the timing of interventions. We wrote this before Paxlovid was even a thing.

VR: That's right.

DG: We were already seeing people get a little better and then they get this cytokine storm during week two. How can it be caused by Paxlovid unless someone went back into the past in a time machine? All right. Let's stop withholding treatment because of this mythology. All right. Number two, remdesivir. We're talking a bit about remdesivir today. The article, "Remdesivir Reduced Mortality in Immunocompromised Patients Hospitalized for COVID-19 Across Variant Waves: Findings From Routine Clinical Practice," recently published in *CID.*

I think this is really important because I still - The other day, we had a wife, "I just want to make sure my husband isn't getting that remdesivir." They're still out there on the social media misguiding people. We learned it took us a while to figure out when should we give remdesivir? What's the right patient? Once it's past day 10, it's useless. If you can get it in the first 10 days, as we see here. Data from immunocompromised patients hospitalized for COVID-19 during December 2020 and April 2022 were extracted from the US PINC Healthcare Database.

Patients who received remdesivir within two days of hospitalization were matched one-to-one using propensity score matching. You want to match them to equally sick folks. They matched them to people who did and did not receive, so the folks that got matched the people who did not receive remdesivir. They looked at admission month, age group, which hospital. They did the hazards models to determine the effect of remdesivir on risk of 14- and 28-day mortality, looking at the different variants of concern periods. A total of 19,184 remdesivir patients were matched to 11,213 non-remdesivir patients.

Overall, 11.1% and 17.7% of the remdesivir patients died within 14 and 28 days compared to 15.4 and 22.4 of the patients that were not treated. A reduction in mortality at 14 days of about 30% and 28 days a reduction of about 25%. Not as impressive as Paxlovid or remdesivir in the first week, but still a survival benefit that was significant during pre-Delta, Delta, and Omicron periods.

Next after remdesivir, because as I mentioned, very hard to get it in that first week, is Thor's hammer, molnupiravir, and a nice go-to. There's no renal issues. There's no drug-drug interactions. It's over the counter, not over the counter, but it's oral, should almost be over the counter. Now, the reason it shouldn't be over the counter, as we've talked about, not something recommended in children, not something recommended in a woman of childbearing age who might get pregnant. If you have that discussion, you can use it there. Again, with that caution with a negative pregnancy test, but a great go-to.

Let's say you've got someone in their 80s or 90s, they're on a whole mess of medicines, Eliquis, maybe amiodarone, maybe other medicines that you really don't want to stop. OK, then you can go ahead with molnupiravir. We still have convalescent plasma, but really only in a selected small group. Week two, the cytokine storm week. Person either gets a little bit of a reprieve or not. Week two, they get that cytokine storm, that inflammatory phase.

Remember, steroids, not for everyone, only at the right time in the right patient, so not in the first seven days, maybe during the second week in folks who have oxygen saturations less than 94%. Dexamethasone, six milligrams a day times six days. I don't care if your EHR still has

10 days. Let's follow the science. Number two, anticoagulation. We have guidelines from American Society of Hematology. At this point, most people, it's a prophylactic dose. There are certain situations when you may go up to a full therapeutic dose.

Pulmonary support. Remdesivir again, remember, if we're still in the first 10 days, within a couple days of admission, we can still get some benefit here in the right patients. Immune modulations with tocilizumab in certain circumstances. Let's not throw those harmful, unnecessary antibiotics and other things at folks unless they're warranted.

An exciting week for Long COVID. I don't know if you spent last Thursday listening to the Senate hearing on Long COVID. The committee chair was Senator Bernie Sanders from Vermont. It was indoor. Much of the day, Bernie had his mittens off, so to speak, literally and figuratively. He was keeping his mask on, except for the photo ops, pulls it off for the photo ops, breathes in the virus.

They had patient testimony, testimony from researchers. The discussion actually sounded very bipartisan, calling for a moonshot initiative with the speeding up of Long COVID, drug development trials, expanding capacity, and education among primary care physicians. I think that's huge. Always gets left out, the education component. You need funding for that. People are going to have to not do their day job or take time out of their day job to do this education, and they want to establish a new institute at the NIH for addressing Long COVID, ME/CFS, and other infection-associated chronic diseases.

VR: That would be good to have such an institute, don't you think?

DG: I would like that, actually. Otherwise, I think you always worry when everyone gets all excited, and then how long does that attention span stay?

VR: Sure.

DG: I worry about that with Long COVID. A lot of the people that were all excited sort of -

VR: What would you call this institute, Daniel?

DG: The Post-Infectious Sequelae Institute.

VR: OK. Institute of Post-Infectious Sequelae.

DG: Yes, the I-P-I-S? IPIS, OK.

VR: Not good.

DG: All right. Let's work on that. Now, in *CIDRAP*, that comes out of University of Minnesota, there was a nice piece, I'm going to leave a link here, “Does Paxlovid Prevent Long COVID? Maybe, Experts Suggest.” A nice discussion of the different studies, not every study demonstrates a reduction in the risk of Long COVID with Paxlovid, and really, a call to study further whether the benefit of early antiviral therapy is also seen past this acute period.

Mixed stuff on Paxlovid, not particularly compelling for convalescent plasma or our monoclonal therapies. I think it would be important to know because, as we've discussed

many times, a lot of folks think like, "Well, I'm not going to die, I'm not going to end up in the hospital, but I am really worried about Long COVID." Can this be an evidence-based therapy in that space? We don't know. I think that's the honest answer from this.

Maybe some more clues into mechanisms driving long COVID with the article, “Persistent Complement Dysregulation with Signs of Thromboinflammation in Acute Long COVID,” published in *Science*. Always challenged to go through a *Science* paper, but here, the investigators followed 39 healthy controls and 113 COVID-19 patients for up to one year after initial confirmation of acute SARS-CoV-2 infection to identify biomarkers associated with Long COVID.

At six months follow-up, 40 patients had Long COVID symptoms. Initially, they say 39, but I'm seeing 40 here. Repeated clinical assessments were paired with blood draws, resulting in a total of 268 longitudinal blood samples. They measure 6,500 proteins in serum by proteomics. The top candidate biomarkers were identified using computational tools, further evaluated experimentally. A few key findings because this is a *Science* paper. It's really a lot in here.

They found that Long COVID patients exhibited increased complement activation during acute disease, which persisted at six-month follow-up. They have some nice figures. If you don't remember your classic and alternative pathway, you can get a refresh there. Again, it's that same issue that we've talked about before. They don't really separate into two groups. It's more of the median shifts, standard error of the mean. We get statistical difference.

They looked at antithrombin III. Their data suggests that in general, there was more cleavage, and found serum levels of von Willebrand factor were increased with a decrease in ADAMTS-13, which regulates von Willebrand factor. Increased monocyte platelet aggregates were also found, also elevated levels of CD41 high monocytes. I have to say, this is what I really found interesting. They started this exploration of antibodies that might activate this classical complement pathway. One of the things that we do know, connect the dots here, is that antibodies to the herpes virus family can do this.

Herpesviridae, these would be viruses like EBV or CMV, and we know that there's a connection there with really high EBV or CMV IgG levels. While overall serum positivity for CMV and EBV-specific IgG and thus prevalence of CMV or EBV infection did not differ, we do see these really increased antibody titers. This almost actually starts to separate when you start to look at the antibody titers, particularly for CMV IgG. You start to see this really high group. Now, the people with the EBV, if you look at the IgG, they're all right above upper limit of normal.

VR: I think this was what I was looking at when you showed the initial results about complement, that doesn't have to be SARS-CoV-2 doing that. It could be something else. Here's a candidate for that.

DG: Maybe the SARS-CoV-2, and this is this growing hypothesis, is that you get the latent viruses reactivated. You get this just really incredibly robust, too robust, exuberant response, incredibly high persistent IgG. Maybe that IgG to your EBV, maybe even other viruses that we're not measuring here, are continuing to drive this complement activation.

VR: I think it's important to realize this idea because many people feel it's a persisting replication of SARS-CoV-2, but it doesn't have to be.

DG: We don't have evidence.

VR: There isn't any.

DG: We keep looking, and we're looking desperately. Everyone wants to find that. That may not be the answer and that's what science is about. We want to know what the answer is. We don't just want confirmation of our hypothesis from early on. I think this is really an interesting connection that we have here. The elevated IgG, knowledge that it drives complement activation, here, evidence of ongoing complement activation.

VR: Again, not in every patient. If you look at the whisker plots, the Long COVID patients, they overlap substantially if you go back to the original graph where you're looking at C7.

DG: Yes, there's even a big overlap.

VR: Big overlap. That one that you're showing, the red, see, there's a huge overlap with the other two groups, the recovered and the no-Longs. The Long is hugely overlapping, right?

DG: Yes, it really is.

VR: This is not a homogeneous patient population.

DG: That's true, too. The mechanisms may differ. We say, "Oh, it's all X." Well, it's X in maybe one individual, but it might be Y in the other person. As I've been saying now for quite a while, no one is safe until everyone is safe. We've talked about the number of people that are still at high risk. I do want everyone to pause the recording. I think this might be our last recording that drops during the MicrobeTV fundraiser.

VR: That's right.

DG: Go to parasiteswithoutborders.com, click on the 'Donate' button. We are going to continue. I think we're going to get there, Vincent. I expect that we'll be writing you a check.

VR: Very good.

DG: We'll double the donations up to potential maximum donation of $20,000. Only a little time left for this fundraiser.

VR: Yes, when you hear this, it will just be a few days till the 31st. Please send in your money, parasiteswithoutborders.com. It's time for your questions for Daniel. You can send them to daniel@microbe.tv.

Laurie writes, "I'm an avid masker using KN-95s, and I cringe when I hear things such as the virus is so small that the mask provides no protection since it easily passes through the pores of the material. It occurs to me that while the virus itself is indeed minuscule, when an infected person expels viral particles via a cough or sneeze, the viral particles are likely

contained in moisture droplets that would be large enough for a good quality mask to offer protection. Am I right?"

DG: Yes, you are right.

VR: Very good. Barbara writes, "A regular listener. Thank you for all of your advice. Our family has not had COVID in our household. We test quite regularly, at least once a week. We're vaccinated, boosted, recent shot in November. I had a temperature ranging from 101.5 to 102.5 for eight days with no other symptoms, except for some vomiting, day two. I've taken three rapid antigen COVID tests 48 hours apart. Negative, all three. My husband, no symptoms, no fever, also tested. Two small children, no other symptoms.

Several hours after yesterday's negative test, I noticed that a second faint line appeared. This did not happen with my husband's test. I repeated this morning again, negative, remained negative at the 30-minute, 1-hour, 90-minute, and two-hour marks, and then at the two-and-a-half-hour mark, a second line appeared again. What does this mean?"

DG: Stop testing. We've talked about this over time. There's this issue with positive predictive values and the fact that no matter what test you've got out there, there's a certain amount of false positives. When you give me the scenario and all these loads of negative tests, and then you say, "I see a faint line," that is probably not a true positive. Stop testing, take a deep breath, take some antipyretics, and rest assured.

VR: In fact, the tests tell you not to look beyond a certain amount of time because funny artifacts can happen.

DG: Even if you look super close, there is a line there, which is where the reagents are. I see people taking photos and then they use their iPhone to adjust the contrast. No, a positive line is clear.

VR: Very clear. Nancy writes, "Will we be permitted to get another COVID vaccine this spring?"

DG: They're licensed. If you're having a discussion with your physician, you say, "Boy, that three to four months, we've talked about this." If you have that discussion, you want to do it, your physician can certainly go ahead and facilitate that.

VR: Eric writes, "In January, California changed its COVID-19 guidelines to focus on the mildness of symptoms in order to end isolation rather than the number of days since an infection was first recognized. This is reportedly a move toward normalizing COVID-19 as just one of any number of respiratory viruses, which I know is something Vincent has wondered about relative to flu or common colds in the past. What is your opinion on this shift by California? As the person in charge of COVID mitigation for my company and an avid listener of your *TWiV*, I'm not entirely convinced that symptom severity or fever is a great proxy for contagiousness. "

DG: It's not. I understand the motivation here. This is one of the things you can actually even ask yourself in a capitalist society. Do you want your workers coming to work sick, making other people sick, triggering them to miss work, impacting the productivity, impacting the

well-being of your employees? The science is the science. The science didn't change because we've all gotten tired of COVID.

It's the same with the flu. If you're sick, let's say it's 48 hours later, and you go into work because you got that wonderful work ethic, you're putting your co-workers at risk. You really need to balance this sort of the American ethic with the science of how to keep people safe and how to keep people from being sick and not being able to work. Unfortunately, some of those folks getting really quite sick.

VR: Didn't we just do a paper where most of the transmissions occurred early in infection?

DG: Most of the transmission is right in that before you feel terrible. Let's say it's day six, and you're like, "Oh, man, I'm really feeling crummy." You're less likely to transmit than day one or two when you're just starting to.

VR: Finally, Denise writes, "I'm a pediatric anesthesiologist and have enjoyed listening to your program for the last several years. Many times during the pandemic, I felt like a lone wolf while touting the benefits of masking. *TWiV* made me feel sane and reminded me I was not alone. Anyway, my husband contracted COVID over Christmas, took a course of Paxlovid. He'd had COVID two or three times before but did not take Paxlovid for any of those. He recently noted that his memory was sharper and he was finally out of the COVID brain fog that he believes he has been experiencing since his first infection in March, 2020. Are there any data on Paxlovid providing relief from Long COVID?"

DG: No evidence-based studies yet, but they are ongoing. We've talked a little bit about these. The first one that got rolled out was Stanford. That was give a course of Paxlovid longer than the five days. That study was ended, our understanding is, for futility. Results haven't come out. I think we know what that means. There are several other studies still going on. Duke's got one, got one going up at Yale. I think NYU has another. We're still waiting for the data to come out.

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

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

[music]

[00:54:34] [END OF AUDIO]