This Week in Virology

TWiV 1056 Clinical Update

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pdf of this transcript available (link)

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

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Vincent Racaniello: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1056, recorded on October 26, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

DG: Hello, everyone.

VR: What happened, Daniel?

DG: I finally got COVID, Vincent.

VR: You think you got it at ASTMH?

DG: I'm feeling pretty confident.

VR: This is interesting, because how long before did you have the new vaccine?

DG: It was about 18 days before. I was, I knew I was going to be engaged in this high-risk activity. I did all the things that I thought I should do. I got my booster about two weeks before. Actually, Dickson, Chuck, and I all went to separate locations. That's just in case something happens to one of us, right? You know, one of us is alive. Then I went to the conference, and I made that decision that, I was going to have the mask off. I was going to have lots of face-to-face time with all my friends, colleagues throughout the world. I knew it was a chance. I had some testing. When I did get home, it was a Sunday morning. Saturday night, right before I went to bed, I was like, I feel a tiny bit of a scratchy throat. Whatever, not it. Then Sunday morning, I'm getting up to go for a run. Obviously feeling horrible, I'm like, "You know, before I go for a run, I should probably do a test." I do the test, and I'm getting ready to put my shoes on. I look over, and at 15 minutes, there was a faint positive line.

I started on Paxlovid that morning, Sunday morning. On Monday, there was a solid line. I felt crummy Sunday evening, Monday morning. By about Monday afternoon, I was starting to feel a little bit better. By Tuesday morning, nothing, felt completely fine. I was already antigen-negative by Wednesday morning. I have to say, I never got a fever. I never even got a cough.

My wife was a little bit annoyed with me, "Why aren't you?" I did, I boosted. I got a treatment right away. So far, so good.

VR: Having the vaccine probably gave you a mild infection. We won't know because you took Paxlovid, right?

DG: That's the whole problem with not having the ability to split yourself. One of them takes Paxlovid, one doesn't. See, but no, it was great. basically, about 24 hours after starting on Paxlovid, just like that study we talked about, I basically was feeling fine. I'm still taking the whole week off from work.

VR: Right, except for *TWiV*. You're not taking *TWiV* off.

DG: Not taking *TWiV* off, but all right. Let's jump right into it. "In the end, we will not remember the words of our enemies, but the silence of our friends." That's by Dr. Martin Luther King, Jr. People can figure out where that fits in as we go forward.

The *MMWR,* "Vital Signs: Health Worker-Perceived Working Conditions and Symptoms of Poor Mental Health - Quality of Worklife Survey, United States, 2018-2022," came out this week. This is data from the General Social Survey Quality of Worklife Module. It's a questionnaire with 25 items administered via personal interview, telephone interview, or Web-based questionnaire. The response rate was actually over 50%. They reported that the percentage who reported feeling burned out was very often with 19.0%; 44.2% of healthcare workers reported being somewhat likely or very likely to look for a new job in 2022.

VR: Hmm.

DG: A little disappointing. I'm still going to be here. I'm not looking for another job, just by the way. All right, Mpox, the article, "Mpox Neutralizing Antibodies at Six Months from Mpox Infection or MVA-BN Vaccination: A Comparative Analysis," was published in *The Lancet Infectious Diseases*. Here we read that people vaccinated with the Bavarian Nordic vaccine were found to develop frequently low or median Mpox neutralizing antibodies when compared with infected individuals. One in 10 vaccinated individuals showed no detectable neutralizing antibodies at six months, whereas every person with Mpox infection developed antibodies. One more example of how the best way to get an infection is to not get an infection is to get an infection, or perhaps why measuring antibodies might be like a blind man feeling the tail of an elephant.

VR: The vaccine does induce protection in some people. It's not great, but it does. I'm not sure what this means at all.

DG: Yes, I'm not sure the sky's falling. I'm not sure the best way to protect yourself against an Mpox infection is to get an Mpox infection.

VR: I think you should still get vaccinated, don't you think, if you're in the risk population?

DG: Yes, not only that, but fortunately, it's being, as they say, commercialized. Now this is going to be just a routine vaccine. It's not going to be having to go to some center and the

government deciding who can and can't access the vaccine. All right, leishmaniasis. What is that? Vincent, I see you yawning.

VR: Nothing to do with leishmaniasis.

DG: You've learned all about this parasite on *TWiP.* This is exciting. This is that parasite that one acquires from the bite of a small, delicate sandfly. A study was recently shared at the annual meeting of the American Society of Tropical Medicine and Hygiene in Chicago. The researchers analyzed 1,222 samples sent to the CDC that tested positive for leishmaniasis. I want to point out, the majority of the samples sent to the CDC for leishmaniasis testing came back positive, suggesting to me a bit of underdiagnosis. Eighty-six of the confirmed cases were from patients with no travel history outside of the United States. These are folks living here in the U.S., mostly down in Texas, and they actually develop these non-healing crateriform ulcers.

Actually, there's a nice article by, let's see, Brenda Goodman, and she interviews Gideon Wasserberg. Dr. Wasserberg says he's glad to see the study because awareness of the disease in the U.S. is so low. Most doctors, if you ask them, is there a leishmania in the U.S., they say, "No way", or, "What is that?" I like his quote. I'll leave a link into Brenda Goodman's article. Also, you can go to Parasites Without Borders. You can learn about leishmaniasis so that you're not one of those doctors who says, "What is that?"

VR: Daniel, if you ask most doctors, is there poliovirus in the U.S., what would they say?

DG: "Of course not. That's been eradicated."

VR: Better than, "What's that, right?"

DG: At least a little bit better. Dengue. Are you ready for this? The Public Health Department in Pasadena, California, reported a case of locally acquired dengue. This is the state's first case, and the state recommends that you use insect repellents containing CDC- or EPA-approved active ingredients, and they list DEET, picaridin, IR-3535, or oil of lemon eucalyptus. I actually spent a little time going down the rabbit hole of, does oil of lemon eucalyptus work? Apparently, very high concentrations of oil of lemon eucalyptus are equivalent to very low levels of DEET. Got an alternative out there.

Vaccines and monoclonals. RSV. Apparently, we have a shortage of Nirsevimab. Nirsevimab, I like to call it. Beyfortus for the babies. This just reminded me of that question that we had on a previous episode. Mom was trying to decide, should I get the vaccine during the last trimester of pregnancy, or should I go ahead and the baby get the Beyfortus? Limited availability of Nirsevimab in the United States has prompted the recommendation that providers should actually encourage pregnant people to receive the vaccine because there may not be enough monoclonals to go around for all the babies. I'll leave in some links there for that emergency.

VR: Daniel, speaking of vaccines, on Saturday I got, or Sunday, I got flu, COVID, RSV, all at once.

DG: I'm proud of you, Vincent. I'm sure that's why you did it. Just to make me proud.

VR: Just to make you proud. That's right.

DG: All right. What is going on with COVID? We have our BNO weekly update. New cases still about averaging over 200,000; in hospital, down a little to 13,533. The ICU, 1,516. New deaths. We're still averaging over 1,500. Still averaging over 200 a day. Finally, you Italians, you got that wastewater stuff going in the right direction in the Northeast.

VR: Look at that, it's on down.

DG: Finally. No more Italian holidays, no more Columbus Day celebrations I have to worry about, hopefully for a while. No, we expect things to be a little better.

Except for me, of course. Then we'll see what happens December and January. All right. We've been talking about this concept, which I really like, the idea that mom can get a vaccine and then protect the baby. We have the article, "Newborn and Early Infant Outcomes Following Maternal COVID-19 Vaccination During Pregnancy," published in *JAMA Pediatrics*. These are results of a population-based, retrospective cohort study that took place in Ontario, Canada, using multiple linked health administrative databases. Singleton live births with an expected delivery date between May 1, 2021, and September 2, 2022, were included. They analyzed the data, 142,006 infants, about half of them were male, were included; 85,670, mom got vaccinated during the pregnancy, so about 60%, and the infants of the vaccinated mothers had lower risks of severe neonatal morbidity, neonatal death, and ICU admission.

Now this is one that is, hitting close to home for me, Vincent, and as I'm isolating for the infected, for an introvert like myself, there's certain advantages. I would like this to be long, but the article, "Duration of SARS-CoV-2 Culturable Virus Shedding in Children." was recently published in *JAMA Pediatrics*. Here they look at a cohort of children aged 7 to 18 years who had a positive result via PCR for COVID-19 that were recruited between April and September 2022. They obtained pharyngeal swabs during five home visits over 10 days with date zero designated as the date of a positive test result. Samples were refrigerated, delivered within 24 hours of collection to a laboratory for variant assessment. The primary outcome was cytopathic effects, CPE, assessed by bright field microscopy and determination by inoculation of the sample in growth media.

If CPE characteristics were observed in 30% or more of the six-day, post-inoculation images, samples were considered CPE-positive. Of the 76 participants, 68.4% were vaccinated, 55% were right in the 7 to 12, pretty much split 50-50, male, female. Now I will read what they say, but we'll translate. They observed a median duration of infectivity of three days with 14 participants, 18.4%, still as they say, infectious on day five, and 3.9% on day 10. What they really mean to say is the median duration of being able to pick up a cytopathic effect from these procurements was three. The median day of getting those CPE, we saw about 18.4%, still on day five, and only about 4% on day 10. A couple of things, we'll keep translating that, but the median duration of positivity among vaccinated children was three days, and among the unvaccinated children, three days.

VR: That's very interesting, isn't it?

DG: Really interesting. They comment that the lack of association between vaccination status and infectivity was robust when they controlled for demographics. Among vaccinated

children, duration of infectivity was similar for children who received a booster versus those who did not. I'm a little annoyed, I'm thinking with my booster, maybe that's why my antigen test was already negative after only a couple of days. They conclude by saying, "Our findings suggest that current policies requiring isolation for five days after a positive test might be appropriate as the majority of children were not infectious by day five. Additionally, return to school policies may not need to discriminate by vaccine or booster status."

VR: First of all, day three in both vaccinated and unvaccinated, there could be a difference in titer. We're not looking at virus titer here. We're just looking at positivity.

DG: Yes, that bothered me, right? That they didn't do it, that it wasn't quantitative, that it was just...

VR: Yes. this is typical that we don't do plaque assays because I think that would tell us a lot more. Then the other thing is, so they're saying keep kids home for five days. How long are we going to do this? Do you think forever or another year? Because we don't do this for flu, we don't do it for RSV, for coronavirus, common cold. I understand now we're close to the pandemic, but are we going to do this forever? We're going to say you have to stay home for five days after you get a positive?

DG: It's interesting. Because we always talk about the science and now we're sort of wading into, what should the public policy be based upon that? Here's the science, sort of. We're basically saying that, most folks, it's only about three days that you can either culture a virus. We've talked repeatedly about how sensitive is that, right? If I have my son Barnaby try to culture a virus and he can't culture any and, well, he may not know what he's doing. We don't know how sensitive the assay is here. Is this really, if you can't culture a virus, does that really mean you don't have to worry? Then again, if you can culture a virus, well, there's probably a threshold. It's probably not this binary. Then becomes the social policy, vaccination, boosters, ready access to antivirals. Yes, those all become important policy questions. Because yes, most people, they get the flu and they go right to the office and give that to everyone. They go, they get RSV and they go right into work and give that to folks.

VR: You're not going to change that. It may not be the right thing to do, but it's not going to change. The question is just when SARS-CoV-2 joins that not, go to work mentality.

DG: I wonder if it ever will. There's always this thing. I was talking to my communicating, texting on the phone with my partner, Anuja Lee, this week about the fact that everything with COVID somehow is special. We always have this thing in infectious disease where as soon as we can switch to oral, that's great. We go ahead. There's always something about COVID, where, "Oh, it's COVID, it's different, you got to call the pharmacist. They're going to restrict the Paxlovid that's fully licensed." Yes, so it might be a little time, but we'll see.

Let's jump right into what I think is a very exciting article, Vincent. We are now in COVID early viral phase. You've tested positive. What is the number one recommended therapy? Paxlovid, now fully licensed. One day it'll be in special boxes. Mine was in an EUA box, but we have the article, “Retrospective Cohort Study of Prescribing Outcomes in Outpatients Treated with Nirmatrelvir-Ritonavir for COVID-19 in an Interdisciplinary Community Clinic,” recently published in *PLOS One*. Now, the reason I want to talk about this is the headline seems to miss

the point, right? The headlines are like, "Oh, everyone, when you give them Paxlovid, it's really complicated. It's all kinds of trouble." Well, it's a nice article looking at how often a provider needs to make adjustments as they go through the medication list. These are results of a single-center retrospective cohort study of adult outpatients prescribed Paxlovid in a community COVID-19 clinic in Toronto, Ontario, between March 3 and September 20, 2022.

They go ahead and they perform a descriptive analysis of the patient population, the need for renal adjustments, potential drug-drug interactions, the drug-drug interactions that occurred, treatment adherence, adverse drug outcomes. Ultimately, we've got 637 individuals who they want to prescribe Paxlovid to during the study period. The median age was 70. The median number of risk factors for severe disease was two. Almost half, 45%, were immunocompromised and 82% had received three or more COVID-19 vaccine doses. First, we hear about compliance. Ninety-five percent of them completed the five-day course of therapy with 68% having complete symptom resolution by the end of follow-up at day 28. Overall hospitalizations were low, within 28 days, was 3.3% in this high-risk cohort. There were 1.2% was attributable to COVID-19. All these 600-plus high-risk individuals, there were zero deaths of the folks that ended up getting treated.

Now, here's what gets into the headlines. Over 70% had one or more clinically significant drug-drug interactions that required mitigation. Let's go through. Was this insurmountable? This is great outcomes. You've got only 3% ending up in the hospital. Nobody's dying. It was only 1.2% were ending up because of COVID. About 28.7% of these older folks had decreased renal function. You had to click the renal Paxlovid instead of the regular Paxlovid box. When it came to drugs, we're talking mainly about cardiovascular drugs. That was 55% the majority of the time. Most of those were lipid modifying. Most folks were on statins, about 30% on statins. Very simple. Stop the statins for 10 days and restart them when you're done.

Next after that was calcium channel blockers, maybe dropping the dose in half, depending upon how good the blood pressure control is to start. Few other things in there, you can't take your Viagra for five days, oh my. Some of the interesting things I want to say, and you can go through their chart of what they say, is that when you find something, for instance, a patient might be on diazepam, and you go, and I'm going to leave a link, the covid19-druginteractions.org/checker. If you put in that you're going to try Paxlovid, nirmatrelvir/ritonavir, and then you click that you might want to do diazepam, it will actually tell you, diazepam is not recommended, and will then actually give you a suggested substitution, lorazepam, which it says is fine. If you're worried about Eliquis, it'll again give you direction on what to do.

When you actually do this properly, there was only 0.12%, only one person in the over 600 people who actually had a DDI severity of level one where it was contraindicated. The headline should be very easy to overcome and manage these drug-related interactions, and get the excellent outcomes that they reported here.

All right, so this is a, I put this as a Long COVID one, but it's right up front. I also want to share the article, “Nirmatrelvir and Molnupiravir and Post-COVID-19 Condition in Older Patients,” recently published in *JAMA Internal Medicine*.

Here the investigators looked at a cohort of Medicare enrollees age 65 and older diagnosed with COVID-19 between January and September, 2022. Any new occurrence not present prior to COVID-19 diagnosis of the 11 symptoms in the WHO consensus definition of post-COVID conditions between four to 12 weeks after infection were considered as post-COVID condition. Ultimately huge sample, 3,975,690 outpatients with COVID-19 were included in the study. The post-COVID condition incidents among patients receiving Paxlovid was 11.8%; molnupiravir, 13.7; and 14.5% for folks that did not get either of these antivirals. We end up with a hazard ratio of 0.87, so about a 13% reduction in your risk of Long COVID with Paxlovid, a little bit less with molnupiravir. Then we have the added reduced risk we get from our vaccines, all right?

After the Paxlovid, number two, remdesivir, that's that three day, number three, molnupiravir, number four, convalescent plasma in certain contexts, and then avoid those harmful and useless things. We do have other things on the horizon, and recently I've been getting a lot of questions about the oral protease ensitrelvir from Japan. Just an update, what's going on there? Just like with Paxlovid, with the EPIC trials, we have a SCORPIO-HR, a SCORPIO-SR, a SCORPIO-PEP, so that's a high risk, a standard risk, and a post-exposure prophylaxis. For the high risk, there was actually a poster at IDWeek suggesting a reduction in Long COVID if started in the first three days after symptom onset.

In the standard risk, we actually had some data suggesting that we had a quicker resolution of symptoms, and folks tested negative about 36 hours faster than placebo. Fever, congestion, sore throat, cough, impacts on taste, smell, and fatigue resolved about a day earlier. I'll leave a link to a preprint there. Still waiting to find out on the post-exposure prophylaxis. So far, we're waiting, and I think a big thing I've seen a lot of is the FDA slow-rolling this or anything like that. We have yet to see compelling data that rivals that of Paxlovid for a reduction in progression to severe disease in the high-risk folks.

Currently approved by EUA in Japan, I suspect we'll eventually see this on the shelves in the U.S., and I'll leave some links into some news from Shionogi, the IDWeek stuff, and also a nice article in *The Atlantic* by Rachel Gutman-Wei.

All right, isolation for the infected. I'm currently doing this, Vincent. Just to remind everyone, it's not just about taking your drugs and trying to get better, but the reason I isolate is maybe not to spread it to others. For a while, the healthcare providers, the healthcare professionals, HCPs, were in a separate category, and I was wondering if we'd ever get updated. That was updated finally in August 22, 2023, and I'll leave a link in there. Isolation, they say, can be discontinued after five days after symptom onset. Remember the way we count. It's always different. Day zero is the day symptoms appeared. Day one is the first full day thereafter.

Fever has to be resolved for at least 24 hours without taking drugs to make that happen. Then even after that, it's recommended you wear a high-quality mask around others, folks who are at risk. Then they do mention, and this also aligns pretty much with non-healthcare professionals, a test-based strategy for removing the mask sooner. Here they talk about, and I'll leave links, if you have access to antigen tests, you should consider using them with two sequential negative tests 48 hours apart. You may remove your mask sooner than day 10. I'll also leave the link for the non-healthcare provider.

VR: What day are you at, Daniel?

DG: This is good. We can do the counting. Starting to get a little bit of a raspy throat on Saturday night. Sunday was, so I don't get to count until day, Sunday. Sunday I test positive. Day one, day two, day three. Thursday is day four. Friday will be day five.

VR: Tomorrow, OK.

DG: Did I count that right? No, I counted it wrong. Sunday, Monday, Tuesday, Wednesday, Thursday. Today is day five.

VR: All right.

DG: I will do my sequential negative test. I already had a negative test from yesterday. So, 48 hours tomorrow morning, I will check 48 hours after the last one. Hopefully, that will be negative, but I'll make sure to do a very aggressive procurement just to see.

VR: All right, and you're wearing a mask at home now, right, Daniel?

DG: I am actually. I hold it up. It's one of these proper, goes around the back of my head. Yes, so I'm still isolating. We eat outside, quite distanced from each other. Whenever I leave the isolation in my room where I'm not outdoors, I've got a proper tight-fitting mask.

VR: When are you going back to work on Monday?

DG: I will not go back to work until next week. Even then, I'll wear an N95.

VR: OK.

DG: All right. Second week, right? We'll be checking in next week. You can see how I do, whether or not that cytokine storm descends upon me. If it does, number one, if those oxygen saturations get less than 94%, steroids, anticoagulation. If you end up in the hospital, we have guidance there and we're updating. We have another publication in the works from ASH, pulmonary support, remdesivir still in the first 10 days, maybe immune modulation with tocilizumab and avoid those unnecessary antibiotics and proven therapies. Yes, I got something for you here. Vincent, I didn't get enough hate mail about the ivermectin from last week or recommendations to take ivermectin when I tweeted that I had the dreaded COVID. Yes, it was entertaining. Anyway, the article, “Intravenous Vitamin C for Patients Hospitalized with COVID-19, Two Harmonized Randomized Clinical Trials,” the LOVIT-COVID investigators on behalf of the Canadian Critical Care Trials Group and the REMAP-CAP investigators, published in *JAMA.*

In these harmonized randomized prospective trials, patients were randomized to receive vitamin C administered intravenously or control placebo or no vitamin C every six hours for 96 hours. I don't know if you know much of the history here, but there was a paper put forth, which we now realize may have been fraudulent, suggesting a benefit to vitamin C. When it was repeated, they failed to show a benefit. Early on, a lot of folks were getting this high-dose vitamin, IV vitamin C, in the ICU. Enrollment was terminated after statistical triggers for harm and futility were met. The trial had primary outcome data for 1,568 critically ill patients, 1,037

in the vitamin C group, 531 in the control group, 1,022 patients were not critically ill. In there, we had 456 in vitamin C, 566 in the control group.

Among critically ill patients, the immediate number of organ support-free days, so I want to clarify, this is when you're doing OK and you don't need to be supported by mechanical ventilation, et cetera, was seven for the vitamin C and 10 for the control group. You actually ended up doing worse and requiring more support if you're getting vitamin C, just at odds ratio of 0.88. Basically, getting vitamin C had a trend toward increased number of days they needed organ support. Among critically ill patients, survival to hospital discharge was 61.9% for the vitamin C group versus 64.6% for the control group. Among patients who were not critically ill, survival to hospital discharge was 85.1 for the vitamin C, 86.6 for the control group.

Neither of those were trending in the right direction, so they conclude in hospitalized patients with COVID-19, vitamin C had a low probability of improving the primary composite outcome of organ support-free days and hospital survival. I put the curves up there for you to look at, but I did want to actually share the comments from some of the investigators. "The results from this trial suggest that the use of vitamin C in hospitalized COVID-19 patients should be de-adopted", Francois Lamontagne, MD, of the Université de Sherbrooke and co-lead investigator of the trial said in a press release. "The results underscore the health and economic benefits of identifying and abandoning readily available interventions that are ineffective and potentially harmful to patients."

In an editorial on the study, the author said the findings were concerning as they showed the possibility that vitamin C is detrimental in patients with COVID-19 because the probability of harm exceeded 90% for organ support-free days in both critically ill patients and those who are not critically ill. Greater than 90% chance that you are harming your folks when you give them the IV vitamin C.

VR: We hope that this message gets out there now, right?

DG: I really hope it does. It really, there was this idea that, the vitamin C and why wasn't this happening? People were clamoring and yes, this is not good. This is, I think we've learned, we've learned that ivermectin is not helpful. We've learned that hydroxychloroquine probably increased mortality. We have learned that vitamin C is probably detrimental and harmful. We need to stop doing things that hurt our patients.

All right. We will finish up with COVID late phase, Long COVID. Now I think there's a good reason to use PASC, post-acute sequelae of COVID because not everyone we see has a recognizable Long COVID syndrome. We have the article, “Association between Guillain-Barre Syndrome and COVID-19 Infection and Vaccination: A Population-based Nested Case-control Study” recently published in *Neurology*. These are the results of a nested case control study in a cohort of 3,193,951 patients, 16 years of age or older, without a prior diagnosis of GBS from the largest healthcare provider in Israel. Subjects were followed from January 1, 2021, until June 30, 2022, for the occurrence of GBS. 10 randomly selected controls were matched to each case of GBS on age and sex. They assessed both SARS-CoV-2 infection and COVID-19 vaccination administration in the prior six weeks in cases and controlled.

This analysis showed that the odds ratio for GBS associated with SARS-CoV-2 infection was 6.3 and actually COVID-19 vaccination reduced that by more than half. Basically getting one of those natural COVID-19 infections was associated with more than a six-fold higher risk of Guillain-Barre syndrome, ascending paralysis, and getting vaccinated dropped your risk in half.

Now moving on to men and the urinary system and that darn prostate. The article, "SARS-CoV-2 Infection Correlates with Male Benign Prostatic Hyperplasia Deterioration," recently published in the *Journal of Internal Medicine*.

Here, the authors looked at 17,986 individuals and find that when compared to controls, the people that got COVID-19 demonstrated statistically significant higher incidence of retention of urine, about 5.3 times more, hematuria, that's blood in the urine, 3.0 times more, clinical urinary tract infections, about three times higher, and people needing to start on those BPH medications, 25 times higher need. It did not actually seem to matter how severe the bout of COVID-19 was. SARS-CoV-2, it's like sand, it's coarse and rough and irritating and it gets everywhere, Vincent.

VR: Unbelievable.

DG: Is it replicating everywhere?

VR: That is a good question.

DG: Last week, a few of our listeners took issue with the fact that I dug up the study and discussed the brains of the beagles. I have a couple ideas about how we might address this issue. Is there really replicating RNA in these reservoirs that people talk about? One of the things people are doing is these prolonged courses of Paxlovid. Maybe if there's replicating virus driving things, that might help. The other thing is maybe we could take these organs, Vincent, out of people with COVID and then transplant them into people, aggressively immunocompromise them, and then see if the virus grows out. Now that may sound like mad science, but the editorial, "Changing Paradigm: Transplanting Candidates with Coronavirus Disease 2019." It was published in *Transplant Infectious Disease*. It isn't mad scientist because in the early days, there was this challenge is, can we safely transplant those organs from people who died of COVID-19? There are thousands of people who desperately are waiting for those organs. As we shared at IDWeek, thousands of people who had COVID-19 and did not survive, had organs harvested, transplanted into other individuals.

We really did not see replication of SARS-CoV-2 into those recipients of those organs. The "Changing Paradigm" article actually discusses and shares some cases where this was done. Also, in the same issue *of Transplant Infectious Disease*, we have the article, "Favorable Experience of Transplant Strategy Including Liver Grafts from COVID-19 Donors: One-year Follow-up Results." These were the results on 280 patients who underwent liver transplants. Basically, again, they report that the results of this transplant strategy, including liver grafts from COVID-19 donors, was favorable. The only problem they actually had is an increased hepatic artery thrombosis.

All right. I'm going to wrap it up there. As I've been saying, no one is safe until everyone is safe. We're getting this. This is it. This is our last episode in October. This is the end of our

Floating Doctors fundraiser for August, September, and October. We are very close. I think we're going to make it. Pause the recording right here. Go to parasiteswithoutborders.com. Click on that Donate button and help us support what we do and contribute to our fundraiser.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Cynthia writes, "Number one, is there any evidence that older adults with a solitary kidney can safely use Paxlovid? A 75-year-old family member required a nephrectomy a few years ago due to renal cancer. They are vaccinated and receive every booster available, but recently had COVID. Half dose of Paxlovid was offered, but ultimately not taken since symptoms were already improving. It made me wonder if this has been studied. Someone in this position should weigh the pros and cons with their physician."

DG: Yes, so I think it's cute that they got a half dose of Paxlovid. Now, you don't get a half dose because you have one kidney, half the number of kidneys. You get a half dose if your GFR, your kidney function, is below 60. Some folks that donate a kidney, most folks that donate a kidney, compensate and actually continue to have excellent kidney function. When you are offering the Paxlovid to someone who only has one kidney, then you would base it on their glomerular filtration rate. Yes, certainly plenty of folks with one kidney have gotten it. If the person is at risk of progression, we would definitely recommend it.

VR: Number two, "Myocarditis was discussed in your most recent update. As always, it's clear that this is much more common after an infection than after vaccination. As we weigh the risks of continuing to boost our teenage sons, I've been unable to find a study focusing on the risk of myocarditis from a breakthrough infection or after repeated boosters. Mostly what I see are the studies pointing to problems after dose two, greater with Moderna. What's the risk-benefit argument for this population to continue receiving boosters? Our teen boys each have had three Pfizer doses, one to two infections, have no health concerns that would put them in a high-risk group. Curious what evidence may be out there regarding their risk of myocarditis from additional boosters versus additional infections?"

DG: I'm glad you asked this because this is a nuanced discussion, right? I was recently listening to the Paul Offit, “Beyond the Noise,” and where, it is OK to have these discussions. It is appropriate to have these questions. If COVID was gone, then we would no longer be boosting. Is it a super high priority for someone under the age of 65 without risk factors to get boosted? Not the same priority as someone over 65, over 70 with risk factors, et cetera. When they talk about myocarditis, the risk pericarditis with infection versus boosters, it's not just about that.

If you talk about just about that, certainly the incidence is higher if you get infected without the protection of a vaccine. If you're basically saying, "COVID's here, my son's probably going to get infected at some point. Do I want them to be protected when they get that infection?" The binary is really between getting infected without the protection of a vaccine versus getting infected with the protection of a vaccine. As we've talked about repeatedly, the protection of the vaccine goes beyond just the protection of the heart. We seem to see reduced risks of Long COVID, other things. We are moving into unknown territory as we keep boosting and boosting and boosting. These will be areas where we get more and more information.

There really is a gradation between the recommendations for the vaccination across the board. Sure, we recommend everyone get vaccinated, but the recommendation is stronger the older you are, the more risk factors you have.

VR: Karen writes, "I'm a 54-year-old woman who has never had chickenpox. Because of this, when my daughters were young, our pediatrician gave me the chickenpox vaccine when they were vaccinated. Do you recommend someone in my situation getting the shingles vaccine? Could I possibly get another chickenpox vaccine to get a boost instead?"

DG: Yes, so the Shingrix vaccine is better than the chickenpox vaccine, right? The chickenpox vaccine is actually an attenuated viral replicating vaccine. The Shingrix is a protein-based vaccine, which actually we do think gives more robust and better protection. Given the choice, I would actually recommend go ahead with the Shingrix two shots.

VR: Charmaine writes, "My understanding is that scientists are currently working on a nasal COVID vaccine that would elicit mucosal immunity at the point of entry for the virus, thereby protecting against infection. Correct me if that's not quite right."

DG: Vincent, I feel like I want you to jump in on this.

VR: No, not going to protect against infection.

DG: That is quite the bar. There is this idea that if your nose, if your mucosal is just teeming with neutralizing IgA, that maybe to some degree you're going to reduce the risk of infection progressing, of you getting disease. The whole idea that it's going to be instantaneously sterilizing and there'll be no infection at all, that's a pretty high - I was reading about trypanosomes, where trypanosomes get the human body to just keep producing antibodies and they switch and antibodies until finally the human being just dies of exhaustion. All the glucose and energy. Yes, I don't know. Maybe this will be the next weight loss. We'll keep squirting things up people's noses every month or two and the massive protein reduction will ultimately result in weight loss.

VR: Charmaine wants to know, people who exercise breathe through their mouth. If you have a nasal vaccine, would you get infected through your mouth then?

DG: See, that's the problem. I got to stop going to the gym. I might breathe through my mouth and this nasal IgA that I just developed is not going to be helpful. No, people talk about this. There's billions of dollars going in this direction, but it's a whole new area, this whole idea that we're going to produce such a robust and sustained immune response that we're going to protect against even infection.

VR: Daniel, my understanding is that the infection is initiated in the upper tract, the nasopharynx. Even if you're breathing through your mouth, it's still initiating in the nasopharynx. It's not initiating in your lungs. I don't think mouth breathers should worry. All right. Finally, Shirley writes, "You cap your weekly COVID roundup with recommended therapeutics. I'm hoping you'll also address side effects of Paxlovid. I myself haven't gotten COVID, but I have many friends who've recently come down with it. Their doctors don't make recommendations, but when asked for Paxlovid, they tell their patients that it's the patient's choice since they aren't too ill with COVID symptoms.

From listening to your podcast, I urge these friends all over 70 to choose Paxlovid. After starting, they stop due to side effects of diarrhea, gastro distress, and in one case, even white stools. Yikes. My question's, how common is this? Should they stop Paxlovid completely in this situation or switch to the lower dose? Should they continue and take Imodium? Should they switch to a different therapeutic? Your thoughts, and what do you recommend to your patients experiencing side effects?"

DG: Yes. The most common is this, they call it dysgeusia. This impact that it has on your taste. Some people describe it as a metallic taste. Some people call it metal mouth. The most recent description was soapy grapefruit. OK, yes. I'm on Paxlovid at the moment. Maybe it's a little bit of a soapy grapefruit. Some people do have loose stools, but again, a challenge is a lot of loose stools can actually be a presentation of COVID. Is that loose stools meaning that disease is progressing thus for the uninitiated more evidence that you really need the Paxlovid to take?

Now, I think the metric needs to be the equation right up front is what are the potential benefits? What are the risks without treatment? If the person is 23 and taking it, OK. If the person is older, has a number of risk factors, we've talked about Paxlovid can reduce your risk of progressing, reduce your risk of ending up in the ER or a hospital, which is the last thing you want to do when you have COVID, prevent you from not surviving, and also growing evidence that it can prevent you from having those long post-acute sequelae of COVID issues. In general, we do recommend it and 95% plus of people take Paxlovid with minimal side effects other than at most a bad taste in the mouth.

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

DG: Thank you. Everyone, be safe.

[00:46:32] [END OF AUDIO]