This Week in Virology

TWiV 1084 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.

[music]

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1084, recorded on January 31, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: What's on the bow tie tonight, Daniel?

DG: This is my anthrax bow tie.

VR: I couldn't tell what it was from the distance.

DG: It's an artist's rendition.

VR: Artist's rendition. It's bound to be wrong then, right?

DG: It's not quite as obvious as the Ebola right outside where you're recording right now.

VR: 1084, wasn't there a book by Haruki Murakami-

DG: Oh.

VR: At 1084?

DG: I do not know.

VR: Let's see, 1084, Haruki Murakami. Oh, it's *1Q84,* not 1084.

DG: OK, that's close enough. We'll take it. We got a lot to cover today. Let me start with the quotation. "The ultimate measure of a man is not where he stands in moments of comfort and convenience, but where he stands at times of challenge and controversy." That's by M. L. K. Jr. We're going to get right into why I have that up front with the article. This is, I'm going

to say, troubling, disturbing data from the U.S. Census Bureau on Healthcare Workers. This was shared in the article, “Job Flows Into and Out of Health Care Before and After the COVID-19 Pandemic.” It's published in *JAMA Health Forum*.

In this cohort of approximately 18 million healthcare industry workers, the number of workers exiting the industry, the healthcare industry, peaked in the first quarter of 2020, but was elevated above 2018 baseline levels in all quarters of 2020 through 2021. In early 2020, exits were primarily from workers exiting to non-employment. While in late 2021, exits were primarily from workers just exiting to other sectors. They have some nice figures. I'll recommend people look at these to see the exit rate.

It's nice they give you like the 2018 exit rate. You can see that that's pretty much the same in 2019. Then quarter one 2020, it really shoots up. Actually, it's that high in the end of 2021. The only difference being in Q1, people were just like, "I'm done with this," and they just stopped working. In the end of 2021, they're basically saying, "I'm done with medicine. I'm going to find a different job." Then you can actually look regionally and see where the most exits were. 2020 really concentrated in the Northeast. Interestingly enough, in 2021, there are a few hotspots, Colorado, Georgia, Maryland, and Delaware.

The reason I put that quote up there is it is troubling to see so many people leaving the health care sector. I know it continues to be very challenging. I understand a lot of the factors that are driving people out. We all experience it every day. The patient-provider relationship I think is a little bit different than it was prior to 2020. Relationships with administrators, quite a bit different. Majority of physicians, people are aware, are now employees versus used to be slightly more than half actually would be owning their own business and setting the tone. Things are definitely changing in these areas.

RSV, respiratory syncytial virus. We're actually still at a pretty high level, as we discussed last week. We saw that double blip. We're hoping things will start coming down. Here we are. We're recording the last day of January. This will drop just right after Groundhog Day. Coming weeks, I'm really hoping we get off this hump. We're still seeing the hospitalizations. We're still seeing the deaths. What about the tools? There was a nice peer-reviewed article, “Efficacy and Safety of Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults over Two RSV Seasons,” published in *CID*. We're going to get some interesting information here.

Following this out now over two RSV seasons, we get the results of a phase 3, blinded trial where folks 60 or over were randomized one-to-one to get this vaccine or placebo pre-Season One. We're also going to look at the impact of a second dose. They looked at Season Two and this potential need for revaccination. The way they did that is they took the previously vaccinated individuals and they re-randomized those basically to get a second, a revaccination group compared to, they got a placebo. No one knows what happened until we unblind things.

Then they're going to look at the efficacy and safety of the different vaccine regimens against, and we've been always reinforcing against what, against RSV, lower respiratory tract disease over the two seasons, so pretty robust. The efficacy analysis comprised 24,967 participants. You end up with 6,000, get one dose. You end up with another 6,000, who have gotten two doses. Then you've got over 12,000 in the placebo group. The median efficacy follow-up was

17.8 months, so you get to follow the first season and the second season. Efficacy over two seasons with one dose, 67.2%. You're going to get 78% against severe lower respiratory tract disease.

Now, the efficacy over two seasons really did not change whether or not you got that second dose or not. No benefit to revaccination, but the other, which I think is really important, the reactogenicity and safety. Now we have that for the two seasons.

VR: I think it's interesting that they looked at the second dose and decided you didn't need it. That makes a clear public health message, doesn't it?

DG: I think it's really important because, is this going to be, oh, just another shot that you would need to get every year? It doesn't look like you do. It looks like you've got at least two years. Then I think, next year we're going to find out, do you have three years? We're always going to hopefully be a little bit in front of the data here on how often you might need an RSV shot.

VR: Maybe the virus doesn't undergo substantial antigenic variation. Maybe that's part of it.

DG: That may be. We'll see over time, particularly now we're putting another bit of selection pressure on things. Unfortunately, not enough. People still need to get out there and get that. I would say it's not too late because your vaccination is not just for this season. You can get that vaccine and a couple of years of protection.

Flu, more battle of which flu shot is better with the article, "Effectiveness of High-dose vs. Standard-dose Quadrivalent Influenza Vaccine against Recurrent Hospitalisations and Mortality in Relation to Influenza Circulation: A Post-hoc Analysis of the DANFLU-1 Randomised Clinical Trial," published in *CMI*.

They compared the relative effectiveness of high dose quadrivalent influenza vaccine versus standard dose quadrivalent influenza vaccine against hospitalization and found that among 12,477 randomly assigned participants, receiving the high dose was associated with a lower incidence of hospitalizations for pneumonia or influenza, 10 versus 33 events. A relative rate 0.3, p-value 0.002, all-cause hospitalizations 0.87. That's about 13% reduction with a good p-value there. The trends were really favoring the high dose, over time. You can look at hospitalizations for pneumonia or influenza in the figure and really clearly favoring the high dose.

Interesting enough, I have to say, when you looked at all-cause hospitalizations, you didn't see, but I'm not sure a high-dose flu shot is going to protect you against all things that might end up getting you into the hospital. Maybe asking a little bit too much. They concluded that, "our exploratory results correspond to a number needed to treat of 65." We get a really wide confidence level of mega, might be 35, might be 840, and this is getting the high dose compared to the standard dose. Remember, this is, compare that to getting no dose at all, so really reinforcing the importance of getting those flu shots and then here, suggesting that for those 65 and over, the high-dose recommendations really seem to be evidence-based.

VR: I try and get the high-dose, but often they're out of it.

DG: Hopefully, it's interesting because a lot of that has to do with the demand, the perceived demand. If people start really saying, "I really want that," and they start shopping around, then they're going to start stocking it because they're going to realize that's what people want. Influenza. We talked a little bit about sometimes we see a peak and things come down and then sometimes they go back up.

I think if we look at the flu weekly data from the CDC, we're actually seeing that plateau now has a little bit of an uptrend. If you look around the country, not everyone is being as equally hit. We talked about how flu starts in the Southeast and spreads. We're still seeing a lot of activity down in Georgia, South Carolina, Tennessee, Alabama, Mississippi, Louisiana, Texas areas. Getting a little better in New York.

VR: New York is interesting. It's minimal or low and New Jersey is high. [chuckles]

DG: Yes, everything is legal in New Jersey, so I don't know what you guys are doing over there.

[laughter]

DG: COVID. Things are not great with COVID. New deaths this last week, 2,575. That's up 300 from the week before. That's like more than a 10% increase from the week before. Death, in a sense, you could say it's a lagging indicator. I guess that's how you look at it. We're starting to see a little bit of a decrease in the number of folks in the hospital, but we still have over 24,000. Still a little bit decrease in the number of folks in the ICU, and point out that in the ICU, thousands of people in the ICU. We are over 200 deaths a day. There should be a brighter light on the horizon. If we look at the wastewater data, it really looks like it's coming down everywhere. We are hoping we get off this very high winter peak.

We have a bit of a controversial section now. I'm going to discuss the WHO COVID guidance, which, a lot of reactions. There's that nice perspective piece in *CIDRAP* because I suspect few will actually read the full 209-page document. For those of you venturing forth, there is an executive summary. The CIDRAP piece highlights many concerns and criticisms of the WHO guidance. I have to say, unfortunately, a number of the criticisms are valid. They start with definitions. That should be completely innocuous. Then as I started to read the definitions, I realized they were maybe a little more. They're actually really declarations. The big ones, as we might expect.

Airborne transmission. Here, they define airborne transmission as it has been defined for, unfortunately, over 100 years. Referring to the spread of an infectious agent caused by the dissemination of droplet nuclei that remain infectious when suspended in air over long distances and long periods of time. Airborne transmission can be further categorized into obligate or preferential airborne transmission.

Again, droplet transmission. Droplet transmission is the spread of an infectious agent caused by the dissemination of droplets. Droplets are primarily generated from an infected source person during coughing, sneezing, and talking. Transmission occurs when these droplets that contain microorganisms are propelled. They say usually less than one meter through the air and deposited on the conjunctiva, mouth, nasal, throat, or pharynx mucosa of another person, and most of the volume - they say greater than 99% - comprises large droplets that

travel short distances, less than a meter, do not remain suspended in air. Thus special air handling and ventilation are not required to prevent droplet transmission.

VR: I can see where this would be confusing because they're both airborne, right?

DG: What's really troubling, and we're going to get into the comments is that they're still doing what has been done for 100 years is taking respiratory transmission and dividing it somehow in half.

VR: Yes.

DG: A few other issues, so I encourage people to follow the link in the show notes. Let me read some of the reactions from *CIDRAP*. One of the main problems, said Raina Macintyre, MBBS, PhD, professor and head of biosecurity at Kirby Institute in Sydney, Australia, is that the document doesn't incorporate many of the lessons learned during the pandemic, such as the major role of COVID-19 spread among people with no symptoms.

The guidelines suggest using symptoms to screen people. This is seen in health guidance in many countries, emphasis on symptoms. Only wear a mask if you feel unwell, when we know a substantial proportion of transmission is asymptomatic, which is a major rationale for universal masking in high transmission settings. That's what we're doing currently in all of the hospitals where I work in the tri-state area, is universal masking. Because as we well know, that health care provider who comes into your room, who may feel OK, who may not be coughing, may actually potentially put the patients at risk.

Similarly, David Michaels, PhD, MPH, down at George Washington University School of Public Health, said the guidelines don't directly address the modes of COVID-19 transmission. "I was very disappointed," he told *CIDRAP News*, referring to the WHO's adherence to what he calls "droplet dogma."

[laughter]

DG: There are concerns about the lack of guidance, suggesting that the use of N95 respirators over the surgical mask. I was interested to read that the bias against respirators has been evidenced for years, dating back to the 1980s, tuberculosis outbreaks, and the early HIV-AIDS epidemic. Lisa Brosseau, an expert on respiratory protection and infectious diseases at *CIDRAP* said, "OSHA even proposed an emergency temporary standard that required the use of respirators for health care workers who were caring for a tuberculosis patient." Are you ready for this, Vincent? "The CDC, the American Hospital Association, and the AMA lobbied against that."

There are some interesting things here. I think we've talked about it that, OK, in a certain setting, we have good ventilation, good air exchange. If you can get back that six feet, OK, there is a certain benefit. If you are in an older hospital, we talked about a study last week where there's poor ventilation, if you are in that room, if you are in a suburban home, this whole dichotomy of droplet versus airborne really is a historical artifact.

I am going to jump right into what does the CDC have to say, the enlightened CDC, and they just posted, the CDC *Safe Healthcare Blog* post, a CDC update on the draft 2024 “Guideline to

Prevent Transmission of Pathogens in Healthcare Settings.” That was posted January 23, 2024. Here, the CDC specifically addresses the issues with the droplet dogma per the CDC blog. The first issue is the approach to determining how pathogens that are transmitted via air, but not typically transmitted over long distances, such as through ventilation systems, should be managed. The draft document provides two options for this type of pathogen, routine air precautions and the brand new special air precautions.

They go on to write, "Routine air precautions are directed towards infections that are common, for most people not severe, for which the precautions specify that health care personnel should wear a mask, (surgical mask, face mask, sometimes a procedure mask, or even enhanced barrier face covering), while special air precautions are indicated to prevent transmission of infections that have greater or unknown potential to cause severe illness, for which the precautions specify that health care personnel should wear a NIOSH approved N95 or higher level respirator.

“Although masks can provide some level of filtration, the level of filtration is not comparable to NIOSH approved respirators. Respiratory protection remains an important part of personal protective equipment to keep health care personnel safe." It's too bad. Here's the CDC really recognizing that we need to move past this droplet dogma, moving toward new guidance that talks about this enhanced special air precautions, really moving away from the confusion, it's spread through the air, what do you mean it's not airborne?

[laughter]

VR: I guess we're not going to solve it this round.

DG: The CDC seems like they're moving in the right direction. It's just too bad that the WHO just came out with guidance that really seems, unfortunately, quite archaic.

VR You would think the WHO would talk to health organizations around the world like CDC.

DG: It's really tough. I know a lot of people have said, "Let's just say it's airborne." Airborne is an archaic term that we brought back when we realized that things like measles, things like chicken pox, things like tuberculosis. It's not the right word. This recognition that there can be a mixed route of transmission, that sure, in a well-ventilated area, as we talked about last week, you can leave the door open if someone has COVID.

You can actually keep an eye on them so when the high-flow nasal cannula falls off, you don't wander into a room and find that they've died in your absence behind a closed door, that you do need modern ventilation in your hospitals, but you would never leave that door open if the person had measles or the person had tuberculosis. You would take those few negative pressure rooms, and you would reserve those for those particular pathogens. If there's anything we learned from this pandemic, it's hopefully that we need to modernize the language. We can't just force things into those square or round holes.

Moving forward, we're going to jump a bit to the early viral phase. A couple of things here. We'll start off with the *MMWR*, “Underuse of Antiviral Drugs to Prevent Progression to Severe COVID-19 — Veterans Health Administration, March–September 2022,” was recently posted. I'm going to start by just reading the abstract, and then I like their graphical abstract as well.

Antiviral drugs reduce the rate of progression to severe COVID-19 when given to patients with mild to moderate disease within five days of symptom onset. Despite being recommended for patients at high risk for progression to severe COVID-19 because of age or chronic conditions, reported antiviral use among the general adult population has been less than 35%.

To assess reasons for underuse of antiviral medications, to prevent severe COVID-19, here they conducted a detailed review of 110 Veteran Health Administration patients with mild to moderate infection at high risk for progression because of underlying conditions, so organ transplant, hematological malignancies. They're really going to be saying, "Why did these people not get antiviral drugs?"

Looking at 110 patients, they'd all been vaccinated, only 20% were offered treatment, but declined; 80% were not offered treatments. I'm trying to figure out how strong was that recommendation for treatment. Among the 88 patients not offered treatment, provider reasons included symptom duration of greater than five days. That's 22.7%. Concerned about possible drug interactions, 5.7%. Absence of symptoms, 22.7%, but about half of the patients, there was no reason given other than that the symptoms were mild.

Among 55.8% of the patients not offered treatment for no good reason, follow-up was limited to just a telephone call to say, "Oh, by the way, here are your test results. How are you doing?" No documentation of treatment being offered. These findings really suggest that education of patients, providers, and medical personnel tasked with the follow-up calls combined with advanced planning of, "What am I going to do with a positive test," might improve the rate of getting the recommended antiviral medication to prevent severe COVID-19 associated illness, including death.

I'm going to circle back, Vincent. Last week, our listeners might remember our discussion of the preprint, “Persistence of an Infectious Form of SARS-CoV-2 Post Protease Inhibitor Treatment of Permissive Cells,” posted on *bioRxiv*. I was not surprised, but one of the authors reached out to clarify how the experiments were done. Let me read from the email. I took a few lines out, but it was a nice email.

"It was nice talking to you today. We should do it more often. As for our manuscript for all figures, 1, 2, and the SUPs, the experimental settings were: One, infected cells were kept in the presence of the drug for 24, 48, 72, or 96 hours. At each time point, the cells were washed to remove drug and then were subjected to a serial threefold titration for infectious virus," so testing to see how much virus can be released from these cells after the drug was removed.

They did this experiment three different ways. They did pretreatment with the drug prior to infection. They did drug infection concurrently. Then more real-world, as we discussed on the call, they infected first, because most people are not going to take the drug before exposure, then they did the drug treatment. When we were looking at the figure that we talked about, this was actually 24 hours, they wash it off, 48 hours, they wash it off, 78 hours, they wash it off.

The interesting thing I want to point out is that that discussion was then followed with a discussion about what a game-changer Paxlovid has been and how this should not be any kind

of science that prevents people who are eligible, people at high risk of progression, from getting the Paxlovid.

VR: We said that it's in fact more interesting in the sense that it may explain why there's antigen persistence, right?

DG: Yes, I thought that was really interesting, just how stable the nucleocapsid protein really is. So, number one, reinforcing Paxlovid. Remember, rebound, it's not a thing. That's the early inflammatory phase.

VR: By the way, I did a Paul Offit recording today, and he said Tony Fauci is to blame for rebound.

[laughter] Because he said, "Remember, Tony took a second course."

DG: Yes, he really shouldn't have done that. He's a role model, and he's supposed to be a role model of evidence-based medicine, right?

VR: Right.

DG: If you're listening, Anthony, I apologize. You've done a lot of other tremendous things, so that's just my only criticism. Two, remdesivir, not used a lot. Three, molnupiravir. I don't think we talk enough about molnupiravir. I understand there are providers out there, they're a little daunted by potential drug-drug interactions, and I don't know your kidney function, but don't do nothing.

Recently, I had an individual, 92 years old, was on amiodarone, was on Eliquis at a high dose, was on some other medicines. Really came down to choosing molnupiravir, doing the five days. Really, it is definitely better than doing nothing at all, not as impressive as we hoped it would have been efficacy-wise. Convalescent plasma for a certain select number of folks.

Then week two, and this is that cytokine storm. Person's made it through week one. Maybe they've started to feel a little bit better, and then boom, they get hit by week two. I always remember, Vince, and I was having a conversation today, and it was a young mother trying to figure out what to do with her son. Her son is a middle schooler and was sick last week, and she said, "Oh, he just had some common cold virus. Then he felt better and was doing what he does over the weekend. Oh, then this week he got the COVID."

I still remember the way Ian described, "Yes, I just had a cold last week, and then I felt better. Oh, then this week I really got the COVID, the trouble breathing." I was like, so, we all think that we can tell what was COVID or not, but I always point out it's a viral illness. It can present in many ways. The only way you know whether it's COVID or not is you do a test. Now today this child was testing positive, and we're trying to sort out, was last week COVID, and now they're in the inflammatory phase, or did they have something else last week, and now they've got COVID. It always can be quite a challenge.

VR: What do you do in that situation where you're not sure how far into COVID you are?

DG: There's a couple things we talked about. One is trying to go through the story. The other is the child had a negative antigen test but a positive PCR. The discussion was, "Let's see how he feels tomorrow. Maybe we can actually repeat an antigen test. If tomorrow the antigen test is positive and stays positive, OK, maybe that was a common cold last week," but that's not surefire as we talk about. Sometime during the inflammatory week because of that persistent stable nucleocapsid protein in the cells, you start to shed them during the inflammatory phase thinking, "Now it's gotten to a point for antigen detection."

In a perfect world you probably would do CT values and see if they're trending down or up over time. No, often not an easy distinction. For folks that become hypoxic, and that's what you want to be checking during the second week, not those antigen tests but those pulse oximeter readings. Drop down below 94, there can sometimes be a roll of dexamethasone six days. We have guidelines from American Society of Hematology on anticoagulation for hospitalized folks. Pulmonary support, remdesivir if you're still in the first 10 days, immune modulation, maybe tocilizumab in certain settings.

Now, what about prognosis? Here it is, it's the second week, individual's in the hospital, you're trying to figure out prognosis. We have the article, *"*Changes in Markers of Inflammation and their Correlation with Death in Patients with COVID-19 in the Intensive Care Unit," published in *Cytokine.*

Here, they looked at 58 participants, 37 inpatients suffering from SARS, severe acute respiratory syndrome, due to COVID-19, admitted to the ICU, some recovered, some died. They have a control group of 21 community volunteers, and they're going to look at IL-2, IL-4, IL-6, IL-10, IL-17, interferon gamma, and some other parameters, such as levels of urea, LDH, DTIMER, PTINR, AST, ALT, and the lymphocytes.

They found, as confirmatory here, that high levels inflammatory markers, such as pro-inflammatory markers, low levels of lymphocytes, remember that neutrophil-lymphocyte ratio, where the neutrophils go up and the lymphocytes go down, and high levels of IL-6 were associated with disease severity, especially in individuals that died.

Moving into the late phase, PASC, Long COVID, a number of my patients have, over the last few years, been really concerned when we have a discussion about getting formal cognitive testing. Some are scared about what it might show. If I ignore it, maybe it'll go away, but if I get an objective measure of how severe the deficits are, that makes them real. Others are actually concerned that, "Oh, what if I do too well, and then people think I don't have this problem, which is debilitating."

The article, "Long COVID is Associated with Severe Cognitive Slowing: A Multicenter Cross-sectional Study, was published in *eClinical Medicine*. Here, patients with post-COVID conditions, PCC, completed web-based cognitive tasks, Simple Reaction Time, Number Vigilance Test. Two-hundred-seventy patients diagnosed with post-COVID conditions at two different clinics in the UK and Germany were compared to two control groups. Individuals who contracted COVID-19 before but did not experience post-COVID conditions after recovery, that's a no-PCC group. We've got an uninfected group, a no-COVID group, they're still out there, I guess.

All patients with post-COVID conditions completed the study between May 18, 2021, July 4, 2023, in Jena University, Jena, Germany, and the Long COVID clinic, Oxford, UK. They identified pronounced cognitive slowing in patients with post-COVID conditions. Quite different distinguishing them from age-matched healthy individuals who previously had symptomatic COVID but did not manifest post-COVID conditions. The cognitive slowing was evident on a 30-second task measuring simple reaction time: 53.5% of patients with post-COVID condition response speed was slower than two standard deviations from the control mean.

Now, this finding was replicated across the samples in Germany and the UK. Comorbidities such as fatigue, depression, anxiety, sleep disturbance, and post-traumatic stress did not account for the extent of cognitive slowing in the patients. Furthermore, cognitive slowing on the SRT, the Simple Reaction Time, was highly correlated with poor performance of patients when they looked at the Number Vigilance Test. It's a nice figure where you can really see the separation.

What I thought was really interesting is there's what they focus on, but then you find some, what do they call when you find something special, like an easter egg or something? If you look at F in the figure, people had no COVID, 81% solid normal performance. Only about 4% were impaired just in the general population. You move to the post-COVID conditions, 53.5% severe impairment, but then if you look at the people that had COVID but said they were just fine, you saw almost 20% were severely impaired, and almost 10% had moderate impairment.

VR: What, so what do you make of this, Daniel? Is this new? No one's found this before, is that correct?

DG: I think there's a couple things. One is, it's nice to have formal cognitive testing here really. The other which I thought was really concerning is people who had COVID and said, "I'm just fine." We're actually seeing that 20% of them have severe impairment. They don't even notice, they don't even recognize until you get formal testing done. Actually, quite concerning.

VR: They may not have had. Maybe they had something else too, like influenza.

[laughter]

DG: I would almost think that people who had no COVID would be an outlier odd group. The people that had COVID, but said, "I had COVID, but I'm just fine now." Amazing that it had, what, five times the severe impairment of just background people who were fine, never had COVID.

VR: The thing is, people have other things, and they're not asking them about this, so I worry about that.

DG: Like all of science, we need to repeat this, yes. As we've been saying for a while, we're just going to close out here with, no one is safe until everyone is safe, and we are finishing our MicrobeTV fundraiser. Actually, when this drops, we'll be into our new fundraiser. I got to go check my notes and see what that will be for. Keep sending us your money, keep sending money to parasiteswithoutborders.com. Every small amount helps. We want to continue

doing the work we're doing. We also want to support the great organizations. We support MicrobeTV, we support the American Society of Microbiology. No, we don't. We do ASTMH. We do Floating Doctors, and we do FIMRC.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. John writes, "I am a lung doc who sees patients in our Long COVID clinic. I received a lot of questions about the serotonin paper you discussed, and I, too, have some questions about it. The key finding of the paper is that plasma serotonin levels are lower in PASC. If you compare the measurements with those in other papers, you'll find the values for controls are much higher than in the other papers. This makes me worry about technical problems. Most of the serotonin in the blood is in platelets, so how do you prepare? The plasma is crucial.

The authors also do not mention that SSRIs are reported to reduce blood or plasma levels of serotonin, which goes against the rationale for their mouse experiment with Prozac. Another recent paper that measured plasma serotonin had the opposite finding. Increased levels of serotonin in post-COVID patients compared with controls, but this paper may be flawed in that the entire control group appears to have zero serotonin. I would be interested to hear what you think about this serotonin business, and more broadly, what you think about the issue of reproducibility in the various omics papers that are coming out."

DG: This is great, actually. A couple things. The low serotonin came out of the UPenn study, and as they reported, this is something they saw in their cohort. It's something that they saw was reproduced, seen in the Cork cohort, but not something that they saw in a couple other cohorts. One is, this finding was not in every cohort. A low serotonin is not seen in every individual.

The other is, and I think you make a good point here, is that how reproducible is this and in all these issues? The other is, I think a lot of us have taken this and run with it. A lot of us said, "Oh, this may explain why the SSRIs are not working." There's not much serotonin to work with, so moving us into using other medications, like maybe duloxetine that starts to use the norepinephrine system or Wellbutrin that's going to use norepinephrine and dopamine to compensate for this deficiency.

The other is, are there ways to maybe raise that serotonin showing that, hey, if the serotonin goes up, that's going to actually correlate with some benefit that's going to relieve. I think there's really a tremendous amount of work that still needs to be done in this area.

VR: Mark writes, "Available to consumers over the counter are home nucleic acid COVID-19 tests, such as from Cue Health or Pfizer Lucira. Lucira also has a combined influenza COVID test. These tests are more costly than rapid antigen tests, particularly the Cue Health test, since these are more sensitive than rapid antigen tests, claimed to be nearly identical to PCR sensitivity and specificity. How should the consumer use these tests? I have used both Lucira Pfizer and Cue Health tests, and they are easy to use and very convenient.

My wife recently tested positive for COVID, and I was wondering if I could take a nucleic acid test at three days after exposure, instead of a rapid antigen test at five days, and have higher confidence that I was not infected with SARS-CoV-2. Are there any data on this question?"

DG: Yes, these are great questions, and we shared a little bit of a story today, where the mother has this sick child and she's not sure. This is going to be a decision in that case of whether or not that child will go to school, potentially expose others. In the case you discussed, it could be a case of is this an individual who is going to qualify for treatment and should be treated.

Rapid antigen tests are great as far as if they're positive. As we've talked repeatedly, a single antigen test sensitivity 75%, 80%. You're going to miss, you're going to miss a chunk. Because they are more expensive, it's about $40 right now to buy one of these Lucira-Pfizer, Pfizer-Lucira, little combo COVID flu nucleic acid amplification tests. The Rapids might be about $10. Rapids are quick. If they're positive, you got COVID. If it's negative and there's one of these situations where there's going to be an exposure, or where there's going to be a potential treatment decision, then that's when you've got to make that decision about anteing up that extra amount of money.

VR: Craig writes, "When you next use this phrase, can you please explain it? I've seen people see immune dysregulation or immune dysfunction and mention of T cells in connection to SARS-CoV-2 COVID-19 and jump to saying, "This means COVID is like AIDS." This is a case of a little learning is a dangerous thing since you need to know enough to have heard of T cells and understand the prefix dys, but not enough to know what it all really means. I myself only know enough more than that to know that I don't know and I would need to look it up and study more before saying anything myself." [laughs]

DG: I appreciate you saying that because I see this on social media and I'm trying to figure out, this is, "Post COVID is the new AIDS. I'm like, "What?"

[laughter]

DG: I think we have to be careful. The immune system is incredibly complex. It can fail to function properly in a lot of different ways. The fact that maybe you're making autoantibodies or maybe you have T cells that are remaining active, or as we talked about last week, maybe you have really high antibodies that are turning on the complement system, the whole idea that all immune dysfunction is exactly the same and the fact that immune dysfunction is seen in post COVID conditions, that means it's the new AIDS, yes, that is a little bit of learning and not enough wisdom.

VR: There are lots of different kinds of immune dysfunctions, right?

DG: Lots, lots, yes. You can have complement deficiencies. You can have complement activation. You can have antibody deficiencies. You can have specific autoantibodies, et cetera, et cetera.

VR: Jane writes, "Hi, my husband tested negative on PCR on day three of symptoms. Finally tested positive day seven on home antigen. That's too late for Paxlovid. How are people supposed to start Paxlovid early enough if the tests aren't picking up enough viral load to be positive until day five, seven, nine?"

DG: That really probably goes back to what we were just talking about before. In an individual where it really is going to affect a treatment decision, a negative antigen test is not enough.

You want to be looking at getting a more sensitive test. If the antigen test is positive, OK, you're done there. The other thing which I think we'll hopefully learn going forward is what about those individuals who end up being only picked up on PCR, who end up not getting a positive antigen test, or is their body controlling it well enough? Is that a low-risk subset for a progression? Are they as critical that they get Paxlovid?

We don't know the answers to those yet, so I would err on the side of get a test that is sensitive, make the diagnosis, and then follow the recommended treatment.

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

DG: Oh. Thank you. Everyone be safe. I think it's ASTMH for the next three months.

VR: All right.

[music]

[00:44:28] [END OF AUDIO]