This Week in Virology

TWiV 1064 Clinical Update

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

VR: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1064, recorded on November 22, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: What's on your bow tie today, Daniel?

DG: These are bed bugs, actually.

VR: I can't believe they put bed bugs on a bow tie.

DG: Ectoparasites, and I have matching purple socks.

VR: Excellent.

DG: All right, well, let's jump into it. We have a lot to cover today. I imagine, Vincent, that people will be sitting around, family gathering, listening to *TWiV* by the fire.

VR: That's a very bucolic scene, yes.

DG: For those of you that are enjoying *TWiV* with family, hopefully, we'll bring up some topics that will allow for some pleasant non-confrontational discussions. Let's start off with the quotation, "Education is the most powerful weapon which you can use to change the world." That's Nelson Mandela. Really, that's why we're here. We're here as an educational resource. We share the latest science, try to discuss it, make it accessible. Here we go. Starting with RSV, respiratory syncytial virus.

Reminder for our regular listeners, a bit of a primer for those joining us for the first time. RSV is one of the top three. I feel like I'm repeating a consultation I had yesterday, but this is one of the top three respiratory illnesses that we see each fall and winter here in the U.S. in terms of hospitalizations and deaths. Each year, we see about two million medical visits for RSV in

those younger than 5, about 80,000 hospitalizations, 100 to 300 deaths. RSV is also a problem for adults.

This is something I like to point out because a lot of my colleagues seem to think RSV is just for kids. Adults, we have an estimated around 100,000 hospitalizations each winter, and about 10,000 deaths. These are mostly in the adults aged 65 and over. Now, we now have two FDA-approved vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged greater than 60. We've got the GSK-RSV. We've got the ABRYSVO by Pfizer. To protect children, there's the option of the monoclonal Beyfortus. Why am I bringing this up?

A couple of things. Unfortunately, we heard from the manufacturer, from Sanofi, that despite an aggressive supply plan built to outperform past pediatric immunization launches, demand for the product, especially for the 100-milligram doses used primarily for babies born before the RSV season, has been higher than anticipated. Perhaps Reagan was not entirely correct when he said, "I think you all know that I've always felt the nine most terrifying words in the English language are, I'm from the government, and I'm here to help" because November 16, the CDC announced the release of more than 77,000 additional doses of Beyfortus.

That's the nirsevimab, a long-acting monoclonal antibody designed to protect infants against RSV. These additional doses will be distributed immediately to physicians and hospitals through the Vaccines for Children program and commercial channels, improving the availability of nirsevimab for parents seeking to protect their eligible children, particularly those at higher risk of severe illness. I'm hoping this is a chance for maybe some of the people you're introducing *TWiV,* to say, "RSV, what are they talking about?"

This will be your chance to talk about the fact that this is a significant issue. It's up there with COVID and flu, and we have tools to protect people from this. Staying with RSV for a minute, I will share that I was covering this weekend, and we are starting to see those RSV admissions. Unfortunately, despite having these tools that I just mentioned, according to a recent update by the CDC, the percent of adults age 60 plus that have received an RSV vaccine is only 14%. This is your chance, folks, to get out there. Millions of doses. We are seeing good safety.

Moving from a shared decision to really encouraging folks to get out there. I mentioned last week some hospitals down in Texas already at 95% capacity. RSV starts in the South, but it is moving up. Currently, we are seeing a rise in RSV cases. As mentioned, it moves from South. We're seeing a lot in Florida. I did just update our weekly RSV positivity rate. I'm just going to go through these with Vincent. There's two ways we look at this. One is we look at the percent positive.

When folks show up and they have an upper respiratory infection, we're trying to figure out what it is, we're already really skyrocketing in the curve up to about 15% positivity when we're using antigen. You can really see just that the numbers are also going up as well. RSV, it's here. Get that vaccine in. Get that monoclonal in.

VR: I should say that I got my RSV vaccine a couple of weeks ago. You should go out and do it, listeners. I wouldn't have known unless I heard it on *TWiV.*

DG: That's great, Vincent. Vincent, how was it? How was it for you? Because we do love anecdotes. How did it go?

VR: I got it in the same arm, I got it in the left arm with the flu vaccine. OK. Now, I have to say the RSV vaccine is about a milliliter. Yes, it's a lot. When she gave it to me, I felt something shooting down my arm. It wasn't painful. It was just unexpected. What is that, Daniel?

DG: The way you describe it almost seems like there's some pressure. You're getting an activation of the nerve down the arm.

VR: Because if there were enough pressure up there, it would shoot something down the arm.

DG: You need to spend a little more time at the gym there, Vincent. Just get a little more muscle.

VR: The other arm was COVID, and that was fine because it's a smaller volume.

DG: Yes, and my parents, my wife's parents, yes, lots of people are getting that RSV vaccine.

VR: I have to say, I did have an upper respiratory tract infection for the past week, and I'm just over it now. I did a COVID test twice, and it was negative. I doubt it was RSV or influenza. It's probably rhinovirus. I took a sample. I'm going to send it to the rhinovirus guru, Dr. Amy Rosenfeld. She's going to tell me if it is rhinovirus or not.

DG: I look forward to that. All right. OK, moving on to, are you believing this? Measles. Squeeze this in here. Yes, thanks to the hard work and orchestrated efforts of the anti-science community, we are seeing an undermining of vaccination efforts. As we hear from the CDC and the WHO, the *MMWR*, "Progress Toward Measles Elimination Worldwide 2020-22," amid ongoing declines in measles vaccination, cases in 2022 rose by 18%. Deaths were up 43% globally compared to 2021.

VR: I'm guessing these deaths are largely in kids, right?

DG: Yes. These are, and actually, when I was last in Africa last December, I'll actually be back again, well, a week from Friday. About a week from when this gets recorded, dropped. I actually saw a really severe case of measles, just a miserable kid. Yes, these are mainly these young children. It progresses and they don't survive. All right. Influenza, just a heads up. Sort of an interesting graph. I will leave a link into the CDC.gov flu weekly update. We need more colors or something.

If you get a chance to look at this, and people should keep track, check this once a week and see where we are. The 2023-2024 season is this dark red. We're right now, we have crossed the threshold, the national baseline, and we are headed up. This will probably peak just sort of based upon what we've seen in the past in December. If you haven't gotten that flu shot, now's the time to head on out. It's interesting. We're not quite as early with this rise as we were last year. We are a little bit earlier than we have seen in most prior years.

All right. Moving on to, yes, COVID, it is still here.

I got in the car the other day, Vince, and NPR was on. I had done an interview with an NPR reporter, Will Stone. It was half an hour, right? They take the half hour, you get a little clip. At one point, he was asking about testing around the holidays. Are people going to still do

testing? I said, "Yes, my wife asked about that." She said, "We're going to have Thanksgiving with your parents. Should we test before we go?" It's funny because I have this conversation not realizing that this is the piece that will go in. I'm like, "Oh, Jessica, I don't want to test. Because what if I'm positive? Then I can't enjoy Thanksgiving. I'll be left out." Oh, because if I do test positive, would I really want to go and give it to my parents? Interesting. I don't know how much testing will go on this year. We are actually still seeing about 200 deaths a day. If you look at the wastewater across the country, it's actually starting to rise in all the regions. COVID is starting to rise. After the holidays, I think we'll see this coming up with the anticipated peak in December and January. Just letting everyone know, COVID is out there.

VR: Good reason to cancel all the holidays. No more infectious diseases.

DG: I actually have to say, I was a little, well, I was positive. I think most of the people were positive in this NPR piece saying that things are much different this year for most people, right? Ninety-seven percent of our population here in the U.S. at least has some degree of immunity, whether it was through vaccination or prior infection or both for most of us actually at this point. We have the ability to access, should your provider and everyone know, early treatment. For most of us, this is a much better world.

As I sort of pointed out maybe in that story, if you're going to be around vulnerable people and vulnerable people don't necessarily wear it on their chest, right? My mom's 85, my dad's 92. You just sort of know with age that those are people you don't really want to show up with COVID. No, I had a patient actually earlier this week I was talking to and she's like, "Listen, I'm immunosuppressed but I don't like to tell people, because I don't want to be viewed as frail."

Just that, having those windows open, not showing up if you're sick. If you do get sick, then just realize, and we'll be talking about, access to treatment and what the recommended treatments are. All right, children, COVID vulnerable populations. This moves us right into this issue of, are there certain people that still are at a solid risk of progression? The article, “Risk of Severe Coronavirus Disease 2019 Despite Vaccination in Patients Requiring Treatment with Immune-Suppressive Drugs: A Nationwide Cohort Study of U.S. Veterans,” recently published in *Transplant Infectious Disease.* I like this article because it gives some information on personalized risk.

Here, the investigators use the Veterans Health Administration electronic health records to identify patients diagnosed with rheumatoid arthritis, inflammatory bowel disease, psoriasis, solid organ transplants. These are all folks who've been vaccinated against SARS-CoV-2, and then they subsequently end up getting infected. They're looking at patients that have received immunosuppressive drugs within three months before this infection. Then they're going to look for the development of severe disease, right? Hypoxemia, mechanical ventilation, requirement for steroids, not surviving, so death.

Then they're going to compare this to non-severe COVID-19. They, again, find that solid organ transplant and other immunosuppressed individuals are at significant risk despite vaccination. Perhaps those who have not been listening with the current circulating variants, they find that severe COVID-19 was seen in the solid organ transplants, 22.7%. The folks with rheumatoid

arthritis, 13%, right? It's like one in seven. Inflammatory bowel disease, 7%, psoriasis also about 7%. They sort of go through some of the different 4,233 U.S. veterans in this cohort.

One of the things they also put in here, not only are there things that put you at higher risk, but again, here they show that nirmatrelvir, Paxlovid, is associated with a significant reduction in developing severe disease. Now, I will move on to spend a little time here just on the transmission and testing and how to keep ourselves safe at these gatherings. You can do that. You can test before you go. Definitely, if you have symptoms, you should think about doing that. Asymptomatic, we still see transmission there. That's the role of testing an asymptomatic.

If you can crack those windows, if there's an air conditioner, if you're in the South, or a heater, if you're in the North, if you leave that fan on continuous, that can help with better air quality. Because I actually, I have to say, I do think being with loved ones at the holidays is really an important part of mental health, which is tied into everything. There are ways that we keep talking about being safe. Maybe, Vincent, maybe I'm only talking about the family that's going to show up for this Thanksgiving because there are some of my family members that do not help with my mental health.

VR: Yes, I got that. Listen, Daniel, here's the scenario. Let's say the day before Thanksgiving, you have some respiratory symptoms, you have a sore throat, you have nasal congestion, maybe cough, you do a COVID rapid antigen test, it's negative, what should you do? Should you go to the gathering or not?

DG: Two things, the next day before you go to the gathering, you should check again. Then, you've got to go have this decision. If I'm sick, should I really show up? It actually probably has to do with who you're going to be around, right? If it's a bunch of my kids, in their 20s and they know their friends and, that's a different situation, then you're going to show up. You don't want to turn this into grandma's last Thanksgiving because you show up with RSV and you maybe didn't have COVID. Because we're not just seeing COVID, we're seeing RSV, we're seeing flu, we're seeing other things that can be a problem.

VR: I would use it as an excuse not to go. That'd be great.

DG: If there were certain family members showing up, yes, I might just err on the side of caution and stay home for an entire week. All right, so COVID early viral phase, right? Now, unfortunately, you're an individual, you're over the age of 50, you've got some health issues, you end up testing positive, what do we recommend? I need to point that, isn't everyone, Barnaby, 18 year old, gets COVID-19, it's my son. He doesn't necessarily need to run out and get treatment, right? He's been vaccinated. He actually has not had a prior infection. Can you imagine that? The poor kid's got to get out more.

Anyway, so what is the number one recommended treatment? Paxlovid. We're going to be talking quite a bit today about the myths, the concerns, the different ideas out there. Just a little recap of last week's discussion, and then we have a new article this week. What did we discuss last week? We discussed the fact that Paxlovid can reduce the progression to severe disease and death by up to 90%. We also discussed that the majority of folks that feel sick, get Paxlovid, feel better for a while, and then have some symptoms for it in that second week.

When they did that really sensitive, like three checks per week, the majority of those people having symptoms during that second week were not experiencing viral rebound. The majority of time when a patient tells their doc or the doc is told by the patient, "I felt better and now I'm feeling crummy during the second week," that's due to inflammation, not viral replication. We're going to actually return to some new terminology. I want people to start using symptom rebound, virological rebound, and the situation where we see both.

Thanks to the Paxlovid in this last study, we saw that they had effectively turned that second week from wild into mild with no one progressing to hospital or dying, despite the fact that they were describing high-risk people, 30% immunosuppressed due to things like leukemia, lymphoma, solid organ transplants, immunosuppressive therapy. Most importantly, the authors were not suggesting that the individuals themselves would benefit from a longer course, but were actually suggesting that maybe these people might need to isolate longer or take more Paxlovid for a public health benefit for others.

As we mentioned before, we have studies looking at five days, 10 days, 15 days of Paxlovid. Far, no evidence suggesting that more than the three to five days of antiviral therapy provides better outcomes for patients with COVID-19. We've got more this week. I like this article a little bit better than last week. This is the article, “Symptoms, Viral Loads, and Rebound Among COVID-19 Outpatients Treated With Nirmatrelvir/Ritonavir Compared With Propensity Score-Matched Untreated Individuals,” published in *CID*.

First off, I will say they do a much better job of matching cases and controls. Last week they were showing us stuff and then the control group were folks with a median age of 39 who didn't even qualify. Then if you forget about that, say, "Oh, look, we're seeing more here than there," well, OK, you're not comparing apples and oranges. The authors point out right up front that Paxlovid-treated people tend to be older and have more medical comorbidities than untreated people. It's really important that you match. Let's walk through the data here. Let's avoid the headlines. First off, I was hoping to get the clinical data on the progression of disease. I will say I could find no evidence that anyone here treated with Paxlovid had a bad outcome. That's encouraging. Now let's go through the definitions because we want to see what are their definitions, but we also want to actually look closely at the data.

They report symptom rebound as an increase of at least two reported symptoms after treatment completion or treatment completion proxy. Apparently, this definition is so broad that in this study, even 20% of the non-treated people get classified as having rebound. It's really broad. We're going to get back to why so broad, why did they do that? We get a really large confidence interval here with the report using this criteria that they get 24 to 40% for the treated, they get 15 to 25% for the untreated. Let's look at the data. If you take a look at this, you can start with Figure 2, symptom resolution.

If you go through this, they sort of follow them out to day five, right? We've talked about the fact that people get treated with Paxlovid, the experience we're seeing, the data is that by about 24 to 36 hours, the majority of people treated with Paxlovid are fever free, they are starting to feel better. When you look at this figure, by day five, you only see what? Four percent say that they have symptom resolution. You follow it out to day 10, and you're only seeing about 20%. You follow it out to day 15, and only 30% are saying they feel better.

It doesn't quite pass the sniff test to begin. Then they actually go through and they have a second Figure B, median number of symptoms that they're describing. Really, you're seeing one or two symptoms. Is it, "Yes, I still have a headache, I'm still feeling a little tired." Yes, so I want to point that out, because what we've talked about, and we're going to get back to why is there, why is their definition here so broad? Is if you take Paxlovid, and after two or three days, you feel much better. Then on day eight, nine or 10, you got a little bit of a fever, you get a little bit of a cough, that qualifies as rebound.

I'm going to sort of suggest that that's not quite so scary, as feeling crummy for a full 10, 12 days, and not getting rebound, as they say. Let's move on to Figure 3. This is the viral dynamics. Here, they're actually following for people getting a negative PCR. Also, this is a little bit interesting here, right? We get out to day five, and they're only suggesting a couple percent of people actually have negative PCRs by day five. We get out to day 10, they're only suggesting about 20% have negative PCRs by day 10.

VR: That doesn't differ much in the treated and untreated.

DG: Yes, and so that's a little odd, right? How are you going to have rebound if everyone's staying positive the whole time? They do a median viral load, OK? That's a little better than a binary. You actually, and as they'll say, like other studies, we found that individuals who completed Paxlovid had fewer symptoms and lower viral load than individuals who did not take treatment. Why are they using this incredibly broad rebound definition? They say, "Well, the reason we're using it, we're going to find out like the last study, is we want to answer the epidemiological-centered question, will I be infectious after treatment completion?"

It's not really asking, is this going to improve outcomes for our patient? Again, there's this concern about contagiousness. They do, again, point out something that we talked about last week. When a clinician says they're hearing from patients that they felt better than worse, this is symptom rebound and not necessarily associated with virological rebound. The authors point out that this clinical phenomenon is a distinct clinical and epidemiological phenomenon from virological rebound.

We also read that the Paxlovid-treated participants were more likely to have one or more negative results compared to untreated patients, further illustrating that Paxlovid quickly reduces viral load. They do conclude by saying that among community-based individuals with mild to moderate COVID-19, individuals who completed Paxlovid had fewer symptoms and lower viral load. Our results in combination with other clinical trial data showing reduction in severe outcomes following Paxlovid support that Paxlovid be prescribed for all high-risk individuals.

VR: Daniel, we heard so many people say that their physicians would not prescribe Paxlovid because of rebound, but these two papers don't make any sense with that because it's, as they say here, you should treat them. The key is whether you're contagious or not. Those physicians weren't thinking clearly.

DG: I think it's interesting, right? It is important to keep, what is the science here? We do know that there is experience where whether you get Paxlovid or not. People are sick, they might have a period of feeling better, and then they might have a few symptoms during week

two. We know that if you get Paxlovid, when you have those symptoms during week two, you are much less likely to end up needing oxygen, needing therapy, ending up in the hospital.

For an individual patient who goes to their provider, taking Paxlovid is associated with you feeling better quicker, you having less symptoms, and you reducing your risk of a bad outcome. If you don't take Paxlovid, you're going to have this trajectory of just feeling crummy longer, having more symptoms longer. You may not get that reprieve in the center that Paxlovid folks get. This whole concern about contagiousness during week two, and it's interesting, and it's important science. There is some interesting virological kinetics in some people where you get the RNA copy number down and some rise, and you get sort of the skip phenomenon with culture positivity, and look forward to more science.

Are people really contagious on day eight, nine, or 10 with these different viral levels? We'll wait to see. I think for now, we're seeing over 200 deaths a day. We're seeing thousands of people end up in the hospital. We could dramatically reduce that with Paxlovid. There's nothing here in the science we keep sharing that would make an educated clinician hesitant to use this medicine. All right, so remember that while you're chatting around the holidays.

All right, number two, not great access, but remdesivir, we're still talking about that first week. It's three days. That's pretty short, not 10 days. Molnupiravir, Thor's hammer, convalescent plasma in the right people at the right time. While we're talking about convalescent plasma, I wanted to share an opinion piece recently published in *JID* with the co-authors Arturo Casadevall and David Sullivan. “Late Administration and Corticosteroid Usage Explain Inefficacy In COVID-19 Convalescent Plasma Trial.”

They're talking in this piece about why the REMAP results were less than one would have hoped for in the use of COVID convalescent plasma, CCP in COVID. I thought this was interesting. They suggest that the major issue with the remap trial was due to late timing of the administration. I think we all agree that, and hopefully, we've learned that if you're going to use convalescent plasma, timing really matters. Then they raise a really interesting idea about maybe a failure of efficacy of using convalescent plasma later stage when people jump in with the steroids.

They point out that the timing was such that 94% of the REMAP participants got steroids. They suggest that the steroids through their ability to interfere with FC-mediated functions of the antibodies may be preventing this benefit. They talk about how steroids down-regulate the FC receptors, they interfere with phagocytosis, they interfere with antibody-dependent cellular cytotoxicity. I think this really enforces the timing issue that we all agree on. I think that's the key. The first week is that viral phase.

If you can get in the first three days or a certain context, particularly the immuno-expressed individuals where we did see benefit, once you get into that second week, you start jumping in with corticosteroids and immune modulation, you really have missed your window.

VR: Daniel, the steroids are given late. The convalescent plasma should be given early so there shouldn't be an issue, right?

DG: Well, I think the problem here is if you wait too long, it's day eight, it's day nine, you're like, "Let's still try the convalescent plasma." The person is already requiring oxygen, you're

jumping on, you're not going to provide any benefit. All right, and as I say, let's avoid doing harmful and useless things. We keep getting results on things that people were bullish about early on. We have the article, “Higher Dose Fluvoxamine, and Time to Sustain Recovery in Outpatients With COVID-19, The ACTIV-6 Randomized Clinical Trial,” published in *JAMA*.

They asked this simple question, 100 milligrams of fluvoxamine twice daily for 13 days compared with placebo, is that going to shorten the symptom duration among outpatients with symptomatic mild to moderate COVID-19? More data, coming here from the ACTIVE-6 platform, randomized clinical trial that looked at repurposed medications.

Between August 25, 2022, and January 20, 2023, a total of 1,175 participants were enrolled at 103 U.S. sites. Participants were 30 years or older with confirmed SARS-CoV-2 infection, at least two acute COVID-19 symptoms for seven days or less, we’re getting there in the first week. Participants were randomly assigned to receive the fluvoxamine, start off with 50 twice a day. They can then go up to 100 milligrams twice daily or placebo. We end up not seeing a benefit despite this being a well-designed trial.

The authors conclude based on this data that fluvoxamine 100 milligrams twice daily does not shorten the duration of symptoms in outpatient adults with mild to moderate COVID-19. I just wanted to have a little bit discussion here and this is my educational point, is that we had so many passionate people called for everyone to get fluvoxamine over the last few years. Or how is it ethical to withhold this medicine, which we now know doesn't work, or hydroxychloroquine? Or for that matter, we still have, patient this week, are you ready for this, Vincent? “Why are you doctors not using hydroxychloroquine and ivermectin or a high dose of vitamin C?” The list just goes on. The reality here is that we are not as smart as we think we are. Science is really an exercise in humility. Science is not something mysterious either. As we see here, this trial was very simple. Hundreds of people get a medicine, hundreds of people get a placebo or a sugar pill, and we just ask the question, who did better?

Do people do better with that or they do better? And 90% of the time, people do better without us messing. Our peers look over the research, they make sure no one is cheating, like giving vitamin C only to young, healthy people and withholding it from the people in their 80s and somehow comparing elderly immunocompromised people with cancer to healthy people in their 30s. No. If you do these, you have to be honest. When you're honest, you get the answers. They're not always the answer that we thought we would get.

VR: What is the motivation, Daniel, for people saying, "Why aren't you using vitamin C, ivermectin, hydroxychloroquine, fluvoxamine?" What's their motivation?

DG: There are a lot of people, Vincent, who at some point they just - and I remember getting an email from one of these investors saying, "You know what, Daniel, some things you just know are true. You don't even have to do the science." [laughs] I responded back with, "That's not true." [laughs] Nobody has this crystal ball. You actually have to - You have to check.

VR: Yes. You just don't know it's true. I would say that financial people, they think they know it's true, but they screw up most of the time anyway.

DG: [laughs] That's true. Yes. That's why a lot of us buy index funds, right?

[laughter]

DG: All right, moving on to the second week, right? Unfortunately, we still have individuals progressing to the second week, getting that cytokine storm, that inflammatory phase. There are times when you end up in the hospital, steroids in the right patient at the right time, at the right dose when those oxygen saturations drop, not during that first week, you'll do harm. We have anticoagulation guidelines. We've learned a lot about pulmonary support.

There still is a small window for remdesivir if you're in the first 10 days, tocilizumab, right? More immune modulation. What about targeting the complement system? It's going to be short, don't worry. I know I brought up a complement that almost put me to sleep, but the article, "Recombinant C1 Inhibitor In the Prevention of Severe COVID-19: A Randomized, Open-label, Multi-center Phase IIa, Trial" published in *Frontiers in Immunology.*

Lots of things. We've tested steroids, we've tested tocilizumab, they work. What about targeting complement activation?

They conduct a randomized open-label multinational clinical trial where you end up with a 2:1 ratio getting this ConA versus standard of care. The trial was prematurely terminated because of futility after randomization of 84 patients, 56 in the ConA, 28 in the control arm. The results just do not support the use of ConA, this complement targeting to prevent COVID-19 progression.

VR: ConA inhibits complement activation. Correct?

DG: Exactly. Exactly. Yes. All right. Moving on to late phase past, Long COVID. The article with the catchy title, "Epstein-Barr Virus Reactivation is Not Causative for Post-COVID-19-Syndrome in Individuals With Asymptomatic or Mild SARS-CoV-2 Disease Course," recently published in *BMC Infectious Diseases*. I get to take a little issue with that title and maybe I'll suggest a revision.

The authors tell us that they aim in this study to investigate a punitive EBV reactivation in healthy adults after asymptomatic or rather mild COVID-19 without hospitalization that donated blood and reported post-COVID syndrome. They use online surveys, they determine the rate of post-COVID syndrome among seropositive participants documented the symptoms and then they do something interesting.

They're going to compare the amount of neopterin, an unspecific prognostic marker for proinflammatory active antiviral immune responses between individuals with and without PCS. post-COVID syndrome. at different points in time. They're going to look at SARS-CoV-2 anti-nuclear capsid total antibodies. They're going to look for EBV DNA, they're going to look at different EBV serology results.

They end up looking at individuals with pre-pandemic serum samples available that did not report PCS and some individuals who did report PCS. Figure 2 sort of breaks this down. We have this Group 1 asymptomatic, no post-COVID picked up on serology. Group 2, symptomatic infection no post-COVID. We've got 26 and 108 in those two groups. Then we get to slim pickings.

We have a Group 3 with symptomatic infection, post-COVID syndrome three months after initial blood donation five to six months post-infection. Got 15 people, not a lot there. Group 4 where it's nine months after initial blood donation and about a year post-infection, we only have 10 people. A Group 5, no post-infectious syndrome after three months. but then we end up getting the PCS issues later. What kind of issues? We'll talk about these three groups.

That Group 3, these are the folks that three months after initial blood donation report issues, 10 of 15 have that fatigue, generally feeling weak, three out of 15 with shortness of breath, three out of 15 with that taste, smell disturbance. Two out of 15 with nasal congestion, two out of 15 with cough. We get some chest pain, body ache, headache, one of 15 in each of those.

Then we move into the group of 10 where we're still seeing six out of 10 with the smell and taste. We see about half of them with the fatigue, 20% with shortness of breath, 10% brain fog, sleep disturbances, elevated blood pressure, and then that N of four, that smallest last group where fine at three months, but nine months after they have issues, fatigue, general feeling of weakness shortness of breath, brain fog.

All right, small numbers, not happy with that. Then they look for EBV DNA and EBV serology levels and they didn't find much. Not perhaps as strong a conclusion as the title where they say, our study reveals that PCS in per se healthy adults with no known comorbidities may be explained by re-vaccination of EBV as shown by screening for EBV and specific antibodies.

Basically, they don't find it in this small group. They go on to say, "Furthermore, our data do not indicate a persisting pro-inflammatory antiviral immune response or a specific SARS-CoV-2 antibody response. I think I would restructure this is, we looked at a few people with mild SARS-CoV-2, and we didn't find in this group evidence for this EBV reactivation.

I do want to put this in context. Why am I discussing this article, which I'm not particularly impressed by? It's for a couple of reasons. I'm going to start talking about the UPenn study where we actually saw that in the cohort at UPenn, significant low serotonin levels. Then reproducible in the Cork cohort, but not reproducible in all cohorts. Not everyone has low serotonin. Several of my patients, now we're testing for this, we're actually seeing that some patients have very low serotonin. Some patients have high serotonin.

The data information we got out of Mount Sinai and Yale, some people have evidence of this really high EBV serology, but not everyone. Some people have low cortisol, but not everyone. We're starting to understand there are certain people that have one biochemical abnormality, but not another. I think what people are concerned about, and I just want to echo this, is we don't have any tests that rule out Long COVID. If your doctor checks serotonin and cortisol and EBV and CMV and these other serology levels and they do not find an abnormality, that does not mean you do not have Long COVID. It just means that you're not falling into these groups, these cohorts that have been studied.

VR: Maybe mechanistically, this is not the cause.

DG: I think there may be different people at different drivers for different phenotypes. I will close this out with no one is safe until everyone is safe with everyone gathered around the fire. Go to parasiteswithoutborders.com. Click on the ‘Donate’ button. Remember right now

we are doing the MicrobeTV fundraiser for November, December, and January. We will double your donations. We are hoping to give a maximum donation of $20,000 to MicrobeTV.

VR: Go push that button, folks. We need your support to keep getting good science to everyone. It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Quinn writes a question for Daniel Griffin about tuberculosis. “There was stigma around tuberculosis, but it went down at some point. Was this correlated with it becoming curable? If so, did it go up when drug-resistant strains became prevalent, thus making it incurable in some or more cases?”

DG: It's a great story and that the history of the white death, as they call tuberculosis, is fascinating. I have to say a particularly fascinating interest of mine. I did actually research in medical school. My original research interest was tuberculosis. There was this very interesting period of time in the 1800s when you just read in the Harrison's textbook of medicine. Twenty, 30 pages, all these ideas about how it was a moral failing or a genetic abnormality. Then Koch comes along, he is like, "Nope, it's a bug." You breathe it in, it makes you sick.

Suddenly, there's two pages. There was a big change then. When I spent time working in Nepal, they actually had two words. They had a word for the tuberculosis that runs in families, the genetic disease, and the tuberculosis you can catch by inhalation. I think as we learn more and the mystery goes away, it changes some impressions. Then as we move into a world of drug resistance and as certain marginalized populations become the ones that are affected, we can see the pendulum swing back to this discriminatory view.

VR: Helene writes, “I'm a 56-years-old woman with no health issues. I received two Sinovac COVID vaccines and three Pfizer, all original vaccine. My last dose was July 2022. Never had COVID, I think. Since the updated vaccine is not available here in the Dominican Republic, neither is Paxlovid. Should I get another shot of the original vaccine or wait to see if it will become available in the Dominican Republic?”

DG: This is not an easy question to answer. What are we thinking with the vaccines here? We think once you've had three shots, we're thinking you're getting that durable 90% reduction in severe disease, a lot of that may be T-cell mediated. The whole concept behind the boosters every fall is for three to four months to really bump up those antibody levels. Do you really do much to bump up the T-cell for a temporary period of time? I'm not sure, to be honest.

Without the latest updated vaccine, I'm not really sure how much of a boost you're going to get for this period of time. I would wait, see if the new updated vaccines come onto the scene hopefully before the numbers really start to rise. Vincent, do you have any thoughts?

VR: I agree. She should wait because there really isn't much evidence that a fourth dose of that original vaccine's going to help much. I think the key here is the inequities around the world and availability of vaccines and antivirals. These were created by humans. They should be available to all humans. It's really a failing of the human race that you can't get these in the DR. It's just terrible.

DG: I would agree.

VR: Irene writes, “Thank you so much for your weekly clinical updates. For those of us in primary care, your summaries of most up-to-date data and recommendations have been a godsend. A while ago, you reviewed treatment for influenza and I believe mentioned that oseltamivir is not actually effective. Now that we're starting to see influenza, could you review your recommended treatment course for this viral illness? UpToDate lists oseltamivir as the preferred regimen.

DG: Excellent. Happy to review this and put it in context. You are right. I'm a huge fan of UpToDate. I sometimes at Columbia be like, "Oh my gosh, you looked at UpToDate." It's a great place to start. You can actually follow the rabbit hole. Read the article. For influenza, that is true. Oseltamivir, Tamiflu, is the recommended preferred treatment. Why do we do that? What do I have to say and why would I say it? Just not as impressed as I would like. There's a couple of landmark articles that people refer to going from UpToDate to a meta-analysis back in 2014 in *The Lancet*.

They looked at a bunch of observational studies. They looked at about 30,000 hospitalized patients with flu back during the 2009, 2010 influenza H1N1 pandemic. They saw overall about 19% mortality reduction with Tamiflu. Nineteen percent, not that great, not so impressive. I keep harping on the guy who talks about timing. If you could get that treatment started within two days of symptom onset, then 52% reduction in mortality. Timing really matters. The recommendation really get this within the first 48 hours, maybe within the first 72, and then you probably really have missed your window.

There was a cohort study that was published right before the COVID-19 pandemic. In *CID* in 2019, looking at about a little over a thousand patients with flu in the ICU. Again, if you got the Tamiflu started within 40 hours, 48 hours about a 30% reduction in mortality. Not quite as robust as I would like to see, but again, the real key with Tamiflu is timing. We actually had a - I thought was a pretty great program with the Medicare Advantage folks for UnitedHealthcare, where they would have the ability to do these in-home flu tests. They actually had these Bluetooth compatible boxes. If you tested positive for the flu, knowing that timing was so key, the provider could activate and the box would open, and in there was your Tamiflu because timing is so key. What about Xofluza or baloxavir because we have a listener, the endonuclease inhibitor. The issue there, why isn't that this recommended more? Why isn't it used more? It's just a question of limited efficacy data has really pushed it up through the guidelines.

VR: Bob Krug, who discovered the endonuclease many years ago, says one dose is effective of baloxavir.

DG: It's interesting. People are like, "Oh, but it's 150 bucks." It's 150 bucks for a course Tamiflu. It's not a price issue.

VR: David writes, “Seventy-year-old male, no particular risk factors other than age, fully, recently vaxxed, recently tested positive for SARS-CoV-2. Reached out to my physician's office for a Paxlovid prescription, which they promptly submitted to the pharmacy after consulting my medication chart. No interaction problems. However, when I picked it up, it was the renal dose. When I looked at my blood work results for the past couple of years, all the functions

were in the normal range. Nothing in the dosage literature that I'm aware of indicated that my situation required to reduce dose.

When I reached out to the physician's office, I got the following response. "We give this dose to patients over the age of 65 to help prevent kidney issues, push lots of fluid, rest when you can, take Tylenol for headache and body aches." I haven't found anything in the literature to suggest this is necessary and wonder whether it might even reduce effectiveness or raise the likelihood of selecting resistance. In any event, it seems rather arbitrary to ignore the dosing guidelines without a better explanation.

Do you know of findings in the literature suggesting this is the proper course? Are they being overcautious here? While this is unlikely to cause me any issues, might it not cause a problem for those more at risk?"

[laughter]

DG: This is certainly going on. Actually, I have run into primary care docs and say, "Whenever my patient over 65, I just do the renal dose just to be on the safe side." That's not being on the safe side. You use the medicine properly. If you have access to the patient's kidney function, you don't discriminate based on age. You discriminate based upon kidney function. A person has normal kidney function and the appropriate dosing is full dose, you get full dose. If a person has between 30 and 60 on that GFR, then you're going to use the renal dose. Yes, this is just, I don't know if it's a little bit lazy or what it is, but take the time, check if you need to get a blood test to see, you can do that. The other is, as we talked about, have a plan, know what your kidney function is. Know what that medicine list and be ready to go ahead of time. Don't keep looking, you're not going to find anything. The dosing is based upon your kidney function, not your age.

VR: Finally, Ginny writes, "Listening to the letters you receive, I'm always amazed at the difference in care that people receive from different medical providers. I'm now 67, was diagnosed with multiple myeloma in March. The recent letter writer, Episode 1062, I am being treated with DARA and REVLIMID, and I also take Decadron two days a week. The letter writer and I are both immunocompromised due to this treatment. Unlike her doctor, though, my oncology team encourages me to get all recommended vaccines, which was also your response to the letter. My oncologist, unlike my PCP, was also quite willing to make an advanced plan for antivirals in case I got COVID.

As a result, when my husband, who'd not been masking in public, as I had, brought home COVID last month, I had my first dose of Paxlovid only two and a half hours after I noticed symptoms and had a positive home test. I felt much better in just a few days, and testing negative, I was able to have my DARA infused in the following week. My PCP is not the only doctor who wouldn't discuss Paxlovid in advance. My friends have tried to make a plan, as you have encouraged, with no luck. Sometimes the doctors say they don't recommend Paxlovid because of the side effects.

Very frustrating. I know it is discouraging for you that many practitioners aren't providing appropriate care because of misinformation or their opinion. It makes me grateful to be in the care of what seems to be an excellent hem-onc team here at Strong Memorial Hospital in

Rochester. I can't tell you how much I learn on your clinical updates has helped me in seeking out care for myself and family."

DG: I'll say thank you. Strong is a solid medical center. It is tough. There are not a lot of, as I think people know, there are not a lot of us infectious disease docs out here. Ninety percent of the COVID treatment is really going to have to be done in the trenches by the primary care docs. Hopefully, we provide education and we'll do as much as we can. Please, get out there and spread the word.

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

DG: Thank you. Everyone, be safe.

[music]

[00:52:55] [END OF AUDIO]