This Week in Virology

TWiV 1050 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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

VR: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1050, recorded on October 5, 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: Daniel, how long have we been doing these now? Is it like, three years?

DG: The clinical updates, we started doing the clinical updates in early 2020, right?

VR: Yes.

DG: It was like, right end of February, early March.

VR: Over three years.

DG: We are coming up on, is it, am I counting? Four, it'll be four years before we know it.

VR: I think it's great. I think a lot of people appreciate it and I think we should keep going. Obviously, you need to also because you're the main driver.

DG: [chuckles] OK. Well, let's get right into it with a quotation.

Vincent: Notice he didn't commit himself.

[laughter]

DG: Well, I should say right up front before the quotation, this might be a slightly longer episode than usual, Vincent. I say that because this weekend, I've got to sail about 100 miles through a rainy weekend, and I need something to listen to as I'm -

VR: [chuckles] You can listen to the regular *TWiV*. It's two hours.

DG: Well, that won't drop till Sunday. Most of the trip will be on Saturday, so I got to fill it up with this.

VR: I got an idea. Joe Rogan has three-hour podcasts, Daniel. Go for that.

DG: OK. All right. [chuckles] There might be children listening. Anyway, so start off with our quotation. "Poverty may be powerful enough to swamp the influence of variants in our DNA." That's from Carl Zimmer. All this talk about variants, I just ran across that and I thought that that was, thought it was appropriate. We try to talk, I think, a lot about all the social inequities and social justice and trying to do our part. Hopefully doing our part with spreading good information.

Right before we jump into COVID, a couple of hot off-the-press issues. I don't know if you've heard about this, Vincent, but malaria now in Arkansas.

VR: Yes.

DG: Apparently Arkansas officials, Arkansas Department of Health officials, said that there is now a locally acquired case of malaria in Arkansas. This is number 10, right? We've had nine other where people did not travel. They never left the U.S. and they end up with malaria. Most of those in Florida. A case down in Texas, a case in Maryland, a case in Arkansas. Just between you and me, Vincent, we actually have a case here in New York that you will be reading about in the future.

VR: Wow. What do you think is going on, Daniel?

DG: I have to admit, I was really thinking this through and I'm like, what's going on? It's not like we're suddenly doing a better job of diagnosing people who get malaria. It's going to progress eventually. It might be a late diagnosis, but it's not like you're going to miss it and the person is going to get all better. I'm not sure exactly what's happening. Obviously, people are coming to the United States who are parasitemic. They're getting bit by a mosquito. You don't get this directly from another person. That mosquito is then biting another person.

We've always had the Anopheles mosquito. Do we have more? Do we have more people coming here who are parasitemic? I'm not sure exactly, but this is a lot. We're up to, well, 10 and I'm telling you, 11. We're almost getting a case per month of malaria here in the U.S. without any travel.

Let's get right into COVID. We've got a lot to talk about today. I say talk about today because, Vincent, I'm pulling you in because I really want this to be a dialogue because there's a couple of things I'm hoping on my agenda for today. Let's talk off with the first.

What's going on with COVID right now? People always want a status update. I pulled this off BNO News, which I still follow on X or whatever that social media thing is. On Monday, October 2, they put this out there, posted it, whatever it's called now, “Weekly U.S. COVID Update. New cases, 251,645.” We're averaging about a quarter million cases each week. In hospital, we have 15,600. In the ICU, we have 1,700. New deaths, 1,500. We're over, last week we passed the 200 deaths per day.

A couple of other things and I'm going to circle back to these numbers. If we follow the COVID-19 new hospital admissions per week in the U.S. reported to CDC, we're actually seeing that it's no longer rising, maybe a little bit of a drop. Then if we look at wastewater, I sure hope you don't live in the Northeast because everywhere else has seen a really nice drop. We started to come down and actually, the Northeast is rising again.

VR: It's a busy place, Daniel.

DG: Yes. There's a couple of things here, and I'm going to try to hit on this several times. I want to do this in a way that's sensitive to the vulnerable people in our population. For most people, COVID is not something that results in death. It's not something that results in hospitalization. As we go forward, we talk a little bit about how our tools apply to this new scenario when we talk about vaccines, when we talk about antivirals. I'm setting the stage for you there.

The next two are children, COVID, and vulnerable populations. This week, we have the *MMWR,* "Effectiveness of Maternal mRNA COVID-19 Vaccination During Pregnancy Against COVID-19-associated Hospitalization in Infants Aged Less Than 6 months During SARS-CoV-2 Omicron Predominance - 20 States, March 9, 2022 through May 31, 2023." Set the stage here.

We have infants who are born. They're coming into this world. For them, they are naive. They do not necessarily have any immunity for COVID, so for them, it's a brand new thing. They will not be eligible for their COVID-19 vaccination until they hit 6 months of age. One potential way to change this is for the pregnant individual to get vaccinated during that last trimester. Now, not only is this an evidence-based intervention to protect mom, but it also might, let's see, offer some protection against infant COVID-19-related hospitalization.

Here we have the results of a case-control study conducted during March 9, 2022, through May 31, 2023, to evaluate the effectiveness of maternal receipt of a COVID-19 vaccine dose of vaccine effectiveness during pregnancy against what? COVID-19-related hospitalization in infants less than 6 months, but we're also going to look at less than 3 months.

The vaccine effectiveness for infants less than 3 months was 54%. Less than 6 months, 35%. Intensive care unit admissions occurred in 23% of all case patients. Invasive mechanical ventilation was nine times more common in infants of unvaccinated compared to vaccinated mothers. Perhaps the most compelling way to view this data is that 75% of the infants hospitalized with COVID-19 were born to unvaccinated women.

VR: The VE for hospitalization is not great, right?

DG: You're right. I would like it better. I would like better than just 35% for the first six months. Yes.

VR: Yes.

DG: I would like to see the efficacy we're seeing with the RSV vaccines, with the RSV monoclonal Beyfortus, for instance.

VR: I wonder why that is, if it has something to do with the levels of antibodies induced in the mother because the transfer is supposed to be good.

DG: The transfer of antibodies is good. I think as we've talked about, mom doesn't just transfer antibodies. There is some cellular immune transfer, but it's not as robust perhaps as we need. I don't know. Maybe with RSV, antibodies are more important than cellular component. I'm not sure I have a great explanation for why this isn't better, but a nice thing, right? The *MMWR* also put out, "COVID-19 Vaccination Recommendations and Practices for Women of Reproductive Age by Health Care Providers - Fall DocStyles Survey, United States 2022," where we actually learned that 82.9% of providers do report that they are recommending COVID-19 vaccination to women of reproductive age.

I'm going to tell a story. We've moved into our pre-exposure, post-exposure transmission testing. Last week, well, this week, I'm sitting at the nursing station with one of our hospitalists, Dr. Jeremy Lawrence, and he turns to me and asks, "Are you taking Paxlovid?" I responded, "Should I be taking Paxlovid? Why would I be taking Paxlovid?" He said, "Well, Mr. R tested positive for COVID." Well, it turns out that there was a gentleman in the hospital who got admitted on a Tuesday, comes in through the ER with concern for a stroke. They had what they call a stroke code in the ER as the patient had an episode of slurred speech and fell out of his chair at home. They did find that he had a right middle cerebral artery stroke on imaging that was likely cardioembolic. On Saturday, after being in the hospital for about three days, he has a rapid response, right? This is when it gets activated. Something's going on with Mr. R. His heart rate is up at 200.

I look through, it looks like first he was hypothermic. First, his body temperature was low. Then when I see him, he has a fever. At this point, he's non-verbal. He's there with his wife. His clothing is soaking wet and his COVID test now is positive. What Jeremy wants to know is can he start taking a medicine and prevent himself from getting COVID?

We've already talked about the Paxlovid post-exposure prophylaxis trial, which did not show benefit there. Hot off the press, what about molnupiravir? We have the article, "Molnupiravir for Intra-household Prevention of COVID-19: The MOVe-AHEAD Randomized, Placebo-controlled Trial," published in the *Journal of Infection*. These are the results of this MOVe-AHEAD randomized controlled, double-blind phase 3 trial comparing molnupiravir, 800 mg twice daily for 5 days, with placebo. Eligible participants were adults, unvaccinated, asymptomatic household contacts of patients with laboratory-confirmed COVID-19.

The primary endpoint was the incidence of COVID through day 14 in this modified intention-to-treat study. Superiority of molnupiravir had a pre-specified one-sided p-value. The modified intent-to-treat population comprised 763 participants randomized to molnupiravir, 764 to placebo - this is actually pretty robust - 83.6% had anti-SARS-CoV-2 antibodies at baseline. It's actually, I think, appropriate, right? This is a population that actually comes into this with pre-existing immunity, which is where we are in most situations. COVID-19 rates were 6.5% through day 14, in folks that got molnupiravir, 8.5% with placebo, so not really seeing much of a difference here.

A couple of things they do point out. The majority of the test-positivity actually occurred after completion of treatment with molnupiravir. They do comment that adverse event rates were

low and similar between molnupiravir and placebo. A couple of comments. They sort of, what can we make with this data? The authors point out that in the small subgroup with quantifiable SARS-CoV-2 at both baseline and subsequent visits, molnupiravir reduced viral load. I'm going to make that RNA copy number to a somewhat greater extent than placebo at days five and 14.

As I mentioned, in the primary analysis population, over 70% of the COVID-19 cases in the molnupiravir arm occurred after the end of the study intervention. Second, trial participants could not be enrolled until after the household index case was confirmed to have COVID-19. They were talking a little bit about maybe some delays there, but just to bring it all together, to date, no evidence to support molnupiravir or Paxlovid in these five-day courses as post-exposure prophylaxis. Is this a situation where timing and maybe duration is the problem? Sort of leaving that as a question for a future study.

All right. Now, this is where we're going to have the meat of today's discussion: Testing. This article, it's being, it's all over the press, lots of headlines. I'm going to just say right up front, I don't think the headlines are accurate if you actually read the article. What am I talking about? The article, "The New Normal: Delayed Peak SARS-CoV-2 Viral Loads Relative to Symptom Onset and Implications for COVID-19 Testing Programs," published in *CID*. Here the authors hypothesized that in a highly immune population, symptom onset might occur earlier in infection, coinciding with lower viral loads.

This is great. I love hypothesis-driven research as opposed to discovery-based, but let's not just look for confirmations. Everyone thinks this is true, but let's ask, is it true? We read that the authors assessed SARS-CoV-2 and influenza A viral loads, or RNA copy numbers, relative to symptom duration in symptomatic adults, 16 years of age and older, presenting for testing in Georgia. This is 4/2022 through 4/2023, so the Omicron variant predominant period. Participants provided symptom duration and recent testing history. Nasal swabs were tested by Xpert Xpress SARS-CoV-2/Flu/RSV assay and Ct values recorded.

Now, as I mentioned, they meant to say RNA copy number and all these different things, so we'll just be trying to substitute that going forward. Nucleoprotein concentration in SARS-CoV-2 PCR-positive samples were measured by a Single Molecule Array. To assess hypothetical antigen rapid diagnostic test sensitivity on each day after symptom onset, percentages of individual Ct values less than 30 or less than 25 were calculated. I just want to point out these are calculated.

They report in this study of 348 newly diagnosed SARS-CoV-2 PCR positives. We have 65.5% women, median age 39.2, 91.1% had a history of vaccination, infection, or both. They say natural infection, but I'm not sure about unnatural infection. Both CT value and antigen concentration measurements, median RNA copy numbers rose from the day of symptom onset and peaked on about the fourth day. Antigen rapid test sensitivity estimates were 30% to 60% on the first day, 59% to 74.8% on the third day, and 80% to 93.3% on the fourth day of symptoms.

In 74 influenza A PCR-positive individuals, similar demographics, median influenza RNA copy numbers peaked on the second day of symptoms. We have a nice Figure 1 where you can actually see the data for the SARS-CoV-2. Figure 2 gives us the influenza A data. Note to

authors, I will point out, they actually don't reverse the Ct values. It almost looks like the Ct values looks like the RNA copy numbers going down, but really what's happening is the Ct values going down, and the RNA copy numbers going up. I always like when they switch those around. It seems like it makes more sense, but let's look at it closely.

When is the Ct value the lowest? It's about day three. They're going to tell us that that's a little bit later than earlier data. Well, I went to earlier data to see if this was true. That is the point of the paper. I found a paper published by a friend, a colleague of mine out at the Everett Clinic in Seattle, and this was an N of 172. Here, when did the RNA copy number peak? Oh my gosh, day three.

VR: Hmm.

DG: That's the same. All right. Interesting.

VR: That was for SARS-CoV-2, you said, day three?

DG: Yes. Day three was for SARS-CoV-2 Omicron variant. Now this is a delayed peak, not until, oh my gosh, the same day, day three for the Omicron variant. It's peaking at the same time for the RNA copy numbers.

VR: Why are they saying in the results that it's 59% to 70%, 80% on the fourth day of symptoms in terms of sensitivity?

DG: Yes. There's two things here that I think they're talking about. One is there, you read your title, delayed peak SARS-CoV-2 viral loads. Not true, right? We're comparing it to Delta. I'm seeing peak on day three during Delta with a N of 172. I'm seeing a peak here on day three also, with a very similar N. Not seeing that. I think that that's a little bit of a challenge to the title. The interesting thing in the actual study, even though they're making a conclusion, they don't show us a comparison. They don't say, here's a comparison early, here's a comparison now. They're just saying, look how late this is.

They're also, I think, sort of echoing this concern that people have, that hopefully we have explained, that the antigen tests turn positive after the PCR tests, and the antigen tests don't have the sensitivity of greater than 90% until we do that second test on day four, right?

VR: Yes.

DG: First day of symptoms, that's day zero. That's, we say, wait till the next day. First thing in the morning, day one, you go ahead and do a test. If it's positive, you've got COVID. If it's negative, you wait 48 hours, you repeat it again. The two tests done like that actually increase that sensitivity. Still, PCRs are more sensitive and will pick up a few more cases.

VR: Yes, this came up last night. People said, is there a later onset? Should testing be done later?

DG: Yes, they look at, we're looking at the data here and this is what everyone has now been told. This is all out there in the media. Everyone's saying, see, this is what we expected. This is what we're seeing. The data does not support.

VR: Yes.

DG: Just to point that out. Also, those rapid tests, I sort of want to point out the disconnect here where we're seeing, when are we seeing these rapid tests turn positive? I know there's "rapid test experts" out there who are suggesting that you can look at the darkness of the line, that this is now a poor person's PCR. You can actually apparently tell based upon the color how many people you have infected. Just want to point that out.

All right, moving on. This is actually something that Amy sent me. This is, "Viral Kinetics of Sequential SARS-CoV-2 Infections," published in *Nature Communications*. Actually, this is interesting. This is the article, "Viral Kinetics of Sequential SARS-CoV-2 Infections," published in *Nature Communications*. This is open access, or so it seemed. Go right to Figure 2 and you actually get to see the viral kinetics of first and second infections. They're not necessarily peaking earlier. We've talked about that. What they are doing is the peak is a little bit lower.

We're not getting quite as high an RNA copy number and the time to the RNA turning negative, the RNA copy turning negative is actually a little bit shorter. It used to be coming right in at day 10 and now it's coming in a little bit shorter. Maybe this does feed in a little bit to this behavior of shortening the isolation period that people are sort of buying into.

All right, I do want to point out, I suspect most of our listeners have heard that Katalin Karikó and Drew Weissman just won the 2023 Nobel Prize in Medicine or Physiology. What did they win that for? mRNA vaccine technology and actually, really the instrumental findings about how to use that technology without triggering this robust immune response. The modified U in the mRNA vaccines.

Also big news for our listeners who've been waiting for this, Tuesday, October 3, the FDA authorizes updated Novavax COVID-19 vaccine formulated to better protect against currently circulating variants. I'll just read that the U.S. FDA amended the EUA of the Novavax COVID-19 vaccination for use in individuals 12 years of age and older to include the 2023-2024 formula. Individuals 12 years of age and older previously vaccinated, you get one dose. If you're unvaccinated, it is two doses separated by three weeks. I was waiting, Vincent, I was waiting for the Novavax. Then yesterday I went ahead and got the Spikevax because I was signed up and whatever. Because I wanted to try, I wanted to try the Novavax.

VR: What were you going to look for with Novavax?

DG: Basically what I was going to look for is that I had no side effects. Remember, I get that little bit of frustration when I open frustrating emails after the Spikevax, which I'm not sure is any different from when I haven't had a Spikevax. I was hoping maybe with Novavax, I could read frustrating emails and have that calmness.

VR: I see.

DG: [chuckles] I guess I won't get a chance to do that trial on myself. All right, so this is, I hope, the exciting part of our episode today. If it's not exciting enough already, COVID, the early viral phase. Number one, what do we do? Paxlovid, now fully licensed. We have the article, "Antiviral Efficacy of Molnupiravir versus Ritonavir-boosted Nirmatrelvir in Patients with Early Symptomatic COVID-19 (PLATCOV): An Open-label, Phase 2, Randomized, Controlled,

Adaptive Trial, published in *The Lancet Infectious Diseases*. First off, this sounds like a horse race. Are we going to bet for which is better, molnupiravir or Paxlovid? There's a lot in here that I'm going to pull out.

These are the results from PLATCOV, which is an open-label, multicenter, phase 2 randomized, controlled, adaptive pharmacometric platform trial running in Thailand, Brazil, Pakistan, and Laos. The component of the trial reported here was conducted in the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. I spent a little time there right before that marathon in Cambodia with the Thai princess. For full disclosure, I only ran the 10K. The princess was much faster. She ran the full marathon.

Now, the investigators recruited low-risk adult patients aged 18 to 50 with early symptomatic COVID-19, less than four days of symptoms. Interesting, right? This is low-risk patients, so we need to keep that in mind. Eligible patients were randomized using block randomization via a centralized web app to one of seven treatment groups. One was molnupiravir, two was Paxlovid, three was one type of monoclonal antibody, the casirivimab–imdevimab. Group four was tixagevimab–cilgavimab, right? These are the old monoclonal cocktails. Next group was favipiravir. Next group, fluoxetine. Then the final, seventh group was the no-study drug, our placebo group.

The no-study drug group comprised a minimum proportion of 20% of patients at all times. It's a little larger, right? We have seven, but here's 20% with uniform randomization ratios applied across the active treatment groups. We're not going to talk, well, we're mainly not going to talk about all these groups. We're going to focus on the results of the randomized molnupiravir and Paxlovid groups compared to the no-study group. The primary endpoint was the rate of oropharyngeal viral clearance, RNA copy clearance, assessed in a modified intention-to-treat population defined as patients with more than two days of follow-up. Safety was assessed in all participants.

Now, this is potentially interesting as we get the viral RNA kinetics for no drug and the different treatments. Between June 6, 2022, and February 23, 2023, 209 patients in Thailand were enrolled and concurrently randomly assigned to molnupiravir. We have 65 ritonavir-boosted nirmatrelvir, so that's the Paxlovid 59, or no-study drug. That was 85. What do we get? Relative to the no-study group drug, who's going to win? Rates of viral clearance were 37% faster with molnupiravir, that's OK. 84% faster with Paxlovid. OK, so Paxlovid wins. Quicker drop in the level of the viral RNA.

Then we hear about something else. We hear about viral rebounds. Here, let's look. They say viral rebound occurred more frequently following nirmatrelvir, and they say 10% compared with no-study drug, 1%; molnupiravir, 2%. No adverse events. Let's look at the data. Let's see what this "rebound" is that we're talking about. We're going to walk everyone through the figures here. I think this is actually open access, so if people get a chance, go ahead. If you have to pay, it's worth it. Let's talk about Figure 2.

We look at Figure 2, and we have SARS-CoV-2 genome copies per milliliter. We're going to get our RNA copy numbers here. We're starting basically about a million, so 10^6 for everybody. Everybody starts off at 10^6, so a million genomes per milliliter. Then very quickly, we see that the study drug, even better with molnupiravir, and really good with Paxlovid. We have

that RNA copy number really come crashing down to, well, we're going to get down to about 100 copies by day four with Paxlovid. We're never going to actually get that low in the first seven days with no study drug. We're not going to quite get there with the molnupiravir, but they're going in the right direction, but yes, Paxlovid is winning. Then we hear that in some individuals, after day seven, they were able to detect RNA copy numbers.

Let's go through. In one person who got no study drug, we see a rise in RNA copies to above 10^4. In the Paxlovid, we only actually get one of these patients getting above 10,000. We're not seeing this teeming rebound. We're actually getting very low-level detectable RNA, only one getting above 10,000. Actually, the same in molnupiravir. Only one gets above the 10,000. I'm going to say that if you look at this, you will find that we are not seeing the virus replicating again with a vengeance, as I quote of our -

VR: Well, as you said, we're not really looking at infectious virus, so who knows what's happening with this RNA?

DG: Yes. I can't expect, I can't anticipate infectious virus being particularly high when only one person gets above 10,000.

VR: The one person with the no-study drug, and then with the ritonavir and nirmatrelvir, right?

DG: Yes.

VR: You've got more people in that study. You've got one, two, three, four, five, right? Looks like.

DG: Yes.

VR: Then you've got two there that go to 10^4, and then one goes above, and then another just hits it also, right?

DG: Yes.

VR: This is all just noise, in my opinion.

DG: It's very low, right? I was sort of - This is the part of the study I found very interesting because we could actually see the data. When someone says, oh, but they say 10% get rebound, I'm like, uh, sure. 10^4, and even some of the others, right? They're all below 10^4, only those two hitting, only one getting above.

VR: Yes. What's the significance of 10^4?

DG: I just sort of drew that as that seems like this because it's only 10,000. Doesn't seem like it's a high level.

VR: I do think you need to have infectivity to know if this means anything, right?

DG: I think that that's key because we always say, oh, but if you start having this, then maybe you become transmissible again. I think you need to actually, is that true? Are we really seeing ongoing transmission? Once someone has taken this course of Paxlovid.

VR: Yes. No, I think if you want to make a claim that you're having a rebound, you need to show it in terms of infectivity, not simply genome copy number.

DG: This is reassuring, I will say, and it's nice to see this and it's good to pull it apart so that people don't just quote, but they said 10% rebound. I'm like, well, take a look at the data, which is good. The nice thing here also is, even though they said they weren't going to talk about it, if you go to Figure 5, you can actually see what's happening with all those other groups. What's happening with favipiravir, what's happening with Ivermectin, what's happening? What do we see? Actually, the people with Ivermectin actually had slower drop in the RNA copy numbers. It was actually worse than doing nothing.

I thought that was interesting, but this is actually what I'm going to sort of suggest is interesting, going back to what's going on with COVID. The main indication for oral antiviral treatment in patients with COVID-19 is prevention of disease progression. As with other potentially serious infections early in the course of disease that effective antiviral drugs are given, the greater we see this clinical benefit, right? As we've seen from the earlier studies, if that's your endpoint, the sooner you start, the higher percent of reduction you're going to get in patients progressing to severe disease. We already have data that waiting until after day three and starting during day four or five is associated with more people progressing.

This is the interesting thing that I wanted to point out. What about symptoms in those people that took Paxlovid and had detectable viral RNA after day five? What is this rebound that people are describing that they experience? Only three of the patients who had a return of symptoms after day - Only three of the patients had a return of symptoms after day five. Sort of look at that, do the math on that, right? We've got 68 and only three actually had symptoms after the fifth day, interesting there. Let's go through those patients.

The first patient had a cough on days one through three, was completely fine, and then on day 14, Vincent, he had a cough for the one day and then he was all better. That's scary. Now the second patient experienced cough on days one, two, and three, completely better. Then they had a cough on day seven, a cough on day 14, and then they were completely fine. The third patient reported a return of URI symptoms, cough, sore throat, runny nose on day 14, and then actually was reporting post-exertional fatigue on day 28. Interesting.

Now what I am going to suggest people do, and I know no one's going to do this, but you should do this. Maybe someone will do it and email in and say, I did do this. There are 153 pages of supplementary data. The interesting thing when you go through this is you will find some data here where people feel better much faster with Paxlovid. If you actually look at the symptoms reported, people that took Paxlovid, 75% of them report that they had fever resolution in a single day. We then go on to look at basically the majority of them reporting that they feel better after a certain period of time very quickly.

If you look at the patients that didn't take anything that weathered the storm, so to speak, longer duration of fever, and actually all the way out even to day 28, almost half of the no-

study drug patients are reporting that they still have ongoing symptoms. What I'm sort of suggesting here is starting to think about this slightly differently. People do not expect they're going to end up dying from COVID. For most people, that's true. We still really want to focus on the most vulnerable patients. They're high priority because death, ending up in the hospital, these are terrible outcomes, but most of us want to feel better.

If you say to your doctor, I've got COVID, is there a medicine that will resolve my fever in one day in 75% of people that take it? Is that available and can I have it, or would you rather that I'm sick for, as we see here, 28 days, if you'd rather my fever actually takes longer to resolve? That's when I have a start thinking about the paradigm slightly differently.

VR: These people with recurrent symptoms are very small numbers, right? That's one thing.

DG: Yes

VR: Most people got better, as you said, but the other thing is, we don't have a comparison of untreated people, right? To see what happens to them.

DG: Yes, well, as I guess we saw, and this is and I think, one of our emailers, one of our listeners wrote in and I've sort of been letting it mull over my head. Maybe a lot of the people who report Paxlovid rebound are the people who got all better after just a few days. Then, oh, my gosh, I had a cough on day 14, it's coming back, where the people who took no study drug, half of them just still feel sick at day 28. They can't rebound because they never got better.

VR: That's right. That's right.

DG: All right. That's Paxlovid.

VR: The drug makes you feel better, and then in a rare number of people, you continue the symptoms that were suppressed, but very few -

DG: Yes. Very few minor symptoms for -

VR: Doesn't seem to me to justify not giving patients Paxlovid.

DG: Yes, that's hopefully the point of this. This is not, this is not scary. These people are not ending up in the hospital. They're not progressing.

VR: Yes.

DG: All right. Number two, remdesivir. Number three, molnupiravir. Number four, vilanterol convalescent plasma in certain people. Let's not do harmful things. All right. Second week, the cytokine storm week. This is interesting. I was in the ICU the other day. I was talking to one of the ICU doctors. COVID really is a different experience, right? People who've had pre-existing immunity, we're not seeing the same rapid crash, the running to the ER to intubate people. It's quite a bit different. We know what we're doing, I think, better at this point. In those patients that do end up in the hospital the second week, right?

A lot of folks are actually in the hospital the first week, elderly individuals who just really with even the viral week, it's too much to handle at home. Week two, if the saturations are less

than 94%, dexamethasone, 6 mg a day times six days. Remember, we talked about the meta-analysis where that's the benefit. Anticoagulation. We have some guidance here, pulmonary support, remdesivir, maybe if we're still in the first 10 days, immune modulation, avoiding those unnecessary and harmful things. This is going to, we're going to wrap it up with our I believe this is our last two articles here in the Long COVID, the late phase. I have a second quotation, Vincent.

A second quotation. This one is from one of the *Star Wars* prequels. "I don't like sand. It's coarse, and rough, and irritating, and it gets everywhere." Anakin Skywalker.

VR: Interesting.

DG: I was going to shoot an email to George Lucas, because I think he's talking about SARS-CoV-2. [laughter]

DG: Well, we have the article, "Long-term Cardiovascular, Cerebrovascular, and Other Thrombotic Complications in Coronavirus Disease 2019 Survivors: A Retrospective Cohort Study," published in *CID*. These are results of a cohort study that used national testing and healthcare claims databases in Singapore to build a cohort of individuals who had a positive SARS-CoV-2 test between 1 September and 30 November 2021, when Delta predominated community transmission. Concurrently, they constructed a test-negative control group by enrolling individuals between the 13th of April 2020 and 31 December 2022, with no evidence of SARS-CoV-2 infection.

Participants in both groups were followed up for a median of 300 days. They estimated risks of new incident cardiovascular, cerebrovascular, and other thrombotic complications using doubly robust competing risks survival analysis, and the risks were reported using two measures. We get hazard ratio, excess burden. They ultimately included 106,012 infected cases, 1,684,085 test-negative controls. Compared with the control group, individuals with COVID-19 exhibited increased risk and excess burden of new incident cardiovascular and cerebrovascular complication.

Risks decreased in a graded fashion for fully vaccinated and boosted individuals. Conversely, risks and burdens of subsequent cardiovascular, cerebrovascular complications increased for hospitalized and severe COVID-19 compared to non-hospitalized cases. The authors conclude, "We reported 1.45 to 2.04 times higher risk of various cardiovascular complications, including ischemic heart disease, dysrhythmias, and other cardiac disorders in the unvaccinated infected group. These results are consistent with Xie, et al., who reported approximately 1.5 to 2 times higher risk of various cardiovascular complications post-infection among U.S. veterans. In our study, the risk of cardiovascular complications post-acute infection were evident even in mild cases who were not hospitalized.

What about mechanism? Maybe, well, maybe my quote is going to come to bear on this next article. The article, "SARS-CoV-2 Infection Triggers Pro-atherogenic Inflammatory Responses in Human Coronary Vessels," published in *Nature Cardiovascular Research*. We have this background: Patients with COVID-19 present with increased risk for ischemic cardiovascular complications up to a year after infection, most in the first six months. As the authors tell us, prior to this study, we knew that patients with COVID-19 were greater than sevenfold more

likely to have a stroke than patients with influenza. The risk for both acute MI and stroke remains high for up to one year after infection.

The extreme inflammatory response that occurs in severe cases of COVID-19, also known as cytokine storm, has been suggested to be a contributor to the increased risk for AMI and stroke, acute MI, and stroke. Is there more to the story? Although this systemic inflammatory response to severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, likely contributes, they are asking the question whether SARS-CoV-2 might directly infect the coronary vasculature and atherosclerotic plaques.

Here, the investigators report that SARS-CoV-2 viral RNA is detectable and replicates in coronary lesions taken at autopsy from severe COVID-19 cases. We're going to qualify that because that's a little sleight of hand there. SARS-CoV-2 targeted plaque macrophages and exhibited a stronger tropism for arterial lesions than adjacent perivascular fat, correlating with macrophage infiltration levels.

SARS-CoV-2 entry was increased in cholesterol-loaded primary macrophages and dependent in part on neuropilin 1. SARS-CoV-2 induced a robust inflammatory response in cultured macrophages and human atherosclerotic vascular explants with secretion of cytokines known to trigger cardiovascular events. Their data, they say, our data established that SARS-CoV-2 infects coronary vessels, inducing plaque inflammation that could trigger acute cardiovascular complications and increase the long-term cardiovascular risk.

Now, I really like the figures and I hope this is open access. I wish everything was open access, but if people get a chance to walk through the figures, particularly if you want to sort of pause here, come back to it with Figure 1D in front of you and you look at these images, you're going to see CD68 positive cells. CD68 is a marker for cells in the monocyte-macrophage lineage, right? You're sort of looking for these foam cells, those macrophages involved in atherosclerotic plaques, and then they're also going to stain for SARS-CoV-2 RNA. They're going to look for these double positive, and you actually see this sort of similar localization of where you're seeing the CD68 and the SARS-CoV-2 spike.

Then they go on to do a number of experiments where they actually infect the cholesterol-laden macrophage foam cells. I want to point out, they're not taking out the plaques and then showing that they can grow virus out of those plaques. They're basically taking the plaques and showing that they can infect the cholesterol-laden macrophage foam cells.

VR: Of course. They're not looking at infectious virus, they're simply looking at genomes, right?

DG: Yes.

VR: We don't know the temporal association with Long COVID. All we know is that, at this point, when you infect these cells, you get this RNA, but we don't know if that - We really don't know. In theory, if there is infectious virus here and it's replicating, it could contribute, but there's no link to Long COVID at all, right?

DG: Yes. I think that's the, yes, there's a lot of challenges here. One of the things I will point out, right, they mentioned cytokine storm right off as one of the pro-atherogenic

inflammatory factors. When you actually do these experiments, you see this significant production of IL-6, sort of making you wonder if people that got steroids or tocilizumab to address the IL-6, if you might see, long-term cardiovascular outcome differences.

VR: Yes.

DG: All right. The last one, just the quick one. This is an area that continues to frustrate many of us trying to help our post-acute sequelae COVID folks. The article, "Efficacy of Gabapentin for Post-COVID-19 Olfactory Dysfunction: The GRACE Randomized Clinical Trial," published in *JAMA Otolaryngology–Head & Neck Surgery*. This ongoing loss of smell is unfortunately really a challenge. Unfortunately, this randomized clinical trial, gabapentin was not associated with statistically significant or clinically meaningful benefit over placebo and is likely not an efficacious therapy for COVID-19-induced olfactory dysfunction, so the search for helpful therapies continues.

I will close, as I have for quite a while, with no one is safe until everyone is safe. A lot of people this last week jumped in and went to ParasitesWithoutBorders.com. Click the 'Donate' button. Everyone, please pile on. We are in the middle of our Floating Doctors fundraiser. It's going August, September, October. We will double your donations up, hopefully making a maximum donation of $20,000. I'll be down there in Panama in December with my daughter helping out.

VR: Time for your questions for Daniel. You can send yours to Daniel@microbe.tv. I have a couple of questions from the livestream last night, Daniel. Last week, you answered, how long after you get COVID can you get a COVID vaccine? Now the question is, how long after you have flu can you get a flu vaccine?

DG: That's interesting, actually, right? Let's think it through. Is it really three months? Now, right now, there's a quadrivalent flu vaccine out there.

VR: Right.

DG: They're actually going to change it to a trivalent because right now there's a couple of B's in there. There's the Yamagata and the Victoria, I guess, is the other. They're going to pull out the Yamagata one because we never see it anymore. It becomes this sort of interesting issue. If you get one of the two A's, are you still potentially, you can get the other A? Do you go right ahead and try to get protection against that other one or do you wait three months and then you're getting a boost of what you just got? You probably actually have protection from that first one.

I think you can actually go ahead when you feel better, get that vaccine, get that protection against the two that you didn't get. I am not particularly worried that it's going to mess too much with the first one that you got. Give yourself a few weeks, feel better, and then go right ahead.

VR: All right. Another question from the livestream. For dialysis patients who test positive for SARS-CoV-2, what antivirals should they be taking?

DG: Yes, so this is a challenge so I'm going to go through. Our regular listeners may remember an episode back in August where we talked about an article that was published in *CID*, “Safety Profile and Clinical and Virological Outcomes of Nirmatrelvir-Ritonavir Treatment in Patients with Advanced Chronic Kidney Disease and Coronavirus Disease 2019.” What they actually did here, this originally was a preprint, but then they published this prospective trial where they actually recruited a bunch of folks who were on dialysis and they actually put them on Paxlovid and looked at the impact on RNA copy number. They also looked at safety data. Basically what they're doing is they're modifying. This is off-label, just want to share the study and the fact that we have this information out there. What they were doing is having individuals take the first day after dialysis, they would take a full dose. The two pills of the nirmatrelvir and the one ritonavir. Then the following days, they would take a real dose just once, but not twice a day for these five days. Actually, they were actually showing good impact on the RNA copy number reduction and something that could be safely done. The package insert has a GFR greater than 60, normal dosing, GFR 30 through 60. You do the renal dosing. Actually, if you go to this publication, you can see that they safely used it in folks with GFRs less than 30 and even folks on dialysis. The other alternative, of course, is remdesivir.

VR: OK. Ileana writes, "I'm over 70 and recently had my updated COVID vaccine at a large pharmacy chain, CVS. It was quite busy with lots of people scheduled for their seasonal vaccines. I noticed that some of these large vaccination centers may not be properly training its staff. Many people listen to your clinical update questions and I thought that perhaps you can give us some guidance. The person who administered my vaccine injected it, not at the center of the deltoid muscle, but instead in the triceps. When I saw her swiping the alcohol below the deltoid, I was tempted to alert her that she had the wrong location and she should inject higher but I was afraid to correct her, fearing that because I'm older and lost muscle mass, she would inject it too high and hit my shoulder bone.

My question to you is, if an intramuscular injection is given too low in the arm, for instance, in the triceps, is it possible for the patient to not absorb enough vaccine content, thereby lessening its immunological effects?"

DG: Yes, these are great. This is a great question. Let's sort of go through it. One is we want to have enough muscle that you can actually get that slightly longer needle, right? This is intramuscular. This is not supposed to be more shallow. You want to actually get it in the muscle and have it stay in the muscle, so that would be an issue. Is there enough muscle mass there? The two approved locations for injections with the vaccines, the two studied locations are the deltoid and actually the lateral thigh. People used to do butt shots. Please don't do those anymore. Those are two. I don't think, from the science, that you're going to have a problem getting it in that tricep, but yes, that's not actually the recommended location.

VR: Roxanne writes, "I've had the pleasure of interviewing three of the *TWiV* team, including you, in my capacity as a science journalist. I'm writing to you now in my capacity as a longtime *TWiV* and *TWiV* clinical update listener. A couple of weeks ago, I heard you answer a question posed by a woman who was pregnant and unsure whether she could take Paxlovid if she were to contract COVID. I believe you said that this would be OK. I have a variation on this question.

My son is exclusively breastfeeding and has cow and goat milk intolerance. If I were to contract COVID, I've not yet been infected during the pandemic, to my knowledge, would it

be safe to continue breastfeeding him? A quick search online turns up a link to the NHS, which mentions the manufacturer's advice that breastfeeding is not recommended during treatment with Paxlovid and for seven days after the last dose. I'm hoping that the hypoallergenic formula will be OK for my son. In case not, I feel like I may have to choose between breastfeeding him or taking Paxlovid and giving him formula that doesn't sit well with him. Has the thinking changed on Paxlovid and breastfeeding? If so, why? Thanks. P.S., my baby is also a *TWiV* clinical update listener now, too."

DG: OK. Never hesitate to go and look stuff up. Here I'm going to recommend, that your provider, you, this will be a shared decision should you end up with COVID. Look at the package insert: 8.1 is where they talk about pregnancy. 8.2 is where they talk about lactation or breastfeeding. 8.1, breastfeeding, very clear, right? Benefit for mom, benefit for the unborn child.

Now, what about breastfeeding? We don't know. That's where we are here. No available data on the presence of nirmatrelvir in human or animal milk. We're in a zone where we don't know. We do have some data that there is ritonavir that ends up in the breast milk. I have to say, when we've used that medication in other contexts, we continue. We have not seen any signal in millions of people, millions of pregnant individuals who continue to do that. There's no information on the effects specifically in this context. What is actually the recommendation?

The recommendation, I'll just read the Paxlovid package insert. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Paxlovid and any potential adverse effects on the breastfed infant from Paxlovid or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Where do we start pulling here? This is going to be a risk-benefit where you look at the mom, you look at the potential benefits. If this is a mom who has a number of high-risk conditions, then you're going to actually seriously consider doing this. Lower risk mom, you might forgo the Paxlovid. This is one of those shared decision-making. This is the data we have. That's the package insert.

VR: Roxanne has one more question. "My son's vaccine appointment for his COVID booster got moved two days after my own booster appointment. Will antibodies he receives via nursing, presumably from my boost, interfere with his own booster shot?"

DG: I would not expect that to have a significant impact.

VR: All right. Jen writes, "In the past years, parents of adolescent boys have been steered away from Moderna. I believe this was based on the data from the original two-dose series when the shots were separated by only three weeks and there was a statistically significant difference in adverse effects, especially myocarditis for adolescent males who got the Moderna shots. If memory serves, this group had to get Pfizer for the bivalent last fall too. I haven't seen anything about this for the 23-24 formulations. Is it six of one, half a dozen of the other in terms of whether adolescent boys get the 50-microgram Moderna or the 30-

microgram Pfizer this year? I'd love to get my son his shot soon and most places around us only offer Moderna."

DG: Yes, I would not have a big, strong objection against going ahead with Moderna in this context. It was really interesting. We didn't quite understand. We were thinking, is it better three weeks? Is it better three months? Turns out, the longer, the three months was safer. Yes, I don't think that there's any strong issue here on why you can't go ahead with the Moderna.

VR: Will writes, "I recently saw reports of a new study from British Columbia stating that the only group protected from severe disease or death were the most vulnerable elderly. I've also seen tweets that studies in BC have limitations because the use of Paxlovid was extremely limited in that province to the very most vulnerable groups. Can you address this since the general understanding is that Paxlovid works for pretty well all groups that are taking it?"

DG: Yes, I think this really - Thank you for this email because it's perfect because it sort of brings us all back to what I talked about at the beginning and really asking, what are our goals? We don't only treat urinary tract infections that have a likelihood of putting someone in the hospital. We treat people with illnesses with appropriate medications. This study I'm familiar with where basically the headline is Paxlovid only benefits frail seniors, basically, is how it's being covered.

We do have compelling evidence that Paxlovid is a very effective antiviral. We have compelling evidence that when you have a solid risk of ending up progressing to severe disease, this medicine can reduce it. We're seeing really good safety profiles, particularly when used by a clinician that is able to handle any renal impairment or drug-drug interactions. Yes, I wouldn't let this one study dissuade you.

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

DG: Thank you, and everyone, be safe.

[00:59:50] [END OF AUDIO]