This Week in Virology

TWiV 1076 Clinical Update

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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

[music]

VR: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1076, recorded on January 3, 2024. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Daniel and I were just talking about whether *One Piece* has more episodes than *TWiV.* [chuckles]

DG: They have 1,088. This is 1,076. We're 12 away.

VR: Closing in. We're going to catch them because I'm sure they don't do two a week.

DG: All right. This is the downwind leg. We're on the inside quarter. We're bearing down. We're about to pass.

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

DG: This is Ebola. I'm wearing my Ebola bowtie. I'll start with my quotation, "You don't have to burn books to destroy a culture. Just get people to stop reading them." That's by Ray Bradbury. We got asked that question on the livestream. What is the biggest mistake during the pandemic? My response without pause is not enough education, not enough good science communication.

Mpox, to keep this on everyone's radar, we read in *CIDRAP,* in its latest monthly update, the WHO reported 906 new mpox cases from 26 countries in November, reflecting an increase of 26% compared to October. I was thinking that was the year, but that's just one month. With nearly 300 cases, the United States reported the steepest rise in the Americas, followed by Portugal reporting 128 new cases, and I suspect that many cases are going underdiagnosed.

RSV, I think we're off the peak. I think we're on our way down. We're still seeing the admissions, but the percent positive, the detections look like they're starting to drop. Flu, different story. Still rising there. Still seeing lots of flu. If you follow across the country, as predicted, some of the data, I wish they would update these maps a little bit quicker for my liking, but really spread up. There's only a few spots where it's not so bad. I think I'm going to take a vacation in Minnesota.

VR: What is that white one next to Minnesota?

DG: I think the white is we're not giving you any data. That's North Dakota.

VR: Oh. You don't want to go there anyway.

DG: Yes, there's not a lot in North Dakota. I do like South Dakota quite a bit.

VR: Where's Fargo?

DG: Fargo? I don't know. Maybe that is North Dakota.

VR: Stay away from Fargo.

DG: Check that for us, Vincent, so we know.

VR: Yes, I'm going to do it right now. Fargo is in North Dakota.

DG: North Dakota.

VR: If you've seen any of the TV show, you shouldn't go to Fargo.

[laughter]

DG: All right. Right into COVID, people always ask, where do I get my numbers? I've been following *BNO News*. They tweet out each week what's going on, new cases, what's the average folks in hospital? Over 20,000 in hospital, that's up almost 2,000, so 10%. In the ICU, over 2,000. New deaths, we're averaging 1,622. Still averaging thousands of COVID deaths every month. It's interesting. One of the ER docs was asking me the other day, they keep putting these things out there about there's a new strain. We're all going to die in the next week.

Listen, every December, January, we see an increase in respiratory pathogens, and lo and behold, we are seeing that again. The wastewater data has been updated in a little bit, again, like that, but really big rise in the wastewater all across the country, big rise in cases, hospitalizations, and deaths. There's stuff we can do about that. That's what we're here to discuss.

Let's start off with the article, "Characteristics and Clinical Outcomes of Vaccine-Eligible U.S. Children Under-5 Years Hospitalized for Acute COVID-19 in a National Network," published in *Pediatric Infectious Disease Journal*. Here the investigators enrolled inpatients, aged 8 months to less than 5, with acute community-acquired COVID-19 across 28 U.S. pediatric hospitals from September 20, 2022, to May 31, 2023. They assessed demographic and clinical factors,

including the highest level of respiratory support and vaccination status, defined as unvaccinated, incomplete, or complete primary series.

Among 597 children, we have hundreds of children, 29.1% were admitted to the ICU, 12.6% had a life-threatening illness, including 8.5% of these little kids requiring mechanical ventilation. Children with underlying respiratory and neurologic/neuromuscular conditions more frequently received higher respiratory support. Only 4.5% of children hospitalized had completed their primary COVID-19 vaccination series.

Among 528 unvaccinated children, nearly half were previously healthy, three of them required extracorporeal membrane oxygenation and one of them died. Completion of the vaccine series was low in all regions, but highest in the Northeast, but not so impressive, 12.2%; lowest in the South, 1.5%.

VR: They should be vaccinated, right, Daniel?

DG: Yes. I think we have a growing body of evidence. As you see here, hundreds of children in the hospital, children on ventilators, children in the ICU, children on ECMO, one of these children ended up dying. That was not a vaccinated child that died.

All right. The article, "SARS-CoV-2 Perinatal Transmission and Neonatal Outcomes Across Four Different Waves of COVID-19 Pandemic: A Nationwide Prospective Cohort Study from the Italian Society of Neonatology," was just published in the *International Journal of Infectious Diseases*. These results are from a large prospective nationwide cohort study collecting maternal and neonatal data in a case of maternal peripartum SARS-CoV-2 infection between February 2020 and March 2022. Data was stratified across the four observed waves.

Among 5,201 positive mothers, the risk of being symptomatic at delivery was significantly higher in the first and third waves than in the second and fourth. Almost twice as high, 20.8 compared to 13.2 and 12.2. Among mothers with symptomatic infections, the rate of severe infection was significantly higher in the first and third waves. Interesting, it wasn't just going down. Actually, first wave was 21.4. It was actually 27.4 in the third wave compared with the second was 9.2, fourth 5.6.

Overall, death during hospitalization occurred in 0.2% of the SARS-CoV-2-positive mothers. Didn't see any difference across the periods. Among their 5,284 neonates, the risk of prematurity was significantly higher in the first and third waves, 15.6 and 12.5. The risk of postnatal transmission during rooming-in was higher and peaked at 4.5% during the fourth wave. Eighty percent of the positive neonates were asymptomatic.

Moving to testing and transmission and all that, I'm going to leave in a link in our show notes, the CDC guidance on improving ventilation in your home. We've talked a little bit about this. Leave those fans on. Crack those windows. A lot of transmission. People spending hours together in a poorly ventilated home. Let's improve that ventilation. We've talked a bunch about testing, the benefits of vaccination, but occasionally, people still end up with COVID and just NIH treatment guidelines.

This is not just my opinion. Number one, Paxlovid. Number two, remdesivir. Next, molnupiravir. In some cases, convalescent plasma, and we continue to have the same

recommendations. Five days, most transmission. Next five days, wearing a mask because we're still seeing some transmission in the last five days. Week two, this is not rebound. This is week two, the cytokine storm, the early inflammatory phase. This is when sometimes people start to feel crummy.

If you end up with an oxygen saturation less than 94%, steroids, right time, right person, anticoagulation guidelines, pulmonary support, still might be some role for antiviral therapy with remdesivir. Occasionally, immune modulation with tocilizumab. Then, unfortunately, we're seeing folks who continue to have issues after those first couple weeks. People really liked our discussion, Vincent, a couple of weeks ago about how Long COVID is really just one subset of the many post-acute sequelae of COVID.

This week I wanted to discuss the article, "Corticosteroids for COVID-19-induced Olfactory Dysfunction: A Comprehensive Systematic Review and Meta-analysis of Randomized Controlled Trials," published in *PLOS ONE*. I just want to point out olfactory dysfunction, gustatory dysfunction, issues with taste and smell, this is not just bothersome. More than just bothersome olfactory dysfunction, this could really have significant impacts on quality of life. We could see weight loss. We could see people becoming despondent because this is one of the pleasures of life that they have now lost.

Here are seven randomized control trials with 999 participants. We needed just one more. Compared with the control group, corticosteroid treatment resulted in a statistically significant improvement in olfactory score with a standardized mean difference of 0.55. Topical corticosteroids were found to be effective, but systemic corticosteroids were not. In addition, longer durations and higher doses of corticosteroids may also be associated with significant improvements in olfactory scores. No significant effect was observed on the duration or recovery rate of olfactory dysfunction.

Let me go through a bit, not only going through this meta-analysis but a little bit on how one might want to approach meta-analysis papers. I'm going to recommend people, I don't think this is behind a paywall, but one of the first things I usually have people look at is the forest plot. There's a nice Figure 2 forest plot. What's here is the different studies pulled out. Then you can see for each study, not only the number of participants in the treatment and control groups, but you can also see the analysis as far as the difference that each study was showing.

One of the things I like people to look at is the number of folks in the different studies, how much each study might potentially contribute. Is this really just a meta-analysis of many papers or is the meta-analysis just a republication of a just large single study that pushed things in one direction? The next thing that this paper has that I really like is a Figure 3, which is an assessment of each of the studies. You can go back and forth where they're high risk or low risk of any bias, where there are a lot of concerns.

Fortunately, here, we weren't seeing any of the included studies were at high risk of bias. About three of the studies, really solid, low risk of any concerns. Four of the seven studies, there are actually concerns as far as selection of the reported result, the measurement of the outcome, maybe missing outcome data, randomization process, which is always really important.

Then they also have a nice Figure 3, where they show the impact on duration of recovery. Really interesting, really four studies that get included there. Two of them don't really show much difference. Actually, two of them seem to be going in the wrong direction, suggesting that corticosteroid therapy may actually have a negative impact upon your recovery. All right, so just something to keep in mind there.

The article, "COVID-19 Convalescent Plasma Therapy: Long Term Implications," recently published in O*pen Forum Infectious Diseases*. Here, this reminds me of the paper we published where we looked at monoclonal antibody therapy, not just what happens acutely, but let's follow these folks out a little bit. Here, we see the data from the CONTAIN-Extend study. The CONTAIN-Extend study examined 281 participants from the original CONTAIN COVID-19 trial at 18 months post-hospitalization for acute COVID-19. Symptom surveys, global health assessments, and biospecimen collection was performed from November 2021 to October 2022.

Multivariable logistic and linear regression estimated associations between randomization arms, self-reported symptoms, and PROMIS scores adjusted for co-variables. Just by the way, PROMIS stands for Patient Reported Outcome Measurement Information System. What we're really doing here is we're asking folks with patient-reported outcomes, how are you doing, and are we going to see any impact basically on Long COVID between the folks that got the benefit of the convalescent COVID plasma?

While some previous studies have shown benefits in certain populations if given at the right time, in short-term outcomes, looking at longer-term outcomes, there was no difference in symptoms or PROMIS scores between the convalescent COVID plasma folks and placebo. CCP demonstrated no lasting effect on PASC symptoms or overall health in comparison to placebo in this particular study.

VR: Do you know when the plasma was administered? It would have been in the first few days, I assume, right?

DG: Yes, that's always the challenge and we try to even do that with our monoclonal antibody, trying to figure out exactly. Because you'd love to say, maybe if we looked at people that got it in the first three days and they got the right high-titer convalescent plasma. This doesn't necessarily tease out subtle things like that, that might actually have an impact.

Before we get to our letters, I will say, as I've been saying for a while, no one is safe until everyone is safe. We are in the third and final month of our Parasites Without Borders MicrobeTV fundraiser. We're now raising money for MicrobeTV, November, December, January. We will double your donations up to a potential maximum donation of $20,000.

VR: It's time for your emails for Daniel. You can send yours to daniel@microbe.tv. Now, Daniel, as you might imagine, we had a lot of letters about the Florida surgeon general statement about COVID mRNA vaccines. For example, one from Winnie, "I live in upstate New York. I work as a flight paramedic in the U.S. Virgin Islands, which requires me to maintain a Florida license. I'm embarrassed to be associated with the Florida every time I receive an email like this one. Could you please discuss the science or lack thereof behind these assertions?"

DG: I'll encourage people to listen to our livestream where Vince and I have a little bit of a deep dive into this. The surgeon general of Florida, he has the right credentials, MD, PhD, Harvard trained. You expect to hear good science-based advice. Unfortunately, that's not what you're getting here. You're hearing more anti-science communication here, more of an anti-vaccination, more of an undermining trust in the vaccines coming from this individual. It really is one of these throw the hands up and confuse the issue.

The concern is that there is some DNA in these vaccines. There's DNA in every vaccine. DNA is really pretty ubiquitous. There's a suggestion that instead, people should go get the Novavax vaccine, which is grown in insect cells. By the way, also some DNA in there. The whole fear is that this DNA could somehow incorporate into our cells. No science to suggest that's a concern. Billions of vaccine doses. We're not seeing this.

I think this feeds into this crazy turbo cancer. I don't know if you've heard about that, Vince, on social media stories of like, I knew this guy who got a vaccine and six days later died of a turbo cancer. None of this makes any scientific sense. Unfortunately, seeing a person in a position like this undermining what are really incredibly safe, effective vaccines.

VR: Hannah writes, "In early 2023, I had strep throat and COVID at the same time. I only found out about COVID since I was given rapid tests for strep influenza and COVID at the urgent care. COVID was either asymptomatic or outshined by the dramatic symptoms of strep throat. The strep rapid was positive. A throat culture was not performed. Influenza negative. Pretty consistent with my symptoms. Rapid fever onset, swollen tonsils with putrid discharge, and pain when swallowing and speaking.

I was given a 10-day course of amoxicillin. My symptoms began to improve quickly. However, of day nine, I developed disturbing swelling and deeply itchy patches of rashes on my hands and feet. Telehealth appointments surmised I probably had amoxicillin allergy or mono. The rash swelling went away over a couple of days with dexamethasone and diphenhydramine. I later tested for pen amoxicillin and other antibiotic allergies, all negative, and have taken amoxicillin since then without issue.

A quick and dirty PubMed search linked mono with a delayed B cell reaction causing the swelling and rash, which is commonly referred to as an allergy, but isn't a true allergic response. I wouldn't ever know for sure if I had mono in addition to COVID and strep, but do you know of penicillin amoxicillin rash occurring in COVID patients? Could you explain the immunological mechanism of the delayed reaction? Would/could COVID reactivate latent mono EBV infection?

DG: There's a lot in here. I'm going to answer my own questions. The first, and I think this is really important. Did you, like John Hickam says, get two things at the same time? Did you get COVID and strep throat at the same time? Hannah, I'd love to know your age and risk factors for strep throat because we are certainly seeing COVID present as an acute pharyngitis. People go in, "Oh, my gosh, I've got a horrible sore throat." My gentleman today described it as it felt like someone had glass in the back of his throat.

A lot of times, that really severe sore throat is actually COVID. Twenty percent of people will have strep in the back of their throat. They won't necessarily have a strep pharyngitis but it'll

be purulent back there. It'll look horrible. All that can actually be from the COVID. I just want to point that out. It can be hard to make the distinction. Eighty percent of people getting antibiotics with acute COVID, there are certain circumstances where I could see where you say, "Gosh, I'm really not sure." You've got tender lymph nodes. You've got fever. You've got purulent exudate. You don't want to not treat the strep throat. That's the first thing I want to point out.

The next is that we have seen this is the classic with mono, where someone has mononucleosis and they get amoxicillin. They have this rash that gets triggered. We don't actually know what is involved, what triggers that. They're not allergic to penicillin. They're going to be fine again in the future. There's been a few case reports where people got amoxicillin, oh, my gosh, with acute COVID and then developed a rash and then were fine afterwards. Not sure if there's really a causal connection there or if it just happened a few times.

VR: Russell writes, "I'm a family doctor acting as the sole hospitalist with two nurse practitioners in a rural hospital, as well as being the medical director of two nursing homes with 100 patients. By default, I became the local COVID-19 expert, which after 40 years in practice has been highly interesting. I've read a gigantic amount, but certainly have learned much from your podcasts as well.

In 2020, we had a terrible outbreak in both homes, lost 40 patients to COVID before vaccines became available. Recently, we had another outbreak of 28 patients in a facility, six of these patients with positive tests seemed to have no symptoms, at least that we identified. Eventually, three of these ended up being hospitalized with apparent COVID-related symptoms, including one that needed biphasic CPAP. My inclination and my question is, should we just treat all positive tests in the nursing home patients with Paxlovid, remdesivir/molnupiravir? I appreciate your thoughts."

DG: This is something that's come up since these medicines got this indication to treat COVID-19. The indication is not to treat a positive test, but the indication is to treat a disease. You have an individual and there almost was this binary suggestive. A person says, "I got a little bit of a cough, I got a headache, I got some congestion." "OK, you got COVID-19. Your risk of progression is whatever, 40%. The vaccine has dropped that to 4% or 5%." It's sort of the numbers you're giving me, six out of 28. Pretty high percent of your folks end up progressing.

We also know, and this is the lesson that we've tried to repeat over, how bad your symptoms are during that first week do not necessarily predict what's going to happen during the second week. What predicts the second week? It's age, it's risk factors. It's pretty hard for me. I had a gentleman today. He's in the hospital. He's got bacteremia. We're treating him for endocarditis, get ready to leave. They do the COVID test, it comes back positive. Really minimum symptoms. It's hard to know. Are these symptoms even attributed to the COVID? Are they attributed to just being an older gentleman? Are they attributed to the bacteremia?

I almost err on the other side. If I say, "You know what? There's anything here that allows me to make the clinical diagnosis of COVID-19, these medicines are incredibly safe. If what you know what you're doing, and it sounds like 40 years of experience, you probably know what

you're doing by now. It's always better to err on the side of treating with an effective antiviral rather than missing that window and having folks progress.

VR: Ben writes, "I'm an urgent care physician seeing many patients with mild COVID. My question is, how do you approach those newly positive patients with a diagnosis of asthma or COPD who always get steroids from their PCP from their clinician when they get a URI who are minimally hypoxic in that first week of infection? Do you prescribe steroids with a CXR or a wheezing guide? Your decision? Many patients are hesitant to go to the ER with a SAT of 92% to 94%. The worry, of course, is blunting the immune response in that first week compared with actuality of hypoxia or potential COPD exacerbation."

DG: This is a great question. This comes up all the time. Hopefully, we'll get a chance to walk through it here. I really try not to use steroids during that first week. It's really like, think of it as the anti-Paxlovid. We've discussed studies where a five-fold increase in your risk of progression to the hospitalization, you're really shutting down. Why did you even bother to vaccinate someone if now you're going to shut down their immune system with those steroids? Maybe this is tempered to some degree if you are able to get that person on an antiviral during that first week.

The inhaled steroids, those are reasonable. I don't think those are harmful. Actually, were studied for potential benefit. Maybe no benefit, but also doesn't look like there's any harm. Really try as much as possible to avoid steroids in those first seven days. A person who's got COPD, that's probably a higher risk person, so really want to be looking at which antiviral to get them on. Still really trying to avoid those steroids during the first seven days.

VR: Finally, Kathy writes, "My question has to do with testing. While visiting family recently, I had an illness with many COVID symptoms but tested negative five times in as many days. On day four, my brother and his son turned positive, so despite the lateness, I did start Paxlovid. I'm taking the Crohn and multiple vaccinations, and previous bouts of COVID, it can take two to three days to get a positive. This makes it hard to start Pax on time, wherein one gets the maximum benefit. Have also read that yield may be higher by combining throat and nasal sampling. Could you please comment? Thank you."

DG: There are several things that you talk about there. If you're going to combine, we'll start off with the testing, if you're going to combine NARES and oropharyngeal testing, use a test that's validated for that. You want to use the test, get a reliable answer. Most of the tests out there are not validated for those double tests. PCRs are. PCR, it's just a PCR. You can actually swab, and not swab in your tongue or the buccal mucosa, you're actually back there in the palatine tonsils, the back of the throat.

The PCR, particularly oropharyngeal and nasal, you can get an earlier detection, more sensitivity there. I don't want people to feel like you fall off a cliff here. We talked about a 2% difference, whether or not you're getting treatment in the first three days versus day four and five. We talked about a Hong Kong study where they actually were after day five and still getting a benefit. We really are trying to get the Paxlovid in, in the first five days, but it's day five or six, it's not like you just fell off a cliff.

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

DG: Oh, thank you. Everyone, happy new year, and be safe.

[music]

[00:28:03] [END OF AUDIO]