This Week in Virology

TWiV 1080 Clinical Update

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

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VR: From MicrobeTV, this is *TWiV, This Week in Virology,* Episode 1080, recorded on January 17, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from South America, Daniel Griffin.

Daniel Griffin: Hello, everyone. Yes, basically, I'm about 20 miles north of Venezuela. I'm a bit south. I guess we're recording this pretty late in my time zone at the moment. Let's get into it because people will be listening to this I guess, what is it, East Coast right after midnight, and then everyone else adjusted accordingly. I'm going to start off with a quotation. I'm having a little bit of a break, so I've been reading the book *Dune,* so my quotation will come from Frank Herbert. "The beginning of knowledge is the discovery of something we do not understand."

I like that. it made me think of science. It's that humility of going into the unknown and learning. That's what I think this is all about. We will jump right into RSV. We were a little worried. I was a little worried. I'll share that we might see one of those little double dips where RSV starts to go down, and then we see another. We saw that second peak. We're hoping in the next week or two, we really come off that high level of RSV. I just keep talking to people about this. We have tools this year. We have those two different vaccines for adults, for pregnant individuals in the last trimester. We've got the nirsevimab, the passive vaccination.

Just want to point out, we will probably lose over 10,000 adults this winter. We typically lose 100 to 300 children. If we don't use the tools, we can't get those numbers down. I also want to move into flu. We may be coming off the peak, and there's interesting studies that we've seen in the past where once we get past these holidays and all the gatherings, sometimes those numbers can come down. A little bit of a twist, and sometimes the challenge is when all the kids go back to school, we can, again, see a little bit of a persistence.

We'll see what happens here in the coming weeks. Flu activity all across the country is basically up at pretty significant levels, except somehow, what's going on in Minnesota? How are they still in the minimal level? I don't know what's going on up there. Most of our country,

we're seeing lots and lots of influenza. What about COVID? We are still at over 2,000 deaths a week. I was recently on *The Brian Lehrer Show*, and I just want to put this in context. The number of folks in hospital has gone up. We've got about 30,000 in hospital. That's up about 10%. We've got about 3,000 in the ICU. That's also up about 10% from a week ago. New deaths this last week, over 2,000.

I don't know if people remember, but at one point, we were having 2,000 deaths a day in New York alone back in the early days. 2,000 deaths a week in the entire country is still way too many. Just start adding up those weeks, and 2,000, 4,000, 6,000, 8,000, 8,000 to 10,000 a month. I do think, if we're looking at our wastewater data, we do seem to be coming off a peak here. Particularly in the Northeast, it really looks like we're heading down, and we're seeing things starting to drop in other parts of the country. I will point out, we're starting to drop from this new high set point of 2,500 copies per milliliter of sewage.

I got quite a bit this week on children, COVID, and other vulnerable populations, as well as Long COVID, so let's get right into it. I like to remind people of the article, "Coronavirus Is Bad. Comparing It to the Flu Is Worse," by Roxanne Khamsi, February of 2020. Can you believe how quickly that came out? One of the issues with regard to children and COVID is this minimizing of COVID in children by comparing it to adults. Over 1,000 children, we estimate, died of COVID here in the U.S. but people say, "Oh, but over a million adults." I don't think the fact that over a million adults died makes over 1,000 children having died of COVID less significant, less troublesome.

Here we have the article, "Outcomes of SARS-CoV-2 and Seasonal Viruses Among Children Hospitalized in Brazil." In this population-based retrospective cohort study that included children and adolescents hospitalized from February 2020 to February 2023 from SARS, the investigators looked at a total of 235,829 patients that had available results of viral tests with SARS-CoV-2 predominance. They're going to look at competing risk survival, and they're going to estimate the probability of a fatal outcome.

These are folks with acute respiratory infections. Not all of them have COVID, as you'll see. The fatal outcome for in-hospital mortality, so this is children and adolescents in-hospital mortality with SARS-CoV-2, 6.5%. Co-infection, because this is something that hopefully people are getting more used to looking for, 3.4%. No virus, 2.9%. Influenza, 2.3. Other viruses, 2.1. And actually, RSV in the children and adolescents, 1.8%.

All right, what do we do? Fortunately, we have vaccines, and they work. The article, "COVID-19 Vaccine Effectiveness Among Adolescents," was recently published in *Pediatrics.*

These are results from a nationwide register-based, one-to-one, matched cohort conducted in Denmark, Finland, Norway, and Sweden between May 28, 2021, and April 30, 2023, to estimate vaccine efficacy for primary COVID-19 vaccine two-dose schedules among adolescents aged 12 to 17 years. Cumulative incidence of what type of efficacy? COVID-19-related hospitalization, that was the primary outcome. Laboratory-confirmed SARS-CoV-2 infection, that's a secondary outcome, were compared for the vaccinated and unvaccinated at six months of follow-up.

The study included 526,966 primary schedule vaccinated adults. Vaccine efficacy against COVID-19-related hospitalization was 72.6% at six months of follow-up compared with unvaccinated. Estimates were comparable when restricting to a period of Omicron predominance and extending follow-up to 12 months. They have a really nice figure where you can actually look at the different countries and the time. Finland, Sweden, Denmark.

VR: Daniel, you said adults, but you meant adolescents there.

DG: Oh, did I say it? Yes, adolescents. Thank you. Not only do vaccines work for kids to protect against acute issues, but we also have the article that I think a lot of people hopefully will find interesting, "Vaccine Effectiveness Against Long COVID in Children," published in *Pediatrics.* Here, the adjusted vaccine effectiveness within 12 months was 35% against probable Long COVID in a retrospective cohort study that used data from 17 health systems that looked at 1,037,936 children. I also want to talk in the same section about the article, "Socioemotional Development of Infants and Toddlers During the COVID-19 Pandemic," published in *JAMA Pediatrics*.

I think people may remember from the early days my suggestion of perhaps we should close the bars and open the schools. The background of this study, as the authors point out, is that the COVID-19 pandemic and its related social distancing negatively affected children and families. Caregiver stress increased, which can negatively affect infant development and health. Children's screen time increased, which we have prior studies showing is associated with poorer language, problem-solving and social development. Daycare and preschool closures along with social distancing, decreased peer interactions for young children. They're going to give you links to all the different articles supporting that.

Here, while studies suggest young children's socioemotional development was affected during the pandemic, assessments specifically designed to evaluate this socioemotional development, changes in screening results over time, referrals to early intervention, have not been examined prior to this. Here, they used specific validated early childhood development assessments and looked at 60,171 families and found that the pandemic contributed to delays in young children's socioemotional development. particularly during the first year of life.

VR: Not surprising, right, Daniel?

DG: Yes, I don't think any of this is surprising. I think, one of the things people always talk about, "Oh, what can we do better? What lessons did we learn from this pandemic?" We're going to talk about some machine learning, looking at that next time. I think we really failed our children in a lot of ways. I think that we need to look really closely at that and see how we can do a better job next time.

I will move on to COVID, the early viral phase. A little bit of a teaser, Vincent. Next time I'm going to be discussing a preprint out of the David Ho lab with Yossi Sabo as one of the co-authors.

I've been waiting for this to come out because I've been aware of this data now for actually a couple of years. [chuckles] Yossi swore me to silence. Now that the preprint is out, we'll talk a little bit about viral kinetics. Let's talk about Paxlovid. Early viral phase, you test positive. You meet one of the criteria for being high-risk. NIH treatment guidelines recommend

Paxlovid. There was a really nice news piece in *The New York Times* by Danny Bloom, “I have COVID. Should I take Paxlovid?” Several good points that bear repeating.

When they look at who is a candidate, they note that anyone 12 or older who is considered high risk, which encompasses a broad swath of persons, the CDC includes conditions such as depression, obesity, asthma, history of smoking. They asked Dr. Davey Smith, an infectious disease specialist at the University of California, San Diego. I quote: To be honest, pretty much if you're an adult in the U.S., you can meet one of these little marks. Anyone aged 50 or older is also eligible for the treatment regardless of health status. The older you are, the higher your risk for severe illness tends to be.

I like this, Paxlovid is intended for people with mild or moderate symptoms. My little add is, you don't wait for someone to be severely ill. "Take it as early as possible to nip it in the bud and prevent yourself from being so sick," said Dr. Ziyad Al-Aly, the chief of research and development of the Veterans Affairs of St. Louis Healthcare System. Even if you currently have few symptoms or if you've had mild symptoms with COVID before, the disease is unpredictable and you may still want to consider Paxlovid if you're eligible, Dr. Smith said. Every time someone gets COVID, it's basically another game of roulette, he said. What about Paxlovid rebound?

The Centers for Disease Control and Prevention found no consistent association between antiviral treatment and rebound. As we asked from the CDC -

VR: Daniel, the - sorry.

DG: No, go ahead, Vincent.

VR: There's also an article in *The Washington Post* by Leana Wen, “The Under-prescribing of Paxlovid May Be Our Biggest COVID Policy Failure,” and that's really good also.

DG: OK, excellent. Can you throw a link into that for our readers? That would be great.

VR: Yes, I will.

DG: We will move on to a little bit about cost and access. I was on NPR Monday on the *The Brian Lehrer Show* and a woman called in sharing that her husband had been charged $1,683 for a box of Paxlovid. One of the challenges is Paxlovid is now just like every other medicine where you go to the pharmacy and they run your insurance. If you have prescription coverage, you end up either paying a co-pay or finding out that this is not covered. Now, there is a link to a program called Paxcess. I don't know who came up with that, but it's catchy, P-A-X-C-E-S-S, for those not insured or those with Medicare or Medicaid.

We can leave in a link to Paxcess. To qualify for free Paxlovid through this program until December 31, 2024, patients must be uninsured and do not have a prescription drug benefit at the time they fill their prescription, Medicare beneficiaries, Medicaid beneficiaries. You can either go to the website, which is www.paxlovid.com/paxcess, or you can call 1-877-219-7225 because really, I want to see this happen. I don't want to see someone acutely have COVID, meet criteria, be a person who potentially can benefit, and then have this financial wall between them and the access to the medicine.

Number two, remdesivir. Number three, molnupiravir. Then convalescent plasma for some folks such as those immunocompromised at risk of progression who are not eligible for other options. Then week number two, the cytokine storm week. You're feeling crummy the first week, and then you feel crummy that second week. What is going on that second week? This is the early inflammatory phase, the cytokine storm, a period of time when we have studied antivirals for years and years and never shown that this is a great time to do that. Some folks, steroids at the right time, in the right patient, at the right dose.

I want to just spend a little time because a few questions came up here. You made it past day seven, your patient is feeling crummy, they're in the early inflammatory phase. Do we just give everyone steroids? It'll make them feel a little bit better. Remember, people after a virus are at an increased risk of a post-viral bacterial infection. If we start throwing steroids willy-nilly, if we're not following those pulse oximeter readings, if we're not finding the highest-risk folks, we're actually potentially going to harm our patients. Be careful with those steroids. Let's use them in an evidence-based manner.

Dexamethasone, 6 milligrams a day times six days, in folks with oxygen saturations, less than 94%. Anticoagulation guidelines, recommended for folks that end up in the hospital. We have great recommendations from American Society of Hematology to help guide us. Pulmonary support, remdesivir still in the first 10 days. Immune modulation, avoid unnecessary antibiotics and unproven therapies. As promised, I've actually got quite a bit here, late phase PASC/Long COVID.

Just to put this simply, and I don't know how many times this bears repeating, PASC or Long COVID, this is a thing. It is not just in people's head. Some people have very low serotonin levels or low cortisol levels or evidence of latent viral reactivations, Herpesviridae, or muscle damage with mitochondrial dysfunction and a number of papers showing ongoing immune dysfunction. This week, the paper, “Long COVID Manifests with T-Cell Dysregulation, Inflammation, and an Uncoordinated Adaptive Immune Response to SARS-CoV-2,” was published in *Nature Immunology*. This paper really requires some time. It's complicated, requires a solid background in immunology to fully understand.

I'll share an overview and perhaps Vincent and I can discuss the implications. The authors explain that they used omic assays and serology to deeply characterize the global and SARS-CoV-2 specific immunity in the blood of individuals with clear Long COVID and non-Long COVID clinical trajectories eight months post-infection. They found that Long COVID individuals exhibited systemic inflammation, immune dysregulation evidenced by global differences in T-cell subset distribution implying ongoing immune responses as well as by sex-specific perturbations in cytolytic subsets.

Long COVID individuals displayed increased frequencies of CD4 positive T-cells, poised to migrate to inflamed tissues and exhausted SARS-CoV-2 specific CD8 positive T-cells, higher levels of SARS-CoV-2 antibodies and a miscoordination between their SARS-CoV-2 specific T and B cell responses. Their analysis suggested an improper crosstalk between the cellular and numeral adaptive immunity in Long COVID, which can lead to immune dysregulation, inflammation, and clinical symptoms associated with this debilitating condition. Every figure is complicated with multiple panels and there are supplemental figures as well.

For example, in Figure 1, we see elevated T central memory, T effective memory, peripheral T follicular helper and follicular helper, and T-regs. In Figure 2, we see increased homing receptor expression, perhaps associated, as they say, with migration to inflamed tissue. In Figure 3, we see that SARS-CoV-2 specific CD8 positive T-cells from individuals with Long COVID preferably express the exhaustion markers such as CTLA4. Figure 4, we see this excessive production of anti-receptor binding domain antibodies. Figure 5, we see that in Long COVID, IL-4 is up, IL-5 is down. Lots of differences.

This all seems to make biological sense, but is this data mining? Should we repeat this in different cohorts? What are the diagnostic or therapeutic implications?

VR: Daniel, each of these figures, they're dot plots where each dot is a patient, right?

DG: Yes.

VR: There's a huge overlap between the Long COVID and the other controlled population. There are some patients who clearly have higher of whatever they're looking at, anti-RBD, for example. Then there are many patients whose anti-RBD are the same as in the controlled population. I don't think it's everyone that's having the same issue if this is in fact the issue.

DG: Yes, I think that's one of the tough things. I think as clinicians, we look at this and we want to see two different groups. Like we saw with the data out of UPenn with low serotonin, we want to see a whole group of people or the people with low cortisol, as we saw out of the Mount Sinai-Yale study. We want to see the two groups really separate. I think that's one of the challenges, where we're starting to see that the two groups are biologically different, but we're not really getting that distinction. Yes, I actually think this goes along with the line that Long COVID is probably a number of different processes going on. Not every Long COVID patient has the same mechanism driving their issues.

VR: I would be very interested to know if the dots are the same patients who are similar to the controls in each of the assays that they do. Anti-RBD, PD-1, CTLA-4, is it always the same patient that's higher or is it a mixed bag? In which case it would be very difficult to know what's going on.

DG: Yes, I would love that too. That would be great. I know they're sort of comparing here the blue dots to the red dots, it'd be great if there was some way to turn on that third dimension of, give us a red, green, or something, we could see which person is which. I'm hoping as we get a better understanding of the different drivers for different people, that's going to drive us. If someone has a serotonin of six or eight, I'm going to come up with a plan. If someone has a cortisol, which is in a certain area, if someone has evidence of mast cell activation or histamine-driven symptoms, or maybe we can get a better subtlety here of what might be a way to address each individual. Instead of just throwing stuff at these debilitated people and potentially making them feel worse at times.

The next one, I guess I will talk about, is a couple of investigations looking at vaccination to prevent Long COVID and vaccination to treat Long COVID. The first is the article, “The Effectiveness of COVID-19 Vaccines to Prevent Long COVID Symptoms: Staggered Cohort Study of Data from the UK, Spain, and Estonia,” published in *The Lancet Respiratory Medicine*. Here the investigators conducted a staggered cohort study, so they're starting them at

different times, these different cohorts, using primary care records from the UK, from Catalonia, Spain, from Estonia.

They end up finding that compared with unvaccinated individuals, overall hazard ratios for Long COVID symptoms in people vaccinated with the first dose of any COVID-19 vaccine ranged from 0.49 to 71, so think about it as a 29% to 51% reduction, and consistently was associated with a reduced risk of persistent symptoms after a COVID infection. Now I'll leave in links to some other studies as well, but what about vaccination as a therapeutic for Long COVID? I'm going to discuss the preprint, “Impact of COVID-19 Vaccination on Symptoms and Immune Phenotypes in Vaccine-naive Individuals with Long COVID,” recently posted on *medRxiv.*

There's a number of august authors there, we have Connor B. Grady, sorry about that, Connor. Akiko's in there, Harlan Krumholtz is in there, I see Daniel Griffin misspelled in there. [laughter] I'll leave in a link to a thread posted by Akiko Iwasaki that walks through this, but I have to say, this was a challenging study to enroll for, because what we were looking for here is participants with Long COVID who had not been vaccinated, who would then agree to be in this study, and then they would go ahead and they would get a COVID vaccine dose, and then later they would get a second COVID vaccine dose.

Before they got the vaccination, we would collect blood, saliva, they would do a survey, get their first dose, they'd do another survey, get the second dose, again, blood, saliva, survey, and then we follow them out about three months, more blood, saliva, survey. There's going to be a lot of stuff that gets done here, lots of pretty multicolored figures, but I'm going to jump right to Figure 2. What was really happening as far as just symptoms? When you ask these people, "How are you doing? How are you doing in two weeks, six weeks, and 12 weeks?"

When we look at two weeks, we have about 43% feeling better, six weeks, 79%, 12 weeks, we actually lose a few, and we're down to 62%. Twenty percent, 14%, and 19% say they're about the same. This is what I want to point out, is at two weeks, 7% were worse. When we go to six weeks, 7% were worse. Actually, at 12 weeks, 19% were worse. Not everyone felt better. We actually had some people feel worse. What I would love to do, and we'll go a little further into this, is be able to tell ahead of time, right? Because here we are, we're encouraging people, hey, most people get better, 80%, 60%, but some people actually are feeling worse.

Jumping to Figure 4, this is the analysis of the vaccination response to the immune system, changes to antibodies against EBV and other viruses in response to COVID-19 vaccination. You do see a little bit of a difference, but not really. We're not really seeing a big difference here in those that are improved, those who are worse. Supplementary Figure 2, autoantibody analysis. I think this is a big one that I think is probably the second, but several here, where the idea that autoantibody is somehow related and maybe changes in this. We really don't see any changes.

Autoantibody levels really stay stable. What's going up is the spike antibody levels post-vaccine. Now, this one I liked as it might predict responders to vaccination. Here we have Figure 5, the results of examining plasma factors that are enriched in those who improved

after vaccination versus those who did not. The heat map shows that soluble IL-6 receptor elevated at baseline and after the vaccine in those who improved. In contrast, interferon beta and the ciliary neurotrophic factor were elevated in those who did not improve after vaccination.

There may be ways for us to tell ahead of time who's going to get better. Now, plasma levels of interferons alpha-2 and beta, CNTF, IL-11, SCF, stem cell factor, were consistently higher in those who did not improve after vaccination, while soluble IL-6 receptor was consistently higher in those who reported health improvement after vaccination. This will undergo its peer review and it'll come out hopefully better than it is currently, but starting to see maybe some of the biology hopefully help us because the last thing I want to do is encourage someone who's debilitated by Long COVID to go get a vaccination and have them feel worse.

What we're seeing here is that that is a risk. A lot of people are feeling better, but some people are worse. As I have been finishing every episode for quite a while, I'm going to keep this short because I already tell you, we've got a lot coming next week. No one is safe until everyone is safe. We're in the middle of January. We're getting to the end of our MicrobeTV fundraiser, November, December, and January. We will double your donations up to a potential maximum donation of $20,000. Stop what you're doing. Go to parasiteswithoutborders.com and click ‘Donate.’ Even a small amount, every bit helps us continue our work.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. JoAnn writes, "I have a question about the boosters. I've had each vaccine that has been offered, six or seven, I can't remember. I'm up to date. Had my last shot in October 2023. Would like to get another at the end of January, which will be four months out. I'm 78 with COPD, diabetes, heart disease, et cetera. I have not had COVID and I'm hoping not to get it. I mask indoors. My thought is I would like to keep my immune system primed as much as possible. What do you think of my plan?

DG: It makes a lot of sense. It sounds like you've been listening to *TWiV.* what we've talked about with the vaccines is that each time you get a booster, call it a new vaccine, call it a booster, but each time you get one of these shots, for we estimate three to four months, you're going to get an elevated level of those antibodies. You're going to get that extra level of protection. Antibodies contract. That's just what they do. Now, as a public health policy, I don't think we're going to be able to convince everyone that, "Hey, in this new world, now that COVID is with us, you need to get a shot every four months." I think certain individuals will want to do that. It makes sense.

These are licensed vaccines. That's certainly something you and your physician can discuss. I certainly understand the science and the thinking behind that.

VR: Ellen writes, "A friend of mine who completed the initial series of three vaccinations has contracted COVID five times, twice in the past 90 days. How is this possible? In the meantime, her partner with whom she shares a bed has never had it. She took Paxlovid once in the past, claims it made her feel worse. She also lost her hair during a previous infection, occasional numbness on the left side of her face, ongoing pain in the right calf. This time, her doctor recommended she go to urgent care for COVID vaccination, despite her debilitating fatigue and headache. Was this good advice?"

DG: First, my heart goes out to people like this. Unfortunately, there are people who have repeated infections who, as we've discussed, are not fully recovered after these infections. We've talked about how devastating losing your hair can be. It is tough. As we talked about that article, each time you get COVID, it's Russian roulette. People who, it was a mild case, they weathered the storm. Three months later, I'm taking care of them in the hospital because something about maybe their genetics, who knows what, but each time can be different.

A mild case doesn't necessarily mean the next time you get COVID is going to be mild as well. That's always a tough thing. "People say, "Oh, I took Paxlovid and it was worse." What was worse? Were you continuing to have COVID-19? How would this have been without Paxlovid? We really don't get to do that. The challenge is, when do you get that next vaccine? Coming to your last question. Really frustrating for folks that get COVID and we're recommending wait 90 days before you get that vaccine. Then they got COVID again, and they're wondering, how do I ever get that 90 days? This is where we've got to start talking about behavioral modification.

What's possibly going on? What are the exposures? Five COVID infections. If we're spending a little time trying to figure out, there's some way to mitigate that exposure and actually get vaccines instead of getting boosted with the infection and all the risks that come with that.

VR: Lori writes, and this is about Paxcess, "Wrote to you a few days ago about my sister's difficulty in getting Paxlovid. As it turns out, she needed to fill out an application with Paxcess. Pfizer evidently subsidizes the cost for eligible patients. Hopefully, others may benefit from this information." This is what you also mentioned above.

DG: Oh, excellent, thank you.

VR: Finally, Kathleen writes, Kathleen is a hairstylist in Dallas, Texas. Has been listening to *TWiV* since 2020 and is a big fan. "Friend of mine recently tested positive for COVID on December 20. She cleared her infection, and yes, she did get to take Paxlovid. Today is January 11, and she tested positive again. This is the fastest reinfection I have ever thought possible. I know you can have multiple infections. However, it seems to me this immediate reinfection may indicate no short period of relief immediately after an infection anymore. I'm not a scientist, but I do have a large load in the common sense department. COVID continues to keep my attention and my concern."

DG: Again, this is the frustration. What one of our earlier emails wrote about, too, is some individuals not even getting the - thinking, "Oh, I just had COVID. At least I probably won't get it for the next three months." Unfortunately, people are getting reinfected. Some folks within the same month, they get COVID and then they get it again. Verifying it's a reinfection because it might even be a different variant. Very frustrating.

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

DG: Oh, thank you. Everyone, be safe.

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