This Week in Virology

TWiV 1008 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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From MicrobeTV, this is *TWiV*. *This Week in Virology*, Episode 1,008, recorded on May 18, 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: I'm joining you from Geneva, Switzerland where I -

DG: Yes, it's a different background. I should have remembered. It's only been a few days since you told me you were headed there.

VR: Just got off a four-day Nidovirus meeting, which was really, really cool. At the end, maybe this is something you'll cover next time. The WHO announced its new booster policy.

DG: [laughs] You were there for that.

VR: I was.

DG: Yes, we'll just mention slightly, but yes, we'll discuss that more next time. Let me start with my quotation. "Less is only more where more is no good." That's a Frank Lloyd Wright quotation. I'm always a little thrown by his architecture and his quotations, but we'll see what we can make of that. You'll, later on perhaps, understand why I throw that in. I'm going to jump right into COVID, and people ask like, "How's it going? What's happening out there?"

I think I mentioned this last time, and just to reinforce. We do not have as much information about what's going on right now. We're just tracking weekly COVID-19 hospital admission levels, the percentage of all COVID-19 associated deaths, and then we have some secondary information, emergency department visits, hopefully that's an early flag if something's happening there.

Percentage of positive SARS-CoV-2 laboratory tests, and we're still going to be getting genomic surveillance. Still seeing some folks in the hospital with COVID, so it is certainly still with us. I want to move right into testing, because this is a question - I think it's a perennial question, and I will get right into it with the article, "Virus Variant Specific Clinical Performance of a SARS-CoV-2 Rapid Antigen Test with Focus on Omicron VOC," recently published in *CID*.

Now, I wonder how many more of these studies we will get and what the future holds for those rapid tests now that the public health emergency has ended. In this study, they looked at the Sofia SARS-CoV-2 antigen rapid detection test and compared it to the PCR in a real-world, single center study in a clinical point of care setting in patients admitted to a large hospital via the emergency department from 2nd of November 2020 to the 4th of September 2022.

I'm going to say the same general principles that we've all talked about, that we've learned about over the last couple of years, still apply here. The antigen rapid detection test sensitivity continues to be dependent on viral load. Here the sensitivity is 93.2% in samples with a viral load of greater than a million SARS-CoV-2 copies per milliliter, which correlates to a cutoff value about 25-26.

It's interesting, they reported here that those tests were more sensitive in men and older patients. But here's a couple of things I will comment about because I think this is important from real-world translation of this and similar results, is the ideal time for testing has shifted a bit from the early days. It's not that day before symptom onset, the screening programs. It's really not that first day of symptoms. It's really the second and third day that we're getting our best sensitivity.

We're living in a world where people have either seen a vaccine or seen the virus before, or both, so we tend to see the symptoms start early. The viral load, the amount of RNA and antigen then rises. We get our sensitivity. Actually, fortunately, that's still within that window where we might want to jump in. The other thing, and this study reiterated, but during the time of Omicron variant of concern, we are seeing lower viral loads or RNA copy number, let's use the right language here. If you have lower amount of RNA, lower amount of antigen, you're going to have a lower sensitivity if you look at all comers, particularly if you're not really timing the testing properly.

All right, I will move into ventilation. Oh my gosh, this has been in my outline for so long and finally something to say. I wanted to share CDC guidance on ventilation in buildings, and I'll start with the overview. When indoors, ventilation mitigation strategies can help reduce viral particle concentration. The lower the concentration, the less likely viral particles can be inhaled into the lungs, potentially lowering the inhalation dose, contact eyes, nose and mouth or fallout of the air to accumulate on surfaces. Although it isn't known exactly how much the concentration of viral particles in air needs to be reduced to start reducing risk of viral infection, ventilation mitigation strategies still provide a reasonable approach to reducing risk. Not all interventions will work in all scenarios, and their selection must be carefully evaluated prior to adoption.

Now, they recommend a number of things, including, this was the headline, five air changes per hour. Just compare that to negative pressure rooms with 16 to 12 total room air changes per hour, and a standard patient room, which is supposed to have six air exchanges per hour. I'd love to see such ventilation standards and air exchanges posted that might help me make decisions about when I venture indoors and what I might do.

Yes, as you mentioned, Vincent, we will be hearing more about vaccination and vaccine composition going forward. June 15th is when we're going to hear from-- The FDA is going to have their advisory meeting. We also got a little bit - You tweeted about this, Vincent, and I was watching that discussion about XPB, the difference between neutralizing antibodies and the rest of the immune system. I promise we'll do a little bit of a deeper dive here.

One of the things I just want to say that the science remains the same. We've been saying for quite a while that robust protection against severe disease, hospitalization, that has been holding pretty strong, but what we've been seeing over time is that three-to-four-month boost when we've got high antibody levels and our risk of even getting an infection is lower. If you can't get infected, you can't progress to severe disease.

When we lose that reduction in infection, when you compare that to a baseline, you see this dramatic reduction, but it's not a dramatic reduction to being completely unshielded. This is not the situation that newborns are entering the world with. This is going back to that baseline. A lot of discussion about WHO, which we will touch on more. It's a short read. It's really funny, when they put things out, they tell you how long it should take you to read, and apparently it's six minutes to read what the WHO put out to the public today, so six minutes well spent, and we'll get back to it next time.

Passive vaccination. We are still waiting for an Evusheld replacement. When that's available, I will certainly mention it. Now, what do we do? We've done everything we wanted to do, everything we hoped to do. Now, you've tested positive. Your patient has tested positive. Someone you care about has tested positive. Still, number one, Paxlovid. Number two, remdesivir. Three, molnupiravir. Certain contexts, convalescent plasma.

I just wanted to hit again on avoid doing harmful things. Sometimes the best thing you can do is keep your hands in your pockets. I wanted to discuss the article, "COVID-19 Mortality Among Selective Serotonin Reuptake Inhibitor Users - Results from a Nationwide Cohort," published in *CMI*, and then talk a little bit about the big picture implications and why evidence-based medicine is so critical.

These are the results of a retrospective cohort study including all Danish residents above the age of 18 with a positive SARS-CoV-2 PCR test from February 26, 2020 to October 5, 2021. Follow-up period was 60 days. The primary outcome was all-cause mortality, and the secondary outcome was severe acute respiratory syndrome. Exposure of interest was SSRI use, those antidepressants. Differences between SSRI users and non-users were examined.

Here we've got 286,447 SARS-CoV-2 positive individuals, 7,113 met the criteria for the SSRI use. Now, a little bit of difference here, I want to point out. SSRI users had a mean age of 50.4, 34% were male. Now, the non-SSRIs not perfectly matched, mean age of 41.4, 50%

were male. Similar vaccination frequency, so that was good, were seen between the two groups. Sertraline was the most common used SSRI followed by citalopram and escitalopram. They reported that SSRI use was significantly associated with increased mortality with a hazard ratio of 1.32, even when we adjusted for age, sex, vaccination status, comorbidities. Now, they gently say that their study speaks against the hypothesis of repurposing SSRI drugs for COVID-19 treatment.

Here we're seeing a 32% higher mortality. Let us say we see a practice pattern where people are all taking an SSRI to be safe from COVID. I know that certain people out there on social media encouraging that. In that setting, let's say 132,000 people die, that's an extra 32,000 people that would still be with us if we had not been adopting that strategy. I think this is another one of these, maybe a wake-up call. I think I've talked before about physicians overestimate the amount of good we can do and we underestimate the harm that might come with our interventions, but repeatedly we have seen our brilliant ideas, our great ideas, our preliminary data, when we finally really study it properly, most of the time humility should prevail. Here, again, we are seeing concern at throwing SSRIs at folks without proper science.

COVID, the early inflammatory phase, right? That's that second week, that's that cytokine storm. We still are certainly seeing this. People get a little better. There's a little bit of a pause, and then they might be starting to have fevers. Those fevers might be during that second week, there might be shortness of breath. Remember, everything about the first week is trying to keep this cytokine storm, this inflammatory phase reigned in so we can keep those folks out of the hospital, keep them from having long-term issues.

I will move into a long-term issue. Long COVID, and I've been saying for a while, as hoping this would become a more major part of our weekly updates. I mentioned on a previous update that I recently sat down with my colleagues that run and see patients in our post-COVID recovery center here at Optum Tri-State. The comment was made that they are making a fair number of new diagnoses of sleep apnea.

I stored that away wondering what was up with that until I saw the article, "Risk of Post-acute Sequelae of SARS-CoV-2 Infection Associated with Pre-coronavirus Disease Obstructive Sleep Apnea Diagnoses: An Electronic Health Record-based Analysis from the RECOVER Initiative," published in the journal *SLEEP*. Now this article has me wondering, is the sleep apnea triggered by the COVID, or is the sleep apnea a pre-existing, undiagnosed, and now may have triggered, so other musings, but I thought it was interesting that here we're seeing an increased number of new diagnoses. Let's talk about what this particular article had to tell us.

In this investigation, they assess the impact of pre-existing obstructive sleep apnea on the risk for probable PASC in adults and children using electronic health record data from multiple research networks through research networks within the researching COVID to enhance recovery initiative, and they have cute little acronyms. I will skip those. They employed a harmonized analytic approach to examine the risk of probable PASC in COVID-19-positive patients with and without a diagnosis of obstructive sleep apnea prior to pandemic onset.

Unadjusted odds ratio were calculated, as well as odds ratio adjusted for age group, sex, race, ethnicity, hospitalization status, obesity, and pre-existing comorbidities. They reported that the unadjusted odds ratio for probable PASC associated with a pre-existing obstructive sleep apnea diagnosis in adults and children range from 1.41 up to 3.93, so up to four times as likely to end up with Long COVID. Pretty impressive, and a lot of questions there. Is it the chicken? Is it the egg?

The other thing I should say is when you treat these folks, it makes a huge impact. If you've got an individual that you're taking care of, post-acute sequelae of COVID, Long COVID, might be worth considering testing a number of these folks for sleep apnea and addressing that issue.

Now, this study, “Trajectories of the Evolution of Post-COVID-19 Conditions up to Two Years after Symptom Onset,” was recently published in the *International Journal of Infectious Diseases.* They described the ComPaRe Long COVID e-cohort, and I encourage people to look at how they spell that and which capitals. This is a prospective cohort of 2,197 patients with symptoms lasting at least two months after SARS-CoV-2 infection. They were enrolled in the cohort between December 2020 and July 2022 when the Omicron variant was not dominant. It's pre-Omicron. At a high level, they reported that 91% of patients improved over a two-year course, 5% improved rapidly, but then 4% had a persistent condition.

It is interesting. They go ahead and they describe three trajectories. I'm going to go through these a little. Part of it is helpful for understanding the disease. Part of it is also helpful for having conversations with patients. Something it's quite reassuring for individuals when you understand what they're going through. You recognize, and also they are able to recognize that they're not the only one going through this.

We have trajectory number one. This is participants with persistent symptoms, older, more likely to report a history of systemic diseases. These participants often have tachycardia, bradycardia, palpitations, arrhythmias, paresthesias, hot flushes, sweats, heat/cold intolerance, photophobia, phonophobia, and they're seeing this in the first year, approximately half of the participants with persistent symptoms reported daily relapses. I think that's something that we often see. People are getting better. Then they have these relapses.

We have a trajectory two. These are participants with rapidly decreasing symptoms, younger, more likely to be reporting neck, back, lower back pain, diarrhea, interesting clustering here, in the first year after symptoms. Among participants with rapidly decreasing symptoms, the proportion of participants reporting less than weekly relapses increased from 26 to 75% between symptom onset and greater than 18 after.

Then last is trajectory number three. These were folks that were reporting less than weekly relapses, so sort having these stretches and then having some relapses.

Now, I'm going to talk about a next article. Interestingly, I was surprised. Some people seem encouraged by this. Some people seem, dare I say, offended by this article. The article, "Efficacy of Cognitive Behavioral Therapy Targeting Severe Fatigue Following COVID-19: Results of a Randomized Controlled Trial," was published in *CID*. These are the results of a

multi-center, two-arm randomized controlled trial conducted in the Netherlands with patients being severely fatigued, three to 12 months following COVID-19.

They looked at 114 patients randomly assigned one-to-one to cognitive behavioral therapy or a control group, a care-as-usual group. They were targeting perpetuating factors of fatigue. Patients were mainly not hospitalized, self-referred. Patients who received CBT, cognitive behavioral therapy, were significantly less severely fatigued across follow-up assessments than patients receiving the care-as-usual (CAU).

All secondary outcomes favored cognitive behavioral therapy. Eight adverse events were recorded during cognitive behavioral therapy, 20 during care-as-usual, so better there. No serious adverse events were recorded of the cognitive behavioral therapy group; 63% were recovered, reporting they were no longer severely fatigued at six months compared to 26% in the control, so 63 versus 26.

Just to explain, what is this CBT? What were they doing? Now the seven perpetuating factors addressed were: one, a disrupted sleep-wake pattern. Two, unhelpful beliefs about fatigue. Three, a low or unevenly distributed activity level. Four, perceived low social support. Five, problems with psychological processing of COVID-19. Six, fears and worries regarding COVID-19, and seven, poor coping with pain.

Now, little bit of a discussion here, because a couple of the comments that I got was, "Well, it works well because what does cognitive behavioral therapy do, it convinces people to stop complaining." I am not sure that that's my takeaway from this. I also was concerned people had the idea that this was suggesting that this was just a psychological problem, somehow gaslighting these folks, and I don't think that's the case as well.

I think these folks are having a really difficult time. Whether you're engaging in formal cognitive behavioral therapy or if physicians taking care of them can use this as some roadmap to help. If we can intervene and help with the sleep-wake issues, if we can help them with some of their concerns and negative beliefs about fatigue, if we can help them find that much-needed social support, I think there's actually a lot in here that can be helpful.

I'm going to close out with some helpful links before we hit email. Virtual physical therapy resources. There are certain individuals who really can jump into some of the physical therapy approaches. There's other folks who need pacing. We've talked about this quite a bit. For many with long COVID, the idea of getting to and from a physical therapy appointment seems overwhelming. Also, others are quite concerned that the physical therapist will not understand what is appropriate for particularly those folks with the post-exertional malaise.

There actually are some resources, I'll leave links in here, and I'm even going to leave in a link from the American Physical Therapy Association that contains resources for physical therapists caring for those with Long COVID. This can be helpful, but only if done by the right people who have an appreciation. This isn't something you just exercise your way out of, but exercise can play a role if guided properly.

I will close with, no one is safe until everyone is safe. We're three-plus years here. A lot of people are deciding that this is not an emergency anymore, but it still is an important issue. For us to continue to share what we do, we ask you to go to parasiteswithoutborders.com. Click on that 'Donate' button. I shall say, right now, we are in the middle of our Foundation for International Medical Relief of Children fundraiser. May, June, and July donations made to Parasites Without Borders will be matched and doubled up to a potential donation of $20,000 for Foundation for International Medical Relief of Children.

VR: The episode of *TWiV* I recorded here, actually it was in Montreux, at a Nidovirus meeting. One of my guests was Maria Van Kerkhove, the face of COVID of the WHO. You'll want to listen to that. That's dropping on Sunday, the day after this report. She has some interesting things to say as well.

DG: Oh, that's fantastic. I'm jealous. I'm a bit of a fan. Is she as impressive in person as she seems?

VR: Yes, she's very good at answering questions, and yes, she's very well-trained there. She's quite good. She knows what to say and what not to say.

DG: I've been impressed. She is a star when it comes to communication.

VR: All right. It's time for your questions for Daniel. You can send them to daniel@microbe.tv. David writes, "Writing for a friend. Patient had B-cell lymphoma in 2020, was treated by standard therapy, including B-cell depletion with rituximab. He has been immunized several times. COVID in April, he responded well to Paxlovid, but relapsed a month later, and is virus-positive, has fever, pulmonary complications and is hospitalized on remdesivir and supplemental oxygen. Any comments or recommendations for dealing with what looks like persistent viral replication since Evusheld is no longer useful, is convalescent plasma recommended? Is it possible to ever completely eradicate viral replication without an immune response?"

DG: Great question. We shared several episodes back, a case series, several patients very similar to this, inability to make that B-cell response, inability to clear the virus. These were older variants, so actually it was a multi-pronged approach where they were using small molecule, so remdesivir, as you mentioned. They were also using monoclonal antibody therapy, even though it wasn't in that first 10 days because you're using it to try to address this ongoing viral replication. Actually those case series that we discussed, it was successful. Here's the problem. We're now in the time of Omicron, particularly the XBB. It is not clear to us that any of those monoclonal antibodies or monoclonal antibody cocktails are still effective, so you do raise an interesting question. Is this a time to maybe consider, we'll talk about Arturo Casadevall and the Artisanal, someone who's recently recovered, who made a robust XBB response. Could that play a role here? That makes sense. You're stepping outside the box, but that may be what needs to happen here, so maybe this is a time to loop someone like Arturo in on this, and see if there might be some way of trialing something like that.

VR: Roland writes, "I'm a 49-year-old male with no pre-existing conditions, currently on day three of COVID-19 infection, first time and triple vaccinated. Last night began with a nasty

cough. Coughs tend to persist with me. My physician has recommended Symbicort Rapihaler, but I have heard you say over and over to never use steroids in the first week. Can you please give me your thoughts on whether Symbicort qualifies as a steroid and should be avoided? If so, how long do I wait?

DG: Great question. The big distinction here is when we say no steroids in the first week, we're talking about systemic steroids. Systemic steroids several-fold increase in the risk of progression, even maybe an increased risk of mortality doing the systemic steroids in the first week. Now we have had some trials, uninhaled steroids, though they did not make a difference. They were not of benefit. It doesn't look like they were harmful. Not a bad thing to consider, a safe thing to consider in the first week.

The other thing, which is interesting, and I'm not sure I fully understand the mechanism, but Tessalon Perles, at a higher dose, at 200 milligrams, three times a day, tends to be quite effective for folks with the COVID cough. Interesting enough, why do that? Well, one is it's nice not to be coughing and address the symptoms, but the other is the more you cough, the more you irritate. Inhaler as suggested is reasonable and safe as opposed to systemic steroids, and you might actually talk to your provider about the Tessalon Perles at the 200 milligrams, three times a day dose.

VR: Jeff writes, "I am a practicing pediatrician in Connecticut. Many families and patients are reluctant to undergo testing for COVID because of the strict five-day isolation rule. Missing work and school for what seems mild viral symptoms is something people are increasingly uninterested in doing. The logic seems to be, don't ask a question when you'd rather not know the answer. My question for you is this, given our current state of affairs, how relevant now are the data that led to the five-day isolation recommendation? Will there be a time when we can treat COVID-19 more like we do other viral respiratory infections? Stay home when you have a fever, return to work or school when you're feeling better, plus maybe wear a mask if you're symptomatic.

"I no longer recall the specifics that led to that recommendation, but back then, we were dealing with other variants in an environment of lower vaccine and infection-derived immunity. If the community seroprevalence is high enough to change the vaccine recommendations, might it also be high enough at some point to modify how we approach the risk posed by patients who might be contagious? From what I can see, the strict five-day protocol is making it harder for us to know how much COVID is actually out there."

DG: This is a great question, and it's a tough topic. We came up with these rules, these ideas early on, the whole idea that 85% of transmission is occurring in that first five days. We've also talked a little bit about that Pareto principle, where 20% of people are doing 80% of the transmission. I think what you're really including here in your email is the public health reality.

It's gotten to the point where people don't want to test because they're not willing to do the five days. They're not testing because, "Oh my gosh, what if my child is positive? What about right now, it's the spring, they've got finals, they've got AP exams, whatever it is, they can't afford to miss school." Parents are sending kids to school because the five days is

considered too much of an ask to the point that people won't test because they're afraid of the consequence.

The five days and then the five days of the mask. Then we also, I think, dare I should mention this, what about someone who makes the "mistake" of doing an antigen test on day eight, and it's positive again, do they go back for another 10 days? Then healthcare workers, we're still dealing with healthcare worker guidance from the CDC from September of 2022, where it's even much longer if you actually follow those guidelines. Again, we're seeing healthcare workers, not wanting to miss work for a couple of weeks. This is the challenge of public health, balancing the science, and the science says that there is a period of transmission which may have actually changed over time, and I am glad you bring that up. What is the current window for transmission in a vaccinated, maybe hybrid immunity? Plus the current variants. We really need to know that data, so we're giving updated guidance on the science, but then this is the challenge for the public health folks. If you go ahead and give guidance, and the guidance says people doing it about 2% or 3% of the time, that's not helpful.

Yes, this is a huge challenge, and I wonder, are we going to get the science? Are we going to get updates in the guidance? Or now that the public health emergency is over, are we going to be just stuck with the general guidance that came out in March of 2023, and the healthcare worker guidance that came out in September of 2022? I agree. It's time for people to really look at the science again, and make sure we update public health guidance that actually is something that people are willing to follow.

VR: Deborah writes, "I'm 71. My husband is 79. Both relatively healthy. Gotten all our COVID vaccines, including Moderna and Pfizer shots. Neither of us has had disease. For my first booster, I was given a full Moderna dose, because I have both ulcerative and microscopic colitis, and that's what the doctor wanted to do. Second booster is Moderna. The last fifth vaccines for both of us, the bivalent Pfizer booster. Here's my question.

If the latest bivalent vaccine doesn't protect against the current iteration of COVID-19, and I suppose the ones that will soon follow, why get it? Why not just protect ourselves as we've been doing with masking, being cautious, asking friends and family to test before they come by? No one has had a problem with this. Is there a downside to not getting this newest bivalent booster at our ages?

DG: All right, we're going to go into this deeper next time. This is an excellent question. First, I want to dispel the myth. It's not that the vaccines have stopped working. What has happened over time is levels of antibodies have dropped, and also the ability to generate neutralizing antibodies against the current circulating XBB variants has gone away. That three-to-four-month boost above a protected baseline, that's what we're not able to get at the moment with our current boosts. The idea is that certain individuals sense the more the better from a public health, particularly times where we would expect a lot of folks to be indoors, peak transmission.

If we can update vaccinations, so that people get a boost, let's say they get it in early November, and we actually reduce transmission with neutralizing antibodies for some three-to-four-month period, certain individuals, that can be a wonderful tool to have at

hand from a public health aspect. That can be a wonderful tool to have at hand. Unfortunately, as we've talked about right now, it's not clear that the current bivalent boosters give you that three-to-four-months of neutralizing antibodies that reduce that risk of infection.

VR: Yes, the WHO released those data today, so we can talk about that next time for sure. That's *TWiV* weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

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

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