This Week in Virology

TWiV 1172 Clinical Update

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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 1172, recorded on December 5, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from somewhere outside the US, Daniel Griffin.

Daniel Griffin: Hello, everyone. I am recording from Northern Tanzania. Vince and I are going to be piecing this together, so I'm hoping this works. I will start off with a Tanzanian proverb, I guess this is. "*Mwenye pupa hadiriki kula tamu*." "A hasty person misses the sweet things." Maybe my suggestion here in the holiday time is that people take a little more time and try to not miss the sweet things. All right.

Just an update on flu. We're starting to see a little bit of activity down in Louisiana, down in Georgia, but in general, other than the District of Columbia, which still baffles me, the influenza, the respiratory viruses are staying a bit low. Looking at wastewater, seems about the same for influenza A, but interesting enough, we're actually getting reports about higher levels out there in Arizona and also down in Virginia. My daughter Eloise is down there. Be careful. All right. What have we got here? We get the flu vaccine to protect ourselves, but does getting the flu vaccine protect those around us? What about those who actually care about the loved ones that we surround ourselves with?

This is the altruism aspect of vaccines, and we have the article, “Estimated Effectiveness of Influenza Vaccines in Preventing Secondary Infection in Households,” published in *JAMA Network Open*. This is a prospective case ascertained cohort study of 699 primary cases, 1,581 household contacts. The secondary infection risk of influenza infection among household contacts was 18.8%. The estimated effectiveness of influenza vaccine for preventing

secondary infections among household contacts was 21%. Just to give this a little a case ascertained household study.

What's going on here? This is where the households are recruited after an index case is identified, and household cohort studies are where households enrolled before. This is actually a nice way to conduct these studies because it allows us to maybe use less individuals because once we identify that positive, we can move forward. The challenge, of course, is there may have already been some exposures going on, but again, we're looking at influenza vaccine. So, wrap it all up: That influenza vaccine protects you against severe disease, but it may actually also protect your friends, your loved ones, those that you live with from getting the flu as well. All right.

We also have an article which I think is important. You get the flu. What do we do about it? This is an article, "Benefit of Early Oseltamivir, Early Tamiflu Therapy for Adults Hospitalized with Influenza A: An Observational Study," published in *CID*. These are the results of a multicenter U.S. observational study that prospectively enrolled adults aged 18 years or older, hospitalized with a laboratory-confirmed influenza, looking at 24 hospitals during October 1, 2022, through July 21, 2023. A multivariable proportional odds model was used. Basically, they're going to look at people all age, sex, severity, oxygen requirement, and they're going to compare folks that get started on Tamiflu on Day 1 versus those who either don't get treated or they start it later.

A total of 840 influenza-positive patients were analyzed, including 49% who started Tamiflu on Day 1 and then 51% who did not, falling into the other. Compared with late or not-treated patients, those treated early had a lower peak pulmonary disease severity. They also had lower odds of ending up in the ICU, that was about a 76% reduction, less acute kidney replacement therapy or vasopressor use, that's about a 60% reduction, and your chance of dying in the hospital was reduced by 64%.

Now, maybe David on the YouTube will post this up, but there's a nice figure where you can actually break this down by age category, and you can look at early treatment versus late treatment. I'm going to say interesting enough, early treatment, oseltamivir, you're looking here at numbers that are pretty similar in 18 to 49, 50-64, but then you see a nice drop in the 65-74.

All right, moving into RSV, what is going on there? As mentioned, still at fairly low levels, but we're starting to see the rise in the wastewater, particularly down there in the south, so Georgia, Florida, Alabama. I'm starting to see some rises down there. All right, and what about COVID? Right into COVID, and we're only five minutes in, so we're moving quick this week. You look at the percentage of provisional deaths due to COVID in the past week all throughout the U.S., and pretty much everybody's under that 2%. We continue, if we track our wastewater, to see that we are across the country in the minimal activity level. Really, I think Vincent's idea that we might have earned some mileage with immunity from this last surge might be holding true.

All right, fascinating article. The article, "Maternal Infection of SARS-CoV-2 During the First and Second Trimesters Leads to Newborn Telomere Shortening," published in the *Journal of Translational Medicine*. Fascinating study, but maybe a little disturbing, but let me give a little

bit of background here. Telomeres, what are telomeres? We'll start with Wikipedia, and everyone should make a donation to Wikipedia to keep them going.

We read, a telomere, they tell us how to pronounce this, from the ancient Greek, end part is a region of repetitive nucleotide sequences associated with specialized proteins at the ends of linear chromosomes. Telomeres are a widespread genetic feature, most commonly found in eukaryotes, folks like us. In most, if not all, species possessing them they protect the ends of the chromosomal DNA from progressive degradation and ensure the integrity of linear chromosomes by preventing DNA repair systems from mistaking the ends of the DNA strand for a double break. Elizabeth Blackburn, Carol Greider, and Jack Szostak, who I hung out with, was awarded the 2009 Nobel Prize in Physiology or Medicine for this discovery.

I got a chance, as I mentioned, to meet. I actually spent some time with Jack Szostak a number of years ago at a talk with him at dinner, as well as sharing an interest in telomeres and human B1 cells that were a bit touched on in the last deep dive *TWiV*, so I'll leave a link into human B1 cells in Wikipedia there. Here's the crux. Why do we care? Telomere shortening is associated with aging, mortality, age-related disease in experimental animals. Longer telomeres may be associated with lifespan in humans, so longer telomeres, we think, are good. Shorter telomeres may be a shortened lifespan, and from some studies, may be an increased risk of cancer.

Here, these investigators recruited 413 normally delivered newborns whose mothers were either non-infected or infected with SARS-CoV-2 during the different trimesters of pregnancy, otherwise, healthy. They measured the telomere length using cord blood control, non-infected maternal telomere length was significantly longer from that from folks that had maternal infection. Now, they only saw this difference if that COVID infection occurred in the first or second trimesters of pregnancies. No differences when you looked at controls and infection during the third trimester. Unfortunately, across the first trimester, there was a positive correlation between the newborn telomere length and gestational weeks with maternal infection. The earlier it seemed that a mother would get infected, the shorter those telomeres.

They basically conclude that folks should get vaccinated, particularly in advance for women who plan pregnancy. Maybe getting before the pregnancy is going to protect mom and her ability to protect the baby. Then we've actually talked about how getting a vaccine during that last trimester can actually carry forward protecting the newborn. Actually, during that third trimester, it's probably right at the beginning of when we recommend to really protect the baby. So, concerning, concerning.

All right. COVID active vaccination. I feel like we keep returning to this important question, why should I get vaccinated? This week, as promised, we have the article, “The Effect of Pre-COVID and Post-COVID Vaccination on Long COVID: A Systematic Review and Meta-analysis.” If I get vaccinated, is that going to keep me, is that going to help reduce my risk of long COVID, which for a lot of folks is the biggest risk? This article was published in *Journal of Infection*. Now, with COVID, we now know that there are several potential outcomes, including asymptomatic infection, symptomatic infection that does not require medical attention, symptomatic disease that requires medical attention, including disease severe enough to

require hospitalization, maybe end up in the ICU, maybe you don't survive the infection, and then post-acute sequelae of COVID-19, including a syndrome of Long COVID.

Now, the larger umbrella term, and I've talked about this a bunch, PASC, includes a number of things. Having a stroke, having a heart attack, developing diabetes, autoimmune disease, new onset dementia, but under this umbrella is this recognizable syndrome of Long COVID. Several characteristic features such as severe debilitating fatigue preventing individuals from working, unable to go to school, unable to participate in life, cognitive issues, breathing and cardiac issues, and in some cases, but not all, there may even be objective physiological abnormalities and biochemical abnormalities.

Now, to be honest, the development of PASC or Long COVID dwarfs the number of deaths, even with the lowest estimates from experts who suggest, "We have overplayed this, and we're only seeing Long COVID about 2% of cases." Doing the math here in the U.S., even if you take this low estimate, 2% of our population of 350 million still gives you seven million individuals suffering, and we keep seeing new cases. Here they go ahead, and they're going to look at this issue. Certain characteristics we know, such as being hospitalized, female sex, higher body mass index, smoking, pre-existing comorbidities, not receiving early antiviral therapy, and not being vaccinated are associated with an increased risk of Long COVID.

Here, we're going to go through a meta-analysis involving more than 14 million people published in the *Journal of Infection* showing that COVID-19 vaccination is associated with a lower risk of developing Long COVID, with two doses reducing the odds by 24%. After reviewing the literature, these investigators obtained 6,717 studies, and after sorting through these, they systematically reviewed 25 studies. They included data from 19 studies that reported pre-COVID vaccination, six studies reported post-COVID vaccination. They have a couple really nice forest plots, so you can really see where they're getting this data. You can see some studies where it's just really compelling, other studies where there is a little bit of an overlap. Pretty much across the board.

Vaccination prior to getting infected, we are seeing either statistically significant or trend towards reduction in Long COVID. Not as much data if you get three doses in, but we're also seeing that moving in the right direction as well. Not as much of a benefit, but it does look like there's a trend towards benefit, and we reach statistical significance when we pile them together, those cow pies, vaccination after getting infected. Just in a nutshell, not only can that vaccination reduce the severity of disease, but it looks like it can reduce your risk of even getting long COVID.

All right, the article, ”Delayed Induction of Noninflammatory SARS-CoV-2 Spike-Specific IgG4 Antibodies Detected One Year After BNT162b2 Vaccination in Children,” was recently published in *The Pediatric Infectious Disease Journal*. Now since we periodically get comments from people asking why we don't talk about IgG4, here you go. Humoral immune responses after BNT162b2 vaccination, so that's the Pfizer-BioNTech. These are looking at the antibodies we produce, that's the humoral immune response, are predominantly composed of IgG1 and three subclass antibodies, so we've got four different types of IgG1, 2, 3, 4, there's even some subclasses among those. Previously described in adults, S1-specific and receptor-binding domain-specific IgG4 levels increased significantly one year after the second of the Pfizer-

BioNTech vaccination, and now these investigators are reporting this in children 5 to 11 years of age.

Now, this may be mRNA vaccine-specific as it has not been observed after other vaccinations such as homologous vaccination with adenovirus-based and Modified Vaccinia virus Ankara-based SARS-CoV-2 vaccines. Now, why do we care? What does it mean? In general, the protective immune response, so the protective antibodies after vaccination or infection, we think are predominantly due to IgG1 and IgG3 antibodies. These are both capable of mediating effector functions such as antibody-dependent cytotoxicity, phagocytosis, complement activation via their FC portion. Real-life data, passive and active immunization studies in mice, suggest that the engagement of that FC region is required for vaccine-induced antibody-mediated protection.

Now IgG4, as the least abundant of the IgG subclasses, has some unique structural and functional features resulting in them being described as blocking or anti-inflammatory antibodies. Now, we're seeing some, but these still make up a minority. At the end of the day, we're not really sure, but let's look at a little more data.

I'm just going to mention the article, “The Relative Effectiveness of Homologous Novavax and VxCoV2373 and BNT162b2 COVID-19 Vaccinations in South Korea,” published in the journal *Vaccine*. Now you're trying to decide which vaccine to get. To estimate the relative effectiveness, Novavax versus the Pfizer-BioNTech in preventing SARS-CoV-2 infection and severe COVID-19 disease during the Omicron variant period in South Korea, these investigators conducted a retrospective cohort study among folks 12 years of age and older. Among homologous, meaning they got the same shots, primary series with Novavax versus the Pfizer-BioNTech at day 180 post-vaccination, the adjusted hazard ratio was 0.90 for laboratory-confirmed and 0.65 for severe infections. Among homologous first booster recipients, it was 1.15 for all laboratory-confirmed and 0.39 for severe infections.

Now, I also will leave in a link to an article published in *BMC Infectious Diseases* back in February, “Comparative Efficacy and Safety of COVID-19 Vaccines in Phase 3 Trials: A Network Meta-analysis.” I want to point out, Novavax is a great and underutilized option for people with concerns about mRNA vaccines with less reactogenicity, but we still have a lot to learn about the comparative efficacy of those vaccines.

All right. Remember PEMGARDA, pemgarda.com, as your passive antibodies for folks that have severe immune compromise. About a 70% risk reduction when this came out based upon circulating strains at that time, circulating variants. PrimeInfusions.com is how we're giving folks access in our local area. All right.

COVID early viral phase. We have our treatment guidelines still. Number one, Paxlovid, number two, remdesivir, number three, molnupiravir, convalescent plasma in certain contexts and remember those isolation guidelines.

All right. COVID, the early inflammatory phase. Just to remind people that this is the bad week. People feel rotten. Then they might get that hypoxemia that drives hospitalizations and deaths. Number one, steroids at the right time, in the right patient, at the right dose, anti-coagulation, pulmonary support.

What about remdesivir? Any more data on that? Yes, the article, “Remdesivir Effectiveness in Reducing the Risk of 30-day Re-admission in Vulnerable Patients Hospitalized for COVID-19: A Retrospective U.S. Cohort Study Using Propensity Scores,” published in *CID*.

Here we have the results from a retrospective study that utilized the US PINC AI healthcare database to identify adult patients discharged alive from an indexed COVID-19 hospitalization. They end up looking at 326,000 patients hospitalized for COVID-19, 210,586 met eligibility criteria, about half, 52% treated with remdesivir. They reported a lower odds of 30-day COVID-19-related readmission in patients who received remdesivir versus those who did not, about a 22% reduction. Elderly population, about 22%, and folks with underlying immunocompromising, about a 14% reduction. They were seeing this benefit irrespective of your oxygen requirements.

All right, and here we have just a little bit in our Long COVID section. I continue to leave in a link to our post-acute sequelae of COVID, PASC, or Long COVID evidence-based paper. Also, I'll leave in the telephone number and a link to the Long COVID Treatment Center at Columbia to schedule your in-person or telehealth appointment. Here we are in 2024. Before we know it, it'll be 2025. I have to say, our therapeutic options for Long COVID remained limited. Today we have this article that I'm going to spend a little time on, but pay attention.

This is the article, “Transcutaneous Electrical Nerve Stimulation for Fibromyalgia-like Syndrome in Patients with Long COVID: A Pilot Randomized Clinical Trial,” published in *Scientific Reports*.

Here, they investigated the effect of transcutaneous electrical nerve stimulation, or TENS, for fibromyalgia-like symptoms, including chronic widespread musculoskeletal pain, fatigue, and/or gait impairment in 25 individuals with Long COVID. The participants were randomized to a high-dose, this is the intervention group, where they got this low-dose placebo group so you can feel this device. Both groups received three to five hours of TENS therapy. They used this brief pain inventory, so the BPI, to assess functional interference from pain and severity. We've got a BPI-I for interference, BPI-S for severity. They also used the Global Fatigue Index to assess functional interference from fatigue.

Wearable technology was used to measure gait parameters. That's clever to do this, so they're actually getting some objective data here. They found a number of positive findings. They're actually going to tell us that they conclude that daily TENS therapy showed potential in reducing functional interference from pain, fatigue, and gaiter alterations in Long COVID individuals. Let's spend a little time in the weeds here. They're using this FDA-cleared wearable device, Quell® by NeuroMetrix Incorporated. The device was unilaterally attached to the patient's upper calf via four hydrogen pads containing an electrode array secured to a stretchable band strap. There's actually some nice images. You can see this device. It connects to your smartphone via Bluetooth. They go ahead and they do this.

Is this too good to be true? I do want to point out a couple of things. This is a pilot study. The biggest limitation this study encountered, limitations they tell us, including a small sample size and substantial missing data. We're only dealing with an n of 11 patients, we're missing a lot of data in the second unblinded phase due to challenges such as patients managing in-person clinic visits, coordinated appointments with specialists, folks having issues

participating because of brain fog. They say the prevalent brain fog hindered participants from remembering study-related tasks, including completing those questionnaires. Also, it was a short TENS therapy duration. We're not sure. It's interesting, it's encouraging but there still is a lot to learn. All right.

There's this last one, before we get to our questions, is a clever design. I think we have two more, actually. This is, Mitigating the Risks of Post-acute Sequelae of SARS-CoV-2 infection (PASC) with Intranasal Chlorpheniramine: Perspectives from the ACCROS Studies," published in *BMC Infectious Diseases*. I think if this data came out a couple of years ago, we'd all be spraying antihistamines up our noses each time we got COVID. That's what they're doing here. Here we have a prospective survey study that included 259 participants in ACCROS 1 and 3 RCTs. They compared the effect of intranasal chlorpheniramines, so squirting antihistamines up your nose versus placebo, on reduction of PASC symptoms. A PASC questionnaire containing 17 symptoms regarding the most common PACS symptoms were used.

Basically, what they're going to see is that the intranasal chlorpheniramine cohort had a lower proportion of patients with fatigue or tiredness versus placebo. Sort of a nice way they break this down, looking at the different cohorts. Encouraging, interesting. We still need a little more data, I think, on this. Also, it'd be great if we actually studied currently available products so that people can potentially use this therapy.

The last article I'll talk about, "Measurement of Circulating Viral Antigens Post-SARS-CoV-2 Infection in a Multi-cohort Study," published in *CMI*. Now, plasma and serum samples were collected from adults participating in four independent studies at different time points, ranging from several days up to 14 months post-SARS-CoV-2 infection. The primary outcome was to quantify SARS-CoV-2 antigens and they're going to look at commonly reported PASC symptoms. Now, of the 1,569 samples analyzed, 706 individuals infected with SARS-CoV-2 were positive for S1 spike or nucleocapsid. Spike was predominantly detected, and the highest proportion of samples were spike positive of those that were positive.

In total, and this is what we're going to break this down. In total, 82% of the folks that had a spike positive, that were positive, reported at least one of the 34 PASC symptoms. Cardiopulmonary, musculoskeletal, neurological symptoms had the highest reported prevalence in over half of all participants and among those participants, 43% on average were antigen-positive. Contrast this to the finding here that among the participants who reported no ongoing symptoms, antigen was only detected in 21%. The presence of antigen was associated with the presence or one or more PASC symptoms. After all the age, we're seeing about a 1.8 odds ratio so almost twice as likely. I'm going to call this another biochemical abnormality.

All right, and I will wrap it up here before we get into questions with, as I've been saying for a while, no one is safe until everyone is safe. A little bit of an update from Tanzania here, if I dare share this. There's a bit of this myth out there that, oh, in Africa, COVID was not a big thing. There were so few people died. COVID was really an issue in the West because we all have horrible diets and we don't deep-fry our foods. I have to say that a lot of ways, this was a myth derived from an information vacuum.

Here in Tanzania, I was visiting one of the hospitals and talking to some of the folks there, and they said, "Hey, this whole area here we couldn't use, we had to turn it into a COVID ward. It was full of COVID patients. We were just seeing people dying left and right of COVID but as per the Tanzanian government, we were not allowed to report anything as a COVID death." I just want to point out, don't just use numbers. Be careful of these convenient myths. COVID was terrible as we saw in the U.S. You compare Caucasian to African American and you saw about twice the mortality. It is not something that - yes.

All right. Hopefully, we can continue to combat the vacuum of misinformation and the lack of information with our science education. Hopefully, you'll continue to enjoy these. Folks, we're in December, so I want everyone to pause the recording right here. Go to parasiteswithoutborders.com. Click on Donate. We are doing our microbe.tv fundraiser right now. November, December, January we will double your donations up to potential maximum donation of $20,000 for *MicrobeTV*.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Susan writes, "Dr. Griffin, just was listening to your pre-post T-day podcast, and two things came to mind. You were talking about vaccines. My dad was a physician, graduated around 1950. As I grew up, I remember him saying many times, vaccines are certainly better for the population, not necessarily for the individual. People today generally have never heard that. The other is a quotation for you. 'This, my dear, is the greatest challenge to being alive, to witness injustice in the world and not allow it to consume our light.' That's by Thich Nhat Hanh. PS, my dad installed seat belts long before they were mandated."

DG: All right, Susan, I enjoyed that. It's great to hear about your dad being a physician and living through the period of time that you described there. Actually, I have to say that my dad also installed seat belts before they were mandated and I really appreciate that quotation, to witness injustice in the world and not allow it to consume our light.

VR: Karen writes, "I had COVID December 22, age 75, three times vaccinated. Long COVID symptoms are now slowly resolving. Smell has partially returned. Tinnitus resolves for 15 to 20 minutes a week. Bursts of quiet. Hard to evaluate energy level at this age. Will vaccination with the new variants cause the immune system to be boosted and cause return to worse symptoms of this autoimmune disease? Your show was a great comfort during the pandemic."

DG: All right, Karen, well, I am sorry to hear about your Long COVID symptoms. We're starting to get to the point where we're always behind the gun because we keep having different variants. As I presented a study up above, vaccination continues to seem to reduce your risk of getting Long COVID and to a certain degree, with the data we have available, it does look as though getting a vaccine after the fact, if you have Long COVID symptoms, is associated with resolution of those symptoms.

VR: David writes, "On this week's *TWiV* clinical update, you joked that we would never be able to pass seatbelt laws today. My father, Dr. John States, worked to pass the New York State seat belt laws. It wasn't easy back then either. He was always a car buff and worked as a race physician at Watkins Glen. As a race physician, he realized that drivers who stayed in their cars usually survived crashes, but those thrown from the car were severely injured or died.

He developed an accident injury scale and showed conclusively that the same was true for highway auto accidents as well.

Even with the data, the legislature was unmoved. What finally got the law passed was the support of Mothers Against Drunk Driving. I sincerely hope we don't repeal these laws because they save many lives each year. Airbags help, but seatbelts are probably more important. Take care, David."

Can you imagine, the legislature was unmoved? Here you give them science, you give them data. They're not scientists. They don't know how to interpret it. They're only thinking about, "Will my constituents vote for me again if I vote for this seatbelt law," is the big problem with this country.

DG: All right, David, it looks like the seatbelt comments generated a lot of email. I appreciate. We're driving around here in Africa, and I was mentioning to my colleagues that wearing the seat belts, it's common, like, "Oh, we're on dirt roads, and seat belts are not required." They may not be required, but they're certainly really important and encouraged. Everyone always worries they take their trip to Africa, are they going to die of malaria or some exotic disease? Actually, driving around unrestrained in a vehicle is one of the riskiest things you can do.

VR: Paul writes, "I'm a first-year medical student interested in infectious disease and addiction medicine. If you could wave a magic wand and have all prospective ID clinicians receive training with one to three experimental techniques at the bench, what would they be and why?" Paul is a MD candidate, class of 2028 at the UTHSC College of Medicine.

DG: All right. A hard one. I feel like I'm talking to my son, Barnaby, like, "What is the most important experimental technique? You can pick three, if that's easier, Daddy." It's really tough. I don't know if there are particular experimental techniques that are critical. PCR is one that we like to teach. Probably worthwhile doing ELISAs. You get a little bit of an understanding of how the antibody assays work, but more important than the experimental techniques, I would say, is understanding how to construct an experiment, understanding how to analyze the data, and also journal clubs. Understanding how to read the medical literature so you can move forward so that the end of your education isn't at the end of your training.

VR: Susan writes, "I was diagnosed with COVID 10 days ago and just completed five days of Paxlovid. I was just about to take the booster when I got sick. Should I get the vaccine booster now or take advantage of my current immunity and wait? Many thanks for your thoughts and for all you do. Long-time listener. Susan."

DG: All right, Susan. Yes, our recommendation here is this, wait three months. The whole idea that an infection, and I probably should have recognized this sooner, really counts in this. You get your infection, you wait three months and then you go ahead and get that vaccination.

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

DG: All right. Thank you and everyone, be safe.

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