This Week in Virology

TWiV 1030 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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Vincent Racaniello: *This Week in Virology,* the podcast about viruses, the kind that make you sick. From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1,030, recorded on July 26, 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: As you would say to Sara, "Where are you anyway, Sara?" Daniel.

DG: I am just south of Manhattan here. I'm on a boat. I'm not wearing a bow tie. It is quite hot. If my glasses, reading glasses, fog up, you know why. I'm not sure I'm quite in New York, but I can see New York City. Let me jump right into it. "The optimist thinks this is the best of all possible worlds. The pessimist fears it is true." That's by Oppenheimer. I don't know if people have gotten a chance to see that movie yet. It's interesting movie. I had to choose, was I going to watch *Barbie* or *Oppenheimer?*

VR: What a choice.

DG: Apparently, I must watch *Barbie* next. I hear *Barbie* is a little bit more uplifting. All right. RSV, the *MMWR,* "Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023," just came out. As if they heard Vincent's question when we recorded last week. As a reminder, May 2023, the FDA approved the first two vaccines for prevention of RSV, lower respiratory tract disease for use in adults, two for adults. We have an option to vaccinate, vaccinize, I like that, aged 60 or older.

VR: It's a good word.

DG: It sounds better. I've been vaccinized. The two vaccines are the RSVPreF3 that's Arexvy, like R-X-V, by GSK. That's a one-dose adjuvanted recombinant stabilized prefusion F protein vaccine, and RSVPreF, that's ABRYSVO by Pfizer. It's also a one-dose recombinant stabilized preF vaccine. Now, the Advisory Committee on Immunization Practices recommended, sounds familiar to folks, aged 60 or older may receive a single dose of the RSV vaccine using shared clinical decision making, so really echoing that. It's not necessarily for everyone.

This is going to be the first year we do this. Want to be focusing on those higher-risk individuals and then as we get more - what do we call it, real-world experience, then we're going to talk about maybe more folks getting set up for this.

All right, leprosy. Oh, my gosh leprosy. What are we doing talking about leprosy here in the United States? Aren't we safe from that? Well, in the recent edition of *Emerging Infectious Diseases*, the research letter, "Case Report of Leprosy in Central Florida, USA, 2022," appeared.

Here we read that Central Florida has accounted for 81% of cases reported in Florida and almost one-fifth of nationally reported cases of leprosy in recent years. Whereas leprosy in the United States previously affected persons who had immigrated from leprosy-endemic areas, about 34% of new case-patients during the 2015-2020, about a third appear to have locally acquired the disease. Crazy, but yes, we are seeing leprosy in people living in the U.S. with no obvious travel exposure. Several cases in central Florida demonstrate no clear evidence of zoonotic exposure or traditionally known risk factors.

In this research letter, they report a case of lepromatous leprosy in central Florida in a man without risk factors for known transmission routes. We read a 54-year-old man sought treatment at a dermatology clinic for a painful and progressive rash. The lesions began on his distal extensor extremities and progressed to involve his trunk. I love this. He denied any domestic or foreign travel, exposure to armadillos, prolonged contact with immigrants from leprosy-endemic countries, or connections with someone known to have leprosy.

He lives his entire life in Central Florida, works in landscaping, and spends long periods of time outdoors. Biopsies of multiple sites demonstrated a diffuse dermal infiltrate composed of disorganized aggregates of foamy histiocytes. Fite stain revealed acid-fast bacilli. He was referred to an infectious disease specialist who, under the direction of the National Hansen's Disease Program, prescribed triple therapy. Now, this is like something Mark Crislip will love, they conclude with, "our case adds to the growing body of literature suggesting that Central Florida represents an endemic location for leprosy. Travel to this area, even in the absence of other risk factors, should prompt consideration of leprosy in the appropriate clinical context."

VR: I don't understand, Daniel. It's one case, and they're concluding it's endemic in Florida?

DG: Yes, it seems a little much. I have to say when you look at the photos, they have a lot of photos in this article. Really, you're like, "Wow, he's missing his eyebrows. He's got really this classic lepromatous leprosy." Wonder how long it really took people to have the light bulb go off.

VR: What's the incubation period for this disease?

DG: That's one of the challenges, is, it could be a really long time, which is why it's hard to know. It could be years. It could be decades, so many years, so it's a challenge.

All right, well, COVID update. Let's move right into it. I was all excited that maybe I might have a special genetic feature that protected me. Maybe that's why I don't think I've ever had COVID when I read about that HLA-B*15:01 but then I read this article, "Blood Group A Enhances SARS-CoV-2 Infection," published in the journal, *Blood.*

Can you guess what blood group I am? I'm A+ by the way. Disturbing, but very interesting. The authors start by pointing out that the receptor binding domain of SARS-CoV-2, which facilitates host cell engagement, bears significant similarity to galectins, an ancient family of carbohydrate binding proteins. As ABO(H) blood group antigens are carbohydrates, these investigators compared the glycan binding specificity of the SARS-COV-2 RBD with galectins. Similar to the binding profile of several galectins, the Receptor-Binding Domain of SARS-CoV-2, including Delta and Omicron variants, exhibited specificity for blood group A.

Not only did each RBD recognize blood group A in a glycan array format, but each SARS-CoV-2 virus likewise displayed a preferential ability to infect blood group A expressing cells. An enhancement of SARS-CoV-2 infection, while similar incubation with a galectin that does not recognize blood group antigens failed to impact SARS-CoV-2 infection. Now, the authors conclude that these results demonstrate that SARS-CoV-2 can engage blood group A, providing a direct link between ABO(H) blood group expression and SARS-CoV-2 infection.

Open access and just for fun I do, encourage people to take a look at the figures. I have to say, I'm not sure I quite understand how this engagement facilitates entry of the virus.

VR: It's already engaging ACE2. What is this doing?

DG: Yes, try to figure out how this enhances that binding or somehow how this leads to. Despite this impressive affinity, the really nice figures. As an A+ person, I'm liking to not believe that this is really relevant for me, of course.

All right, also a chance to discuss wastewater with the article, “Predicting COVID-19 Incidence Using Wastewater Surveillance Data, Denmark, October 2021-June 2022,” published in *Emerging Infectious Diseases*. How helpful is wastewater monitoring in actually predicting incidence of COVID-19?

Could it be just one person's dumping a whole lot in there and that makes us worry? Is it really a reliable indicator? Well, the authors start by pointing out that while analysis of wastewater is used in many settings for the surveillance of SARS-CoV-2, it remains unclear how well wastewater testing reflects incidence. Do the levels, as I say, reflect just a few people? Maybe one particular person getting lots of RNA in the wastewater? Or is there really a connection with incidence in people? They had to look when people were still testing. Denmark has had an extensive wastewater analysis system that conducts three weekly tests in about 200 sites and has 85% population coverage. The country also offers free SARS-CoV-2 PCR tests to all residents, that might be past tense at this stage. In this study, they found that wastewater data combined with information on circulating variants and the number of human tests performed closely fitted the incidence curve of persons testing positive. The results were consistent at a regional level and among a subpopulation of frequently tested healthcare personnel.

They conclude that these results imply that data from a large-scale wastewater surveillance system can serve as a good proxy for COVID-19 incidents and for epidemic control, so encouraging for those of us that actually have a wastewater system to surveil. All right. Now, I wanted to, as I move through my COVID active vaccination section, I wanted a quick plug for *TWiV* 1028, 1,028, How do I say that?

VR: Whatever you want.

DG: Asymptomatic SARS-CoV-2 infection and T-cells, a great discussion and deep dive into that paper, "A Common Allele of *HLA* Associated with Asymptomatic SARS-CoV-2 Infection." I briefly mentioned this last week, but this is what I really like. It really got me thinking. I like the idea that in certain individuals, T-cells are what are responsible for asymptomatic infection. Do we really need a mucosal vaccine with boosting every three to four months? Or an *HLA* optimized T-cell targeting vaccine with years of durability to prevent COVID-19?

VR: That's a good question because these individuals had previous infection with common cold coronaviruses and there's a T-cell epitope that cross-reacts, right?

DG: Yes.

VR: Common cold infection is enough to do it, but it's not 100%, right?

DG: Sounds interesting, yes. That was sort of the deep dive. Like if you had, if you are homozygous, if you also had some other HL-I's, but yes, you never got to 100%. We're certainly nowhere near 100% when it comes to some mucosal-boosted vaccine that keeps people from having asymptomatic. All right, just another idea to be working on, there's so much science that needs to be done and we will move into COVID early viral upper respiratory non-hypoxic phase. Number one, person tests positive, Paxlovid. Well, the article, "Prevalence of Low-Frequency, Antiviral Resistance Variants in SARS-CoV-2 Isolates in Ontario, Canada, 2020-2023," was published in *JAMA Network Open*.

This is this whole question. Once Paxlovid is being used or not being used, are we going to see a lot of resistance? Now, these are the results of a retrospective cohort study conducted at four laboratories that serve community hospitals, academic tertiary care centers, and COVID-19 assessment centers in Ontario, Canada. Participants included symptomatic or asymptomatic patients who tested positive for SARS-CoV-2 virus, and submitted virus samples for diagnostic testing between March 2020 and January 2023.

Samples with sufficient viral load underwent next-generation genome sequencing to identify low-frequency antiviral resistant variants that could not be identified through conventional sequencing. This study included 78,866 clinical samples with next-generation whole-genome sequencing data for SARS-CoV-2. Low-frequency variants in the viral *nsp5* were identified in (0.16%), so a fraction of a percent, with no single variant associated with antiviral resistance predominating. Percentages from each laboratory were similar, all of them being less than 1%. Let me break this down.

For starters, *nsp5,* did I lose you? This is the gene that encodes the main protease, the M^{Pro} of SARS-CoV-2. We are here looking at nonsynonymous mutations, so changes in RNA that change the amino acids in the protease that is targeted by Paxlovid, then a few caveats. We may not see much here because the use of Paxlovid has been relatively limited in Ontario. We hear because of an initially limited supply of the drug government restrictions and prescribing guidelines, not to mention all the forest fires, which could have limited the selective pressure placed on the virus.

On the other side, variants detected at low frequencies could be due to artifacts of this sequencing process. Also, I will say if you look at the supplemental data, and by the way, don't just read the title, don't just read the abstract, don't just read the paper, got to look at supplemental data too. We see that they did not observe more variation in residues that are known to interact with Paxlovid compared with other residues.

VR: I think there's another possibility, which is that these resistance changes confer low fitness to the virus and so they don't spread.

DG: Yes, I mean that'll be a challenge going forward when we actually see a lot of Paxlovid being used. Is there any kind of a resistance variant that-? Well, I think we talked about with malaria insecticides, like some changes have fitness and we would expect there to be fitness costs to doing this. All right, remdesivir, so good news for Paxlovid so far. What about remdesivir? "Viral Resistance Analyses From the Remdesivir Phase 3 Adaptive COVID-19 Treatment Trial-1 (ACTT-1)," was published in *JID*, and here is the SARS-CoV-2 resistance analyses from the Phase 3 randomized placebo-controlled trial conducted in adult participants hospitalized with COVID-19.

Among participants with both baseline and post-baseline sequencing data, emergent Nsp12 substitutions were observed in 38.7% and 40% of participants in the remdesivir and placebo arms. Respectively. 38.7% got remdesivir, 40% got placebo. They found minimal change in remdesivir susceptibility among tested substitutions supporting that there is a high barrier to remdesivir resistance development in COVID-19 patients. Reassuring news, we're not seeing much concern as far as resistance with Paxlovid. We're not seeing much concern with regard to resistance with remdesivir. But what about molnupiravir, Thor's hammer, much maligned?

Well, the article, "Impact of Molnupiravir Treatment on Patient-Reported Coronavirus Disease 2019 (COVID-19) Symptoms in the Phase 3 MOVe-OUT Trial: A Randomized, Placebo-Controlled Trial," recently published in *CID*. This is a post hoc analysis of participants' self-reported symptoms in the MOVe-OUT trial, which evaluated molnupiravir initiated within five days of symptom onset in nonhospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed COVID-19. Eligible participants completed a 15-item symptom diary daily from day one, and they were randomization, through day 29, rating symptom severity as none, mild, moderate, or severe.

Time to sustained symptom resolution/improvement was defined as the number of days from randomization to the first of three consecutive days of reduced severity, without subsequent relapse. Time to symptom progression was defined as the number of days from randomization to the first of two consecutive days of worsening severity. When evaluating median time to alleviation of all symptoms for COVID-19, molnupiravir participants had a shorter median time to sustained alleviation of symptoms, but it was really tiny. Median time to alleviation of all symptoms was eight versus 10. Median time to sustain was 15 versus 16.

Where are we with molnupiravir? Well, the systematic review of, "Molnupiravir for Treatment of Adults with Mild or Moderate COVID-19: A Systematic Review and Meta-analysis of Randomized Controlled Trials," was recently published in *CMI*. Here, after reviewing a number of databases, the authors included nine randomized controlled trials

enrolling 30,472 participants. Majority of the patients were outpatients with a mean age ranging from 35 to 56.6 years in adult patients with mild or moderate COVID-19.

Molnupiravir probably reduces mortality by about 57%, relative risk of 0.43. Probably reduces the risk of hospital admission by 33%, relative risk 0.67, and probably time to symptom resolution or clinical improvement. And in the studies, the mean difference was about 2.39 days. Molnupiravir probably does not increase serious adverse events, so it is probably a safe agent to be used.

All right, convalescent plasma, not to leave that off the list, and remember, avoid doing those harmful and useless things. Early inflammatory, lower respiratory hypoxic phase, the cytokine storm, this is that second week. Number one, steroids less than 94% oxygen saturations, pulmonary support. Several times, we've discussed how important proper pulmonary support is for patients who have a severe enough second week or early inflammatory phase that they require pulmonary support. This might be as simple as a few liters per minute of oxygen delivered by nasal cannula or as aggressive as ECMO. There's a growing use of high-flow nasal cannula where a patient gets tens of liters of oxygen per minute delivered through these large-bore nasal cannula prongs.

The article, “Delayed Intubation Associated with In-hospital Mortality in Patients with COVID-19 Respiratory Failure Who Fail Heated and Humified High Flow Nasal Canula,” was recently published in *BMC Anesthesiology*. We've talked a little bit about these issues, and maybe we'll call it a survivor bias or selection bias. These are the results of a retrospective multi-center observational cohort study of 2,720 patients treated, initially managed with high-flow nasal canula within the Banner Health care system. They assess the effect of the duration of the high-flow nasal canula prior to intubation on mortality.

You're going to look at folks, you're going to say, OK, these are folks that you started high flow nasal canula. You say, "Let's just intubate," versus folks where you kept going past a period of time. When they adjusted for covariates, high flow nasal canula duration less than 24 hours prior to intubation was significantly associated with reduced mortality. These are people your putting them on, and then you're going to potentially end up intubating, or putting it another way, being on high flow nasal canula for more than 24 hours prior to intubation was associated with twice the odds ratio of dying.

All right. Also, in hospital, remdesivir, if you're still in the first 10 days, having been hospitalized, this is, I think, an important place to put this in. Recently, they have changed the approval for remdesivir, and now the FDA approve remdesivir for COVID-19 treatment in patients with severe renal impairment, including those on dialysis, so don't have to worry about the renal function even if they're on dialysis. This approval for use in patients with severe renal impairment was based on results from a Phase 1 study as well as results from the Phase 3 REDPINE trial that demonstrated the pharmacokinetics and safety profile of Veklury – remdesivir - in this population.

All right, this is maybe my favorite this week, so drum roll, get focused. I know we're getting to that point where attention starts to wane. The article, “Relationship Between Azithromycin and Cardiovascular Outcomes in Unvaccinated Patients with COVID-19 and Preexisting Cardiovascular Disease,” was published in the *Journal of the American Heart Association*. To

my ongoing dismay, the authors start by pointing out that empiric antimicrobial therapy with azithromycin is highly used in patients admitted to the hospital with this viral disease called COVID-19, despite prior research suggesting that azithromycin may be associated with an increased risk of cardiovascular events.

The study was conducted using data from the ISACS-COVID-19, (the International Survey of Acute Coronavirus Syndrome COVID-19) registry. Patients with confirmed diagnosis of SARS-CoV-2 infection were eligible for inclusion. The study included 793 patients exposed to azithromycin within 24 hours from hospital admission and 2,141 patients who received only standard of care. Interesting. Standard of care without the azithromycin. The primary exposure was cardiovascular disease. Main outcome measures were 30-day mortality and acute heart failure. Among 2,934 patients, 1,066, or 36.4%, had preexisting cardiovascular disease.

In this COVID-19 cohort study, azithromycin therapy was consistently associated with an increased risk of acute heart failure and death in patients with pre-existing cardiovascular disease.

VR: Can we get this message out, Daniel?

DG: I think we need to get it out. It's amazing that people feel like it's innocuous. I don't know. All right, the late phase, Long COVID, not happy with the results here. The article, "The Effects of COVID-19 on Cognitive Performance in a Community-based Cohort: A COVID Symptom Study Biobank Prospective Cohort Study," was published in *eClinicalMedicine*. Basically, what is happening here is they're using this symptom study smartphone app, they're following thousands of people for a period of time. The effects that they're seeing were comparable to hospital presentation and followed over time.

They're seeing about a 10-year age difference in the cognitive hit that some of these folks are getting, and the longitudinal analysis showed no evidence of cognitive change over time, suggesting that cognitive deficits for affected individuals persisted almost two years since initial infection in the study. Now, I want to put that kind of in context of the fact that, as we repeatedly say, in a number of other studies have shown, the natural history of this disease tends to be improvement, so not sure this is consistent with a lot of what we're saying but I did want to make sure I shared this.

On a more positive note, as we near the end here, we have the publication in *eClinicalMedicine* of the article, "Clinical Phenotypes and Quality of Life to Define Post-COVID-19 Syndrome: A Cluster Analysis of the Multinational, Prospective ORCHESTRA Cohort." We are really seeing a theme as these investigators present the results of a prospective multi-center cohort study conducted from February 2020 to June 2022 in five countries, enrolling SARS-CoV-2 out- and in-patients followed at three, six, and 12 months from diagnosis.

Here, they're looking at clinical and biochemical features, antibody response, which Variant of Concern, physical, mental quality of life. The outcome of interest was identification of risk and protective factors for PCS, so Long COVID, by clinical phenotype settings, severity of disease, treatment, and vaccination status. They used a questionnaire to assess the evolution of the quality of life. They identified four clinical phenotypes: A chronic fatigue-like syndrome,

(fatigue, headache, memory loss); a respiratory syndrome, (cough, dyspnea); a chronic pain syndrome, (arthralgias, myalgias); and a neurosensorial syndrome (alteration in taste and smell).

I will wrap it up there. We're getting right near the tail end. This is, I think, the last episode we'll record for our Foundation for International Medical Relief of Children. No one is safe until everyone is safe. Pause the recording right here, go to parasiteswithoutborders.com, click on that 'Donate' button, help us get to that point when we can donate $20,000 to FIMRC.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Mary writes, "I'm 72 with an autoimmune condition but otherwise healthy, vaccinated five times, most recently in May. I have not had COVID, I'm sure because I continue to mask, I don't eat indoors. In other words, it's unlikely that I encounter the coronavirus in my daily life, and I live alone. Most of my friends and neighbors no longer take any precautions, and now that at-home tests are no longer freely available, nobody tests before social events.

My question is this, if I socialize with someone who doesn't have any symptoms, including some they might attribute to allergies or a common cold, how safe am I if they have asymptomatic COVID if I mingle unmasked? I remember that during the initial phase of the pandemic, asymptomatic spread was a major source of illness, but that was before vaccines were available.

DG: You make a great point. The first thing I will point out, this is the reassuring truth, is that at least in many areas right now, there's a lower incidence of SARS-CoV-2, of COVID-19, than we've seen previously. We're also getting down to 600 or 700 deaths per week here in the U.S., which is a low number relative to where we've been, so now is a safer time. A lot of us are worried about December, January, as we get into those times. Also, a lot of opportunities for socialization can be done outdoors, so that is safer.

No, this is a challenge for high-risk individuals for those 600 or 700 people that died this week. Those 600 or 700 people died this week that was not mild by any extent so yes, you're really presenting a lot of the challenges. People who have symptoms that might be COVID-19, they're not going to necessarily test because of all the things you mentioned.

VR: I think you could easily spread asymptomatically, right, Daniel?

DG: I think it's a huge issue. Maybe I applaud my son Barnaby and my daughter Eloise because when we went to see *Oppenheimer*, I had in my back pocket, which I then distributed before we entered, N95 masks which everyone wore while we watched the movie.

VR: Matthew writes, "Can you please review recommendations for use of antiviral therapies in pregnant patients with COVID 19? I recently had a case where I recommended treatment, but the patient's obstetrician told her not to take Paxlovid because "she would do just fine"?"

DG: Yes, that's the big challenge. I'm not sure how we get it through to these people. Do you have to make the phone call when one of their patients doesn't do fine and then dies? Paxlovid is recommended by your professional society, by the way, because being pregnant, getting COVID 19 is a high-risk situation. That's all a big thing. A lot of people will probably be just fine, but the people that are not just fine, once that window closed, you've missed that

opportunity. Paxlovid is recommended during pregnancy. Remdesivir is recommended during pregnancy. That would be the recommendation is to actually go forward with that.

VR: Eli writes, "I just learned that CMV is the most common cause of non-genetic birth defects in the U.S. Some European countries screen pregnant women for CMV, some do not. The U.S. does not screen. Should U.S. pregnant women be informed of the risk? When European screening finds a positive, what then?"

DG: Yes. That is a challenge. The “what then” part of it. When you do the screening, let's say you find out that someone is already CMV positive, but what if someone is CMV negative? What exactly goes into the warning of, "Hey, now you're at high risk? What modification in behavior would you recommend? What modification in behavior is evidence-based?" No, this is actually quite a challenge that you bring up.

VR: In Europe, they don't do anything when you're positive, right? There's nothing to do.

DG: Well, I think the thing, the challenge is acquiring CMV during the pregnancy. If you've got it ahead of time, you've already gotten through it, you already have immunity, you're better off. The challenge is a CMV-naive woman acquiring it during pregnancy.

VR: Well, if you do and it's picked up, right? What would be done?

DG: No, then potentially there could be treatment, but you'd have to really catch it.

VR: Yes, that's hard. All right. Ryan writes, "I saw a study going around Twitter a few weeks ago that showed Paxlovid rebound was much more likely if people started right away, rather than waiting three days after symptoms began. Do you have any recommendations based on the study?" The new journal, Twitter, Daniel?

DG: The new journal Twitter. You got to actually go ahead, write us, send us the actual article that people are talking about as opposed to the thing that is going around on Twitter. Happy to look through it, happy to have an open mind, but as we've seen repeatedly, people are not more likely to have that second week, that early inflammatory phase when they get an antiviral. Actually, the point of the antivirals is not necessarily to prevent that second week, it's to prevent hospitalization, prevent death, ending up on a ventilator. Yes, if there's a good study out there, this would be novel based on history and everything else we know, but happy to send it our way. Let us take a look at it.

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

DG: Oh, thank you, and everyone be safe.