This Week in Virology

TWiV 990 Clinical Update

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Guest: Daniel Griffin

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

[music]

VR: From MicrobeTV, this is *TWIV, This Week in Virology*, Episode 990, recorded on March 8th, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me tonight from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Daniel, is winter over? Is the respiratory virus season over yet?

DG: RSV, flu, some of them were on the downslope, which is nice. COVID, we'll get to but let me hit right into the quotation. “So we beat on, boats against the current, borne back ceaselessly into the past.” That's by one of my favorite authors, F. Scott Fitzgerald, from one of my favorite books, *The Great Gatsby*. I have to say this has been a challenging week where history seems to be in the midst of being rewritten, and I feel like it is like *Groundhog Day* but in a bad way.

Again stepping right in the same puddles and told that water's actually not wet. Let's start with the viewpoint confronting the evolution and expansion of anti-vaccine activism in the USA in the COVID-19 era published in *The Lancet.* It's an article by several of our friends including one of our directors at Parasites Without Borders, Peter Hotez. It's interesting and informative. It's a quick read. This is not a big thing to bite off. It points out that how over the past two decades anti-vaccine activism in the USA has evolved from a fringe subculture into an increasingly well-organized networked movement with important repercussions for public health.

The COVID-19 pandemic has exacerbated this evolution and magnified the reach of vaccine misinformation. There's several recommendations on how to address this great problem in the article, but it's worth looking at. I think this making our jobs more and more difficult as we face the victims of this coordinated misinformation campaign.

Influenza, the article, “Effectiveness of Maternal Influenza Vaccination in Peru PRIME Cohort,” was published in the journal, *Open Forum Infectious Diseases*. This adds to the

tremendous corpus of evidence that getting vaccinated during pregnancy is safer than not getting vaccinated.

I do appreciate many OBs and many who are pregnant have questions about vaccination during or even while they're planning to get pregnant. It's reasonable and responsible, but it's important that these decisions and the advice given be based on what we know, not fear, rumors or misinformation. In this study, women at less than 28 weeks gestation were enrolled from four tertiary-level hospitals in Lima, Peru, at the start of the 2018 influenza season and followed until the end of their pregnancies.

Participants had mid-turbinate, those pretty deep swabs there, collected and tested for influenza by RT-PCR with onset of greater than or equal to one myalgia, cough, runny nose, nasal congestion, sore throat or difficulty breathing, so symptomatic. In this case, they followed 1,896 women for a median of 127 days. Forty-nine percent of these women were vaccinated and the participants vaccinated against influenza had more than 50% lower incidence of RT-PCR-confirmed influenza illness. Just showing the effectiveness of keeping these to-be moms healthy during the pregnancy.

Norovirus, if you look closely maybe there's a little bit of a drop here. Have we reached the peak? We will say, but we are even higher than we were when we recorded last week.

Moving right into COVID. Children, COVID and other vulnerable populations. Children at risk from COVID and Long COVID, as we'll see here, the article, “Characteristics and Predictors of Persistent Symptoms Post COVID-19 in Children and Young People: A Large Community Cross-sectional Study in England,” was posted in *Archives of Disease in Childhood*. This is a *BMJ* journal, another study looking at the prevalence of an associated risk factors for persistent symptoms post-COVID-19 among children aged 5 to 17 in England. They reported 4.4% of the 5-to-11-year-olds, 13.3% of the 12-to-17-year olds with prior symptomatic infection, still having at least one symptom past those three months post-COVID-19. Those are much more reasonable numbers than some of the others we've heard. They then reported that 13.5% and 10.9% respectively reported their ability to carry out day-to-day activities was reduced a lot due to their symptoms.

These are significant symptoms. That gives us about 1% of these kids still with significant symptoms impacting their day-to-day activities at more than three months post-acute COVID-19. What are these symptoms. The most common where persistent coughing 27%, headaches 25%, loss or change in sense of smell 52%, taste 41%. Higher age and having a pre-existing health condition were associated with higher odds of these persistent symptoms. Lots of limitations here, just as so many of these studies have, no control group.

I ask is there such a thing with almost all our children having had COVID? Even if you found those rare children that did not get COVID, would they really be masters or something unique there? Also these are mostly Caucasian children in England answering a survey. From my perspective more reminder that Long COVID in children is still not fully understood. For those thousands of children still suffering, it remains urgent to understand.

The article, “Parental Non-Adherence to Health Policy Recommendations for Prevention of COVID-19 Transmission Among Children,” was published in *JAMA Network Open*. This may

surprise you, Vincent, and our listeners, but they found in this survey of 150 participants, 25.9% they say reported misrepresentation or non-adherence in at least one of seven behaviors. The most common behaviors were not telling someone who was with their child that they knew or thought their child had COVID-19, 24%, and allowing their child to break quarantine rules that was 21%. There's a nice table where they go through the different things, lying about whether or not your child had COVID and then having someone be exposed saying their child was vaccinated, not vaccinated, lying about age to get vaccinated.

The most common reason reported for this misrepresentation, I'm going to use that in the future. I didn't lie. I misrepresented the truth. The most common reason was wanting to exercise personal freedom as a parent. Really? OK. I'll have to tell my children one day when you grow up you'll be allowed to exercise personal freedom as a parent but in the meantime, please stop lying. Additional reasons include wanting their child's life to feel normal and not being able to miss work or the responsibilities to stay home. This was just all across, there weren't any specific characteristics that were associated with lying.

Remember how we all learned that COVID was caused by a virus and antibiotics are not helpful with viral infections? The article, "Community-onset Bacterial Coinfection in Children Critically Ill with SARS-CoV-2," was published in *Open Forum Infectious Diseases,* with 63% receiving empiric antibiotics, but only 7% had a bacterial co-infection and only 3% were respiratory bacterial co-infection. This is a challenging article because often in children or adults, if they're critically ill, we will err on the side of antibiotics till we know or sort it out. Not necessarily pointing fingers here, just pointing out the situation.

Pre-exposure transmission testing, have a plan. Remember those masks only work if you wear them. Remember ventilation transmission, and we're going to have an article about that either this or next week. Active vaccination, we've discussed previously that there's an interest in making COVID vaccinations simple and relatively uniform, same composition for each vaccine, standardization of dosing regimen. This week we heard that Pfizer BioNTech is seeking U.S. authorization for their updated COVID bivalent vaccine as a booster in kids 6 months to under 5.

The Omicron adoptive vaccine is currently authorized by the U.S. health regulator as the third dose of the three-dose primary course of vaccination in the country for children in this age group. This would just add probably this yearly booster to that age group as well. I should say these companies are requesting that the Omicron-adapted formulations move from EUA to full licensing. That's going to be critical come May when the health emergency may be ending.

People may have heard that Britons aged over 75 will be offered COVID-19 booster shots this spring. Not everyone, it's Britons over age 75. Those in care homes are going to be offered these booster shots. We heard this from Britain's vaccine advisors, Tuesday 3/7. That's the Joint Committee on Vaccination and Immunization, JCVI. They're also planning on an autumn boosting program.

We also have the preprint this week, "Bivalent Booster Effectiveness Against Severe COVID-19 Outcomes in Finland September, 2022-January 2023," posted on *medRxiv.* Really we see

here just more evidence of a temporary two-to-three-month boost above the baseline enduring wall of protection.

I want to point that out. The boosts are bumping things up but only for about two to three months. This is above. This is comparing to people with that enduring protection from getting that full, I'm going to say three-dose vaccine series. Moving into COVID, the early viral upper respiratory non-hypoxic phase. This is, you've gotten sick, you test positive. What about reinfection and reinfections with the vaccine thrown into the mix? This is another preprint, "Viral Kinetics of Sequential SARS-CoV-2 Infections," posted on *medRxiv*.

I never really mind preprints if I actually get to see the data. Here we get the data, looking at 94,812 individuals and comparing the SARS-CoV-2, they say viral kinetics, but I think we should say PCR kinetics, of first versus second infections, adjusting for viral variant vaccination status and age relative to first infection. Second infections usually featured a lower peak RNA level and faster clearance time, especially in individuals who received a vaccine dose between their first and second infections.

They do this where they put one on top of the other where they have a figure AB and were looking at A is the first and B is the second, and they're right on top. You can see that earlier peak for first infection, slightly later peak with second infection, not quite as high with second. They actually then look at the impact of vaccination and the pre-Omicron C and E in their thing. Then they look at the impact during Omicron. Nice figure actually to look at the data.

All right. Now, what do we know? Evidence-based number one, Paxlovid; number two, remdesivir, molnupiravir right after that. I'm going to throw convalescent plasma in each week. Remember this is an option in some circumstances.

Current EUA only for immunosuppressed individuals. This is COVID-19 convalescent plasma CCP with high titers of anti-SARS-CoV-2 antibodies. Estimated 37% reduction in mortality in the immunocompromised based on a review of trials. As the IDSA reminds us, this is not for hospitalized patients during that second week, this is really within the first, they say eight days. The best date is within the first three days. In most situations, this is going to be an outpatient or someone who's hospitalized during that first week. Vincent has pointed out, if you're having issues, let us know. Dr. Arturo Casadevall will come to the rescue. How should they reach out to you and then y'all connect them?

VR: Yes, vincent@microbe.tv, and I'll connect you with Dr. Casadevall. He wants to take care of it himself.

DG: [laughs] That is fantastic. Impressive individuals like that will - the unpaid effort that he and others have during the last three years. Remember, there are individuals for whom this is appropriate therapy. Keep that in mind and avoid doing those harmful, useless things. Then we get into the second week, the early inflammatory, lower respiratory hypoxic phase. The cytokine storm, let us return to the original terminology and stop calling this the rebound stage. No rebound here. One steroid at the right time in the right patient.

A word of caution regarding those steroids. The article, "Risk of Coronavirus Disease 2019 and Associated Pulmonary Aspergillosis Based on Corticosteroid Duration in Intensive Care

Patients," published in *OFID*. Right up front is the comment that these are the results of a retrospective cohort study of adult patients with severe COVID-19 pneumonia requiring mechanical ventilation who received at least three days of corticosteroid treatment. Not an RCT and all those caveats. The patients here that get more or less than 10 days, they're not the same.

A total of 278 patients were included. 169 were in the less than 10 days. 109 were in the greater than 10 days. I did the math. I think that adds up. The coronavirus disease 2019-associated pulmonary aspergillosis CAPA developed in 7.2% of all the patients. If you divide them, those that got greater than 10 days versus less, that was 11.9 versus 4.1. The odds ratio of 3.17. People that got more than 10 days were more than three times likely to get the COVID-19-associated pulmonary aspergillosis. Secondary outcomes, inpatient mortality, 77% versus 43%. Secondary infections, 44.9 versus 28.4. I do want to point out, this is a word of caution, but these patients are different.

We don't willy-nilly keep people on more than 10 days. If you're keeping someone on more than 10 days, there's probably something going on. They're not responding well. Here we're seeing this associated issue. Anticoagulation pulmonary support, Remdesivir, if it's early enough, immune modulation good old tocilizumab, the article, "Immunomodulators for Severe Coronavirus Disease-2019 in Transplant Patients: Do They Increase the Risk of Secondary Infection?" This was published in *Transplant Infectious Disease*.

While current guidelines recommend immune modulators such as tocilizumab or baricitinib for the management of severe COVID-19 in patients with increasing oxygen requirements, many do avoid using these in transplant recipients, folks that are immunocompromised with concerns that they already have an immunosuppression is going to trigger more complications or secondary infections. These are the results of a retrospective cohort study of transplant patients with severe COVID-19 between April 2020 and January 2022 at the Mayo Clinic. The primary outcome was incidence of secondary infections after COVID-19. Secondary outcomes were 90-day mortality, ventilatory days and thromboembolic events, and they found no significant difference in the incidence of secondary infections between those who received or did not receive an immunomodulator.

I will point out, there was no difference in 90-day mortality. We're actually not seeing the benefit there which is not seeing the harm that people were concerned about. All right, moving into, and this is a lot, this week the late phase PASC or Long COVID. Number one, we've got the article, "Long-term Cardiovascular Outcomes in COVID-19 Survivors among the Non-vaccinated Population: A Retrospective Cohort Study from the TriNetX US Collaborative Networks," published in *eClinicalMedicine.* Here they're saying this is going to address the recurring issue of the risk of infection and unvaccinated unprotected versus getting vaccinated.

This study looked at the long-term cardiovascular outcomes in unvaccinated COVID-19 survivors. People, I even had this conversation earlier this week about, "Oh, I hear these vaccines and these heart issues." What about COVID-19 and these heart issues? They reported increased risks of cerebral vascular diseases such as stroke hazard ratio of 1.618, arrhythmias such as AFib hazard ratio of 2.4, inflammatory heart disease such as myocarditis 4.4, ischemic heart disease such as ischemic cardiomyopathy, 2.8, heart failure, 2.3. Clotting

disorders such as pulmonary embolism has a ratio of 2.6 and the risk of two composite outcomes, major adverse cardiovascular events, 1.87, any cardiovascular outcome, 1.55. All higher in COVID-19 survivors than in the controls.

The survival probability of the COVID-19 survivors dramatically decreased in all the cardiovascular outcomes. I have to say, these can be devastating. I was taking care of a woman early this week. I've seen her now repeatedly, and she actually developed severe myocarditis after her COVID-19, now has heart failure. This was a young, that's people who are half my age or so, a young nurse who got infected on the job, and now she's debilitated and has these frequent CHF exacerbations and arrhythmias.

Also the article, “Cardiac Abnormalities in Long COVID One-year Post-SARS-CoV-2 Infection,” published in *Openheart,* a *BMJ* journal. Here they looked at 534 individuals with Long COVID and found that cardiac magnetic resonance abnormalities occurred in one in five individuals with Long COVID at six months, persisting in over half of those at 12 months. Interesting. If you look through this article, you're not really finding the issue doing blood work, but they actually, when they did the cardiac MRI, they saw these abnormalities.

Also the original investigation, I guess, as opposed to an unoriginal investigation, “One-Year Adverse Outcomes among U.S, Adults With Post-COVID-19 Condition versus Those Without COVID-19 in a Large Commercial Insurance Database,” was published in *JAMA Health Forum*.

These results of a case-control study of 13,435 U.S. adults with post-COVID-19 condition and 26,870 matched adults without COVID-19. I'm wondering where they found those 26,870 matched adults without COVID-19. Anyway, they reported that the adults with post-COVID conditions experienced increased risk for a number of cardiovascular outcomes such as ischemic stroke. During the 12-month follow-up period, individuals with post-COVID conditions were more than twice as likely to die, with 2.8% of them dying before one year had passed. I found this shocking if a person had passed, they have a one in 35 chance of not surviving the year. Just spend a moment on this.

First off, for an acute COVID infection, median recovery time for mild cases is about two weeks, for severe cases is six weeks. I'd like to point out not five days, but two or six weeks. Some folks continue to have issues past those six weeks, even past three months. They even excluded people that died in the first 30 days. Feel free to add that 1% or 2% case fatality rate. Now you're getting an extra 2.8% if you start looking from one month out to 12 months.

All right. The article, “Long-Term Gastrointestinal Outcomes of COVID-19,” was published in *Nature Communications*. Here the investigators use the U.S. Department of VA national healthcare databases to build a cohort of 154,068 people with COVID-19, 5,638,795 contemporary controls, 5,859,621 historical controls, to estimate the risks in one-year burdens of a set of pre-specified incident gastrointestinal outcomes.

They reported that beyond the first 30 days of infection, people with COVID-19 exhibited increased risks and one-year burdens of incident gastrointestinal disorders motility disorders, dyspepsia, GERD, peptic ulcer disease, functional intestinal disorders, acute

pancreatitis, hepatic, and biliary disease. They have really nice figures where you can actually see all the different issues. Some of them are symptomatic and diagnostic-based, but some of them are actually biochemical abnormalities with pretty significant excess burden.

I am going to close this out here by saying what I always say. No one is safe until everyone is safe. I do want everyone to pause the recording right here and go to parasiteswithoutborders.com and click “Donate.” Every small and large amount helps. We're now having our American Society of Tropical Medicine and Hygiene fundraisers, so February, which has passed. We're now into March and April. Donations will be matched and doubled up to a potential maximum donation of $30,000 from PWB to ASTM&H. We're not doing well. People, you got to click. You got to help us continue to do what we do.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Here's one that relates to an article you just talked about at the top, Daniel.

Jamie writes, "I'm nine weeks pregnant. At my first OB visit, I asked when I should get my COVID booster. My provider said they were not recommending boosters in general. She didn't give specifics, just there was no confidence that we need them. I have had three Pfizer vaccine shots. I had COVID in November '22. I'm generally healthy 42-year-old woman. What do you recommend??

DG: It's reminding me of a tweet I saw where it was something about those that have issues with pronouns are so quick to embrace they. My first question would be, who are they? Who's this they they're not recommending? I think there's a growing amount of evidence that if an individual is pregnant and they get that booster during the last trimester, and we discussed this article last week, not only are they going to protect themselves but that protection is going to actually translate into protection for the child for the first six months of their life. I would say the science supports you are safer, your child is safer getting that booster during the third trimester.

VR: Sol writes, "Dr. Griffin, when you talk about death rates in children, are there any data on underlying conditions for this group? Immunocompromised, diabetes, et cetera? Do we know what percentage are previously healthy children?"

DG: We've talked a little bit about those folks that end up in the hospital. Good data on that. About half of the kids that end up hospitalized have no underlying conditions. I think that's something to point out. We do also know that being unvaccinated, that tends to be the vast majority of those folks, but then the folks that are at higher risk of death are going to be individuals that have other issues going on. Maybe heart disease, maybe Down syndrome, things like that.

VR: Alan writes, "There’s a young physicist, Dianna Cowan, who has become well known and well-loved for her educational physics videos over the last several years. She has Long COVID and her condition has lately deteriorated to the point where a friend made a video as a way to keep her wider circle of friends informed. It's hard to watch.

The situation is obviously a difficult and emotional one for her husband and family, but I'm writing this because despite carefully following *TWiV*, taking Vincent's course online twice,

and keeping up with clinical updates, I had not been aware that ME/CFS could become life-threatening for a relatively young, energetic and active individual like “Physics Girl.” If you have any guidance to offer, even some insight into how this comes about, I would appreciate it and be happy to pass it along."

DG: I had heard that “Physics Girl: was suffering from Long COVID and had this ME/CFS constellation of issues. I have to say, I was quite upset when I heard that. I'm a fan, by the way, of “Physics Girl” as many of us are in the science community. As I've tried to point out every time, we are learning, there's a lot of research going on. I actually take care of a number of people with Long COVID. If any our listeners know “Physics Girl,” have her reach out. She could shoot an email to vincent@microbe.tv or daniel@microbe.tv

VR: Yes.

DG: If there's anything I can do - because we can help these individuals. I think that that's an important thing. This is not hopeless. Sure, we don't know as much as one day we will know, but there certainly are things that we can do.

VR: Zain writes, "Just wanted to bring up this study, which is our Ontario experience on off-label dosing of Paxlovid for chronic kidney disease dialysis. Reduced dose Paxlovid was very effective here and in fact, has been our standard for CKD patients requiring therapy. Remdesivir is really hard to come by locally outside of transplant, and molnupiravir was not approved in Canada so this seems to be a really nice way of getting Paxlovid to those high-risk CKD patients." We have a link to an article that you'll be able to find in the show notes.

DG: Oh, that's great. Well, thank you for sharing.

VR: Finally Donald writes, "I didn't say anything the first time Daniel mentioned norovirus and alcohol-based hand sanitizers, but since he's mentioned it twice, I feel the need to correct some misperception on alcohol-based hand sanitizers and norovirus. While it's true the conventionally formula--" and I want to say that, "While it's true that conventionally formulated," I don't know where the misperception is, Dr. Shaffner. "While it's true that conventionally formulated alcohol-based hand sanitizers have limited effectiveness against non-enveloped viruses, including norovirus, there is research in the published literature which indicates that these products can be reformulated to have greater efficacy."

He gives two links to papers. "These products are available for sale, are used in some restaurant chains, Chipotle, for example, as well as by some cruise lines. While hand washing is always a good idea, it's certainly not magic. Published data indicates that hand washing removes 99% of microorganisms on hands,(2 log reduction), while feces may contain 9 logs of virus particles per gram.

DG: Now, this is helpful. There should be some labeling that should have super power alcohol cleanser or something. I guess when I go to Chipotle, I don't have to use soap and water. I can just lather up with their high-quality alcohol cleanser. I wonder on that cruise ship with those 300-plus people vomiting with diarrhea if they were using the new and improved alcohol. Thank you for the comments.

VR: That's the problem. You have to know if you're using the new one.

DG: Yes. Does it say anything? There should be something special.

VR: That's the problem. Maybe they all need to be reformulated.

DG: Yes. I was wondering about a cost issue. It'd be nice if we got some information.

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

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

[music]

[00:30:16] [END OF AUDIO]