This Week in Virology

TWiV 992 Clinical Update

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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 992, recorded on March 15, 2023. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today from Arizona, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: It just doesn't roll off the tongue like New York, Daniel, sorry.

DG: [laughs] Live from Arizona.

[laughter]

DG: Well, let's get right into it because I am taking a break from being on spring break with my daughters and my wife. I will start with our quotation. "New knowledge is the most valuable commodity on earth. The more truth we have to work with, the richer we become." That's from Kurt Vonnegut. We'll jump right into polio. This is like one of those Marvel crossovers. So the article, “Case Report: Clearance of Longstanding Immune-Deficiency-Associated, Vaccine-Derived Polio Virus Infection Following Remdesivir Therapy for Chronic SARS-CoV-2 Infection,” was published as a case report in *Frontiers in Immunology*.

We previously discussed the prolonged shedding in some people, of vaccine-derived poliovirus after oral vaccination with the Sabin type polio vaccine, as opposed to the injected, inactivated Salk type polio vaccine. Here the authors describe a case of a 50-year-old man with common variable immune deficiency, persistently infected with a neuro virulent vaccine-derived type 2 poliovirus following vaccination in childhood. This immunodeficiency-associated vaccine-derived poliovirus infection had proven resistant to multiple prior attempts at treatment with human breast milk, ribavirin and oral administration of a normal human pooled immunoglobulin product.

His infection subsequently resolved after 12 days of treatment with remdesivir. I will note this was 12 days of IV remdesivir being given for an acute COVID infection. Vincent, any thoughts?

VR: It's very exciting. I think it was bound to happen. With so many people infected and being treated, it turns out the remdesivir looks like it will inhibit polio replication. There are a lot of these individuals globally, and we've never understood how to clear their infection and this may be the key. It's a very good observation.

DG: Yes. It's exciting and also, I wonder about - it's tough with the diagnosis of polio. You're usually making it too late, but could this have any role in treatment? No, exciting stuff. We're doing better with RSV and flu, but norovirus, it looks like it was getting a little bit better there, Vincent, and we're right back still above 16% of our positive. Wash those hands, or apparently, you can use high-quality alcoholic Chipotle. All right, they're going to send us some money, I hope. COVID, right into COVID. What is the story with New York City and rats? The article, "SARS-CoV-2 Exposure in Norway Rats (*Rattus norvegicus)* from New York City," was the editor's pick in *mBio*.

Those planning a trip to my hometown New York City, may not be aware that millions of Norway rats, *Rattus norvegicus*, inhabit New York City, presenting the potential for transmission of Severe Acute Respiratory Syndrome Coronavirus 2, from humans to rats. Well, maybe the other way around too. A little more, I really want to put these furry animals in context because I'm not sure it's politically correct to call them Norway rats. I will quote from Wikipedia, "The brown rat, also known as the common rat, street rat, sewer rat, wharf rat, Hanover rat, Norway rat, and Norwegian rat, is a widespread species of common rat."

"One of the largest muroids, it is a brown or gray rodent with a head and body length of up to 28 centimeters or 11 inches long, and a tail slightly shorter than that. It weighs between 140 and 500 grams, 4.9 and 17.6 ounces," despite people's imagination puts them at several pounds above that. "Thought to have originated in Northern China and neighboring areas, this rodent has now spread to all continents except Antarctica, and is the dominant rat in Europe and much of North America." I'm going to just call these New York rats. The investigators evaluated SARS-CoV-2 exposures amongst 79 rats captured from New York City during the fall of 2021.

Their results showed that 16.5% were serology-positive IgG or IgM, and partial SARS-CoV-2 genomes were recovered from four rats that had qRT-PCR. They then conducted a virus challenge study showing that Alpha, Delta and Omicron variants can cause infections in wild type Sprague Dawley rats, including high replication levels in the upper and lower respiratory tracts and induction of both innate and adaptive immune responses." Additionally, they say the Delta variant resulted in the highest infectivity. The authors summarize by saying, "Our results indicate that rats are susceptible to infection with Alpha, Delta and Omicron variants and wild New York City rats in the municipal sewer systems have been exposed to SARS-CoV-2."

Their findings highlight the need for further monitoring of SARS-CoV-2 in the urban rat population, and for evaluating the potential risk of secondary zoonotic transmission from these rat populations back to humans.

VR: Daniel, did they say if the rats get sick?

DG: They didn't, actually. I mean, they did make the comment about the fact that they could see immune response after a viral challenge, but they didn't really give us a good sense like, are they actually getting sick? I suspect not Vincent, or they would have mentioned it.

VR: Yes. Daniel, dare we say ratatouille?

DG: [laughs] You can say whatever you want there, Vincent. All right, children COVID and other vulnerable populations. The article, "Clinical Characteristics and Outcomes of Children with SARS-CoV-2 Infection During the Delta and Omicron Variant-dominant Periods in Korea," was recently published in the *Journal of Korean Medical Science*. These are the results of a multicenter, retrospective cohort study conducted in hospitalized patients, 18 years of age or younger, with lab-confirmed SARS-CoV-2 infection at five university hospitals in South Korea, and actually divided these into the Delta, August 23, 2021 to January 2, 2022 and Omicron, January 30 to March 31, 2022. A little bit of a gap there.

A total 612 patients were identified, 211 Delta, 401 Omicron. They say that during the Omicron and Delta periods, the proportions of individuals with serious illness, moderate, severe and critical severity was 21.2% during Omicron, and 11.8% during Delta. *P* value is 0.034. Compared with the Delta period, the proportion of patients with moderate illness increased significantly in the age groups 0 to 4, and 5 to 11 during the Omicron periods. Just want to say that one more time. 14.2 versus 3.4, 18.6 versus 4.2, during the Omicron period. During the Omicron period versus Delta, a proportion of patients with croup, went from 0.5 to 11, seizures went up to 13.2% from 2.8%. Just actually, some important data on how Omicron behaved in children in Korea.

This next one is a little bit of a challenge. The article, "Exhaled Breath, Aerosol Shedding of Highly Transmissible Versus Prior Severe Acute Respiratory Syndrome Coronavirus-2 Variants," recently published in *CID*. In this study, individuals with COVID-19, had 93, 32 vaccinated, 20 boosted and they were recruited to give samples including 30-minute breath samples in the Gesundheit-II EBA exhaled breath aerosol sampler. I feel like we may have looked at this technology before. Samples were quantified for viral RNA using reverse transcription, PCR and cultured for virus.

We're going to go through the figure a little bit but they reported they had four individuals with Alpha, three with Delta and 29 cases with Omicron. They've reported that these cases shed significantly more viral RNA copies into exhaled breath aerosol, so EBA's then cases infected with ancestral strains and other variants they had 57 comparators. They reported to have cultured virus from the EBA of one boosted and three fully vaccinated cases. Just to go through Figure 3 a little bit here. I think it's still disturbing that we're still seeing this cutoff of less than or greater than 5 microns.

What they're actually looking at is a fine aerosol defined as less than or equal to 5 microns. Then they're actually comparing that to the amount of RNA in saliva or the mid-turbinate swabs. I'm going to actually say this is worth looking at. I do think this is open access. If you look at the ancestral and you start looking for any RNA positivity you really have to get pretty far out. You know what, I'm also going to say a very similar thing with the fine aerosol

versus the saliva or the middle turbinate when you start moving into Omicron. Very interesting. Again, this is RNA, you would expect less RNA in smaller droplets. How much this plays a role in transmission I think is going to continue to be a challenge going forward.

VR: I do think that we need to stop looking at RNA if we want to make claims or conclusions about infectivity, transmissibility, we need to look at infectious virus because you're always left with the question, what does this RNA mean? You just don't know.

DG: Yes, and maybe it makes sense to really challenge this binary, because as we've seen in settings like the poorly ventilated suburban homes and other situations, just getting that six feet away, that's just not enough. The time starts to develop. We probably need better data, better language going into the next respiratory pandemic. All right. Remember those masks, apparently, they only work if they are worn. Some clarification on some recent meta-analysis that is circulated out there. We did get an update on COVID active vaccination on Tuesday, March 14.

FDA authorized the bivalent Pfizer BioNTech COVID-19 vaccine as a booster dose for children 6 months through 4 years of age, at least two months after completion of primary vaccination with three doses of the monovalent Pfizer BioNTech COVID-19 vaccines. We're starting to get everything on the same page all the way down to 6 months.

All right, COVID, early viral, upper respiratory non-hypoxic phase. This is that viral respiratory, viral replication phase. Now this preprint relates to long COVID but it hits on what we can do during this phase. I wanted to share it right up front here. The preprint, "Outpatient Treatment of COVID-19 and the Development of Long COVID Over 10 months: A Multi-center, Quadruple-blind, Parallel Group Randomized Phase 3 Trial," posted on *The Lancet* preprint server. These are more results from the COVID-OUT out trial. People may remember this trial that looked at metformin, ivermectin, and fluvoxamine for acute treatment of COVID. So my colleagues Ken Cohen at UHG and David Boulware. U of M, among the authors. Here's a study looking at giving 14 days of metformin, 500 milligrams on day one, then 500 milligrams BID for four days, then 500 in the morning and 1,000 in the evenings out to day 14 and asking the question, what about impact on the diagnosis of Long COVID?

They reported in this preprint that when metformin was started within four days of symptom onset, the hazard ratio for Long COVID was 0.37 with a confidence interval of 0.15 to 0.95 reporting a 42% relative decrease, and a 4.3% absolute decrease in the Long COVID incidents occurred in participants who received this early treatment with metformin. This all sounds good so far, but looking into the data further, there are a few issues. One is the significant difference in how much Long COVID we see in the different groups.

The metformin placebo group has 10.6% compared to metformin-treated at 6.3. The ivermectin placebo group had 7.5 with ivermectin treatment 8%, the fluvoxamine placebo group, 7.5 compared to fluvoxamine treated with 10.1. Really different numbers in these different groups. If you look at the treated with metformin group 6.3 and then you match it with one of the other placebo groups of 7.5 or 7.5 it's impressive when you look at the figure and you see this Kaplan-Meier separation day's randomization. I'm still struggling to

understand the mechanism and why there was just such a bad outcome in the metformin placebo group.

VR: Daniel, just briefly tell us what metformin is doing for other treatments.

DG: Yes. Metformin is an oral medicine that we use for treatment of diabetes. A nice thing about it is it will control your blood sugars, but with a relatively low or negligible risk of hypoglycemia, so it's a fairly safe treatment. Yes, I'm not sure, I understand the mechanism of what it's doing here.

VR: What do you think needs to be done next, more trials, Daniel?

DG: I'm not sure if with an absolute decrease of 4.3%, if this is really going to give a lot attraction to doing more studies with metformin. We're going to talk about another study coming up. It doesn't have a mechanism that makes sense. If this was an effective antiviral, if we're seeing blunting of the immune response, if we had more data to support that. Here I'm just not sure that this is enough data to really want to move forward with these studies. Big challenge also, we don't really understand Long COVID, so again, it's really hard to understand how we're going to prevent it without really even understanding the mechanism.

I'll move into our next, another preprint. Speaking of the devil, so to speak, the preprint, "Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19," posted on *medRxiv*. Here the investigators are using the healthcare database of the U.S. Department of VA to identify users of the health system who had a SARS-CoV-2 positive test between March 1, 2022 and June 30, 2022, were not hospitalized on the date of the positive test, had at least one risk factor for progression and survived the first 30 days after the diagnosis. They identified those who were treated with Paxlovid within five days of the positive test.

Those who received no COVID-19 antiviral or antibody treatment, now this is not an RCT. The last one was actually an RCT, so we've got all the potential confounders here, but we actually have a mechanism compared to the control group. Treatment with Paxlovid was associated with a reduced risk of PASC. Hazard ratio 0.74, adjusted relative risk 2.32 included a reduced risk of 10 of 12 post-acute sequelae in the cardiovascular system, coagulation, hematological disorders, venous thrombosis, pulmonary embolism, fatigue, liver disease, kidney disease, muscle pain, neurocognitive impairment, shortness of breath.

Now some new endpoints that we have introduced lately. Paxlovid was also associated with reduced risk of post-acute death. Hazard ratio there, 0.52. Almost a 50% reduction in this post-acute death. Post-acute hospitalization also has a ratio of 0.70. Just bringing it all together, nirmatrelvir was associated with reduced risk of PASC in people who are unvaccinated, vaccinated and boosted, and people with primary SARS-CoV-2 infection and reinfection. I think comparing this one, the mechanism makes sense to me. It's something that we're going to be using for another reason anyway. Just not really sure what metformin would fit in here.

Now this article, "Assessment of the Risk of Venous Thromboembolism in Non-hospitalized Patients with COVID-19," was published in *JAMA Network Open*. I'm going to say this is an important one. For a while, people were not sure what to do with outpatients, with COVID.

We had guidelines for the inpatients from the American Society of Hematology and others. People kept asking, should all these folks be on aspirin or blood thinners or is it better just to keep our hands in our pockets? Are we going to harm these people?

Here the investigators asked a simple question, ''What is the risk of venous thromboembolism among outpatients with COVID-19?" They looked at a retrospective cohort from two integrated healthcare delivery systems in Northern and Southern California. Data for the study was obtained from the Kaiser Permanente virtual data warehouse and electronic health records. Participants included non-hospitalized adults aged 18 or older, with COVID diagnosed between January 1, 2020 and January 31, 2021 with follow-up through February 28, 2021.

Now, the primary outcome was the rate per 100 person-years of diagnosed VTE and they actually found the absolute risk was low, but they did suggest that some groups were at higher risk during the first 30 days.

Moving into, I guess I'll say a review. It's the first week viral symptom phase: Number one Paxlovid, number two remdesivir, next molnupiravir, and convalescent plasma. A couple comments. Why is it so far down in the list?

Well, remember the current EUA is only for immunosuppressed individuals, so the USFDA has an EUA to permit the emergency use of the unapproved product COVID-19 convalescent plasma with high titers of anti-SARS-COVID-2 antibodies, for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment. Then current INDs guidelines among ambulatory patients with mild to moderate COVID-19 at high risk for progression of severe disease who have no other treatment options.

Remember earlier is better, preferably within the first three days. We did also hear that this is being extended, renewed, so to speak so we should continue to have access to this going forward. Even if the EUA ends you can still get this through an IND, so Investigational ND and Arturo Casadevall will help you if you need help getting access.

VR: Investigational New Drug.

DG: Investigational New Drug, awesome, thank you. All right, just when I think of INDs I think of lots and lots of paperwork and hopefully someone will be taking care of that for me. All right, COVID inflammatory lower respiratory hypoxic phase. Let us return to the original terminology, stop calling this the rebound stage, no rebound here. We're saying for a while one, steroids at the right time, in the right patient, at the right dose. Remember this is after the first week and in patients with oxygen saturations less than 94%. What is the basis for our using steroids?

Well, we had the recovery trial out of the UK where we all jumped into this dexamethasone 6 milligrams daily times 10 days. We are often shortening this if a patient improves when they're discharged from the hospital, but what is the optimum duration? We have the, Optimal Duration of Systemic Corticosteroids in COVID-19 Treatment: A Systematic Review and Meta-analysis," published in *Open Forum Infectious Diseases.*

Here the investigators identified 27 eligible studies, consisting of 13,404 hospitalized COVID-19 patients, seven randomized controlled trials, 20 observational trials included in this meta-analysis of mortality which suggested a protective association with corticosteroid therapy. Risk ratio 0.71, so right about 29% reduction in mortality, but the pooled analysis showed the greatest survival benefit for a treatment duration of only up to six days. Survival benefit was 0.65 up to seven, but no additional survival benefit was observed beyond seven days of treatment. They didn't find any confounders for severity of disease, age, duration of symptoms.

Also important in these types of publications, I think, is to go through the individual, look at the forest plot, don't just let all the cow piles get to a certain point with suddenly they're magically gold. A nice thing you can actually go through and look at all the different studies, looking at six days, all trending in the right direction, a lot of them reaching statistical significance. Then when you look at those when you get past six days, interesting including the recovery in there, really getting pretty close to losing its statistical significance.

I think, impressive to look at, see that things are all trending in the right direction and maybe a little more evidence to help us with our duration. All right. Anticoagulation, we have guidance from American Society of Hematology. Pulmonary support, remdesivir if not on a ventilator and still in the first 10 days. Moving into Long COVID, and here I'm going to wrap it up. I really want to offer a word of optimism here. I know many are frustrated and perceive the pace of research in this area to be slow. I'm always hoping that we can get more evidence-based knowledge at a faster rate.

Just to let our listeners know, myself and many others have adjusted our practices, and are successfully working with many Long COVID sufferers, and I think making a difference. I will say, no one is safe until everyone is safe. I do want everyone to pause the recording right here. Go to parasiteswithoutborders.com and click Donate. Even if it's a small amount every bit helps us to continue to do our work. We're now having our American Society of Tropical Medicine and Hygiene Fundraiser, February, March and April about halfway through. Donations made to PWB will be matched and doubled up to a potential maximum donation of $30,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Philip writes, “I have traveled extensively to South America, had yellow fever vaccine in 1991, I still have the vaccination certificate. As I understand it, the one dose is good for life as far as entry requirements, although the vaccine itself is only good for 10 years. I'm 65 years of age and as I understand it, some caution is needed as to receiving a booster. What level of protection do I have after 30-plus years? Is there a test to determine this?”

DG: This is a great question and I'm going to start off with, I don't know, and then I'm going to explain what we do know. It was a number of years ago that they changed that requirement. It used to be every 10 years you had to get your yellow fever vaccine updated, and this was big business. People would go to these places and there were all these yellow fever booster places set up to do it, and then a number of studies suggested that you might get lifetime immunity. I think as a listener to the show you might understand could I look at antibodies?

I'm not sure we know about that, honestly, as a correlative immunity. There probably is a cellular protection as well, but what if you're concerned? What if you're trying to decide what to do? The other thing I will point out is when we talk about risk, it's first vaccine in the older population that is associated with the organ invasive, with the neurological complication. Getting a booster has always been incredibly safe, so I'll just put that out there that this is an area where the reason they've said you only need that once is that we do think that that actually offers this lifetime immunity, but leave it out there for you. Discuss this with your travel doctor.

VR: Ken writes, "I'm curious about a relatively minor long-lasting COVID symptom, a cough. I'm a healthy 71-year-old who has had a cough since getting COVID in mid-December. I'm fully vaccinated and boosted, no other symptoms, was a very unpleasant cough the first two or three days of COVID but minor since. I suspect many people just tolerate it without contacting a medical authority. Could it be very common but largely overlooked or are there data might show how long it might persist?"

DG: It is tough if you describe it as you have that this is something that you had barely mentioned, and so it's hard in trials to really necessarily capture that and really know how common that is. That lingering cough is certainly something we see post-COVID. Getting exact numbers in anything post-COVID, as you're aware, is a challenge. Then becomes the issue, what exactly is triggering it? Is there ongoing inflammation? Is this related to some GI manifestation, and could necessarily be addressed with something, a famotidine, an H2-blocker?

This is something I would actually at least take that visit, talk to someone familiar with post-acute sequelae of COVID. Maybe they can help you with this, but no, this is certainly one of the more common post-acute sequelae of COVIDs that we do see. Fortunately, as you mentioned a lot less devastating than some of the others that we do see.

VR: Kari writes, "Our family has been patiently waiting for our youngest to turn 6 months of age so she can get her COVID vaccine. She will finally be eligible in a few weeks. When I mentioned this to a friend, they told me to do my research carefully because there are new reports of heart problems in children getting vaccinated. This seems untrue to me based on what I have read and in listening to *TWiV.* While the risk benefit is not as high as in the elderly, it still seems that heart issues, especially in those outside of the teenage young men age group, have very low chances in comparison to actually getting COVID or MISC.

"Is this still the case? I noticed some countries are no longer encouraging vaccination in the youngest patients. This nervous mama wants to make sure I have all the most updated information. Should we wait a little more time between the first and second/third doses to improve response and allow it to mature, lower the risk of side effects? Is Moderna or Pfizer a better choice? It seems not many are getting their youngest vaccinated, so I hope there are enough data to glean the rate of rare side effects, et cetera."

DG: I'm glad you asked and this is a challenge. One is, there's no new data and I think, no new scary data that your friend, colleague, neighbor is suggesting. This is just recycled, recycled. One of the challenges is, as we've repeatedly mentioned in that under 4, this under 4, this is this population that still is vulnerable. This is the group with one of the

highest rates of hospitalization until you get up to the over 65. This is a high-risk group. The hope for a lot of us is this will be part of routine vaccinations going forward. This is a safe thing. This is definitely safer than getting COVID without the protection.

I would encourage you to have this discussion with your pediatrician, but no, none of these fears, and comparative Pfizer, Moderna, I think they're both excellent choices. I'm not sure when people say, "do your research," that does not mean go on Twitter. That does not mean do an internet search. Do your research would be talk to your trusted healthcare provider, have this conversation. I think as we repeat over and over again, children are at risk of COVID, children are at risk of Long COVID, children are at risk of hospitalization from COVID, and certainly that zero to 4 years of age is a high-risk group.

VR: Now we have one from Don, Daniel. Don was the physician who told us about the hand sanitizer that apparently works with noroviruses. "Thanks for reading my response. In your reply, Daniel makes the logical point, there should be some labeling. While I absolutely agree, the part of FDA that regulates these products, the Center for Drug Evaluation Research, CDER, does not allow hand sanitizer brands to make viral claims. Or it at least makes the standard of proof so impossibly high that it's not cost-effective for the companies to make the investment.

"FDA would require that killing or decreasing the number of microbes on the skin by a certain magnitude produces a corresponding clinical reduction in infection or disease caused by such bacteria or virus. Essentially, the company would have to do a clinical trial to make the virucidal claim."

DG: This is great. What they could do is they don't even necessarily have the claim. Just let us know if it's one of these high-potency ones that we have heard so much about that they used to get Chipotle, and we'll even give a shout-out to whatever, that high-potency brand out there. Thanks, Don.

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

DG: Oh, thank you. Everyone be safe.

[music]

[00:33:06] [END OF AUDIO]