This Week in Virology

TWiV 1120 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. From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1120, recorded on June 6, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: I am in Helsinki, Finland today, where it's pretty chilly here. I don't know what the temperature is, but below 68, maybe low 60s, but it's sunny.

DG: Wow.

VR: Yes.

DG: All right. I guess the mid to low teens for Celsius for our audience.

VR: That's right. Now, Daniel?

DG: Yes.

VR: Your pop screen is blocking your bow tie. I can't see.

DG: My bow tie? It's a filovirus, one of my favorites, Ebola.

[laughter]

VR: Now people are going to complain that you call Ebola virus your favorite.

DG: All the other pathogens get jealous. Is that what you're worried about?

VR: No, I think since it kills people readily that people might -

DG: Yes, we shouldn't. No, and I understand that because it seems a little bit morbid, right? In a sense, that you're glad that there's people out there that would rather spend time playing with viral pathogens and understanding them than video games. Whatever it takes to motivate people to do the work, to learn more, to help us take care of folks. All right. I'm going to jump right into it with a Paul Farmer quotation. "If I am hungry, that is a material problem. If someone else is hungry, that is a spiritual problem." I was hanging out in the doctor's lounge over at one of our local hospitals.

It's not exactly the nicest doctor's lounge. We always complain. One of the surgeons came in. He's like, "Oh, Dan, you've got to watch this movie. It's called *Bending the Arc*." He starts talking about it. I'm like, "Are you talking about Paul Farmer?"

VR: Good.

DG: Yes, he had just discovered Paul Farmer, who, unfortunately, left us. He died much too young. Actually, I don't know if you were there that year at ASTM and H, Vincent, but there was a memorial to Paul the year he died. Really, a special man. There's a pick of the week I'm going to throw out at our listeners called *Mountains Beyond Mountains*. I think Tracy Kidder may have written that. *Bending the Arc* is a film. It's a little harder to get access to, but just really, a tremendous pioneer. I understand he was a little bit difficult to work with, but some great people are. Thinking of us, I guess.

VR: You mean yourself, right?

[laughter]

DG: I was thinking of us, Vincent, actually. We are a little difficult. All right. Let's jump right into bird flu, H5N1. We'll maybe even mention H5N2, but bird flu. Not so good to read from the CDC that a third human illness from H5, avian influenza in a dairy farm worker. Unlike the earlier cases, the patient was experiencing respiratory symptoms. I think I heard about this right after we had recorded, so I probably texted you at two in the morning, Vincent, or something. We heard that the person is a dairy worker. They were exposed to infected cows, making this another probable cow-to-person spread. What was, I think, unique here was the respiratory illnesses. The patient reported upper respiratory tract symptoms, including cough. There was no fever, and there was the classic eye issue, so, eye discomfort with watery discharge.

VR: A little bit of conjunctivitis there as well, right?

DG: Yes.

VR: OK.

DG: Also, we'll leave in a link because I understand there's now going to be a national wastewater monitoring system based at Stanford University in partnership with Emory. They launched an H5 avian influenza wastewater dashboard. I think, to be more specific, they included this on the dashboard. I looked at the dashboard. It still is coming together, so maybe in the future, it'll be a more helpful resource. I was listening to the last deep dive *TWiV*, Vincent, when this news seemed very much appropriate. The U.S. Food and Drug Administration, FDA, has approved Moderna's mRNA vaccine, mRESVIA, against respiratory syncytial virus, RSV, for people ages 60 and older, bringing the number of approved RSV vaccines to three, I'm going to say, and another mRNA vaccine, not just for COVID anymore.

VR: It's interesting, yes.

DG: Yes. There was this idea, this magic that, oh, now that we have mRNA vaccines, that's the end. We're going to have vaccines against everything. This will be the only modality going

forward. I don't know how true that is. There was a little bit of a conversation about there are challenges with mRNA vaccines. Do you really make all the protein you're trying to make? Is there misfolding? Do you get all that antigen you're after? A couple of our last episodes have talked about, can I make enough mRNA. Maybe I do these self-replicating mRNA where I only put in a little.

I have to make as much, but then it makes more of its own. We're still seeing that a lot of the vaccines are protein-based and other modalities. Here we get an mRNA RSV vaccine. Not only is this made with mRNA, I feel like this is like a sales pitch, but is the only RSV vaccine available in single-dose pre-filled syringes. That's from the company's website. Now, the approval was based on findings from a Phase 3 study that included more than 37,000 adults, spanned 22 countries. After 3.7 months of follow-up, researchers found an efficacy of 83.7% against lower respiratory tract disease from RSV. Further analysis found a vaccine efficacy of 78.7%. A longer-term analysis found protection at the 8.6-month mark.

VR: How much protection at 8.6 months? Do you remember?

DG: I'm not actually sure. Yes, not sure what it was.

VR: It's funny that they just say protection. They don't tell you how much, right?

DG: Yes. This is really important because I think we're going to learn something here because we're starting to get data on the other RSV vaccines like the GSK, Arexvy, the Pfizer, Abrysvo out to two, and actually, I saw some three-year data recently. It's going to be interesting comparing the durability of recombinant protein vaccines and this new Moderna mRNA vaccine for RSV.

VR: Yes, this is a great one because we have both, right?

DG: Yes. I think we're going to learn a lot. This will be available probably in the fall, so for the next 2024-‘25 respiratory virus season. All right. Moving right into COVID, we are in June now. I'm going to try to keep these a little shorter. Get a little bit of a summer break, sort of. The vaccine advisors to the FDA recommended switching. This is going to be the new COVID vaccine from the XBB.1.5 to the JN.1 for the fall COVID-19 vaccine formulations. The measure was unanimously passed 16 to 0. They're going to keep an eye on any of the offshoots of JN.1, such as KP2, and we'll see what's going on there.

The other interesting - I always look at this map every week, and it's the map of what percentage of deaths in the country are due to COVID. There's basically a solid pattern and then this thatched pattern. The amazing thing to me is that the one pattern is, are you less than 1%? A lot of the country, less than 1%, but there's still a bunch of areas in the country where it's really in the 1% to 2% of all deaths are due to COVID. That really didn't ever drop down. Flu, you come to the summer, you really don't see a lot of flu deaths. All across the country, less than 1%.

Interesting here that we're still seeing such a solid number. Maybe apropos of what we talked about last week, and this data, I always say the data is a little bit old. We have data from 5/25 and we're about two weeks forward of that right now as we're talking, but it looks like their trajectory of wastewater viral activity for SARS-CoV-2 in the West is heading in the wrong

direction. We'll see what keeps happening there. I've been hearing some words from the ground that maybe out there in Hawaii, maybe California, we might be seeing an uptick in cases.

We'll see how much that really pans out. All right, moving right into a nice emotional topic, is, COVID and SARS-CoV-2 have been a little emotional. They've been in the news lately. Poor Fauci is getting beaten up. Apparently, now they're going after our buddy, Peter Hotez. Things around COVID have triggered a lot of emotion. It's rather unfortunate that masks trigger more emotion than the actual interest in the science. Let's look at this study, “Relative Efficacy of Masks and Respirators as Source Control for Viral Aerosol Shedding from People Infected with SARS-CoV-2: A Controlled Human Exhaled Breath Aerosol Experimental Study.”

This was published in *eBioMedicine*. I just want to, for clarity, I'm going to change all the times they talk about viral load because they are measuring viral RNA copy numbers. I will not say viral load, as they did not actually measure replication-competent virus. Reviewers step on this, please. Here they compare the efficacy of masks, cloth and surgical, and respirators, the KN95 and the N95s as source control or source control. Someone is sick, they're wearing it to protect you from them. They're going to look at the SARS-CoV-2 RNA copy number and exhaled breath of volunteers with COVID-19, using this, experimental design.

They're going to end up with 44 volunteers, and 43% are female. They're going to end up with paired masked and unmasked breath samples so they can compare them. The methods are great here. Sometimes I really laugh to myself, chuckle to myself as I read one of these studies. Probably shouldn't read them on the train. People look over at me like I'm a bit odd, enjoying my scientific articles. Upon identifying a volunteer with an active SARS-CoV-2 infection, they invited them to a research clinic to provide 30-minute exhaled breath, so EBA samples with a Gesundheit II human exhaled bioaerosol collector, to assess the efficacy of masks as source control.

Volunteers were asked to provide paired breath samples at each visit, first with a mask on and then without, so they served as their own match controls. They were asked to repeat the alphabet three times within the 30-minute sampling period, whereas subsequent cases were asked to shout, "Go Terps," 30 times, and sing “Happy Birthday” loudly three times at five, 15, and 25 minutes, into each 30-minute sampling period. How'd they do this with a straight face? In instances where volunteers were too unwell, I'm thinking people were too unwell to show up, so these are people who were too unwell but still well enough to show up, they provided two sets of samples.

A single 30-minute breath sample was collected. The masks were all brought by the volunteers, the cloth masks were, and they had a whole bunch of different cloth masks. The other masks were supplied. Now, they reported that all masks and respirators reduced the exhaled RNA copy number without fit tests or training. A duckbill N95 reduced exhaled RNA copy number detected by 98% and significantly outperformed a KN95 as well as cloth and surgical masks. The cloth masks outperformed a surgical mask, which that was interesting. I pasted in some of the data so we can look at it.

As Vincent and I are going to go through this data, important context here is related to this history of particle sizes. We will see that they analyzed what they referred to as two aerosol

size fractions: Fine, which are less than or equal to 5 microns in diameter, and coarse, which are going to be greater than 5 microns in diameter. Also, they're going to do this combined total analysis. If you look at the fine EBA, and they compare the cloth mask to no cloth mask, yes, that mask is a little bit better. Surgical is a little bit better. The KN95, yes, that's clearly better than no KN95.

We also see a move in the right direction with the N95s. Interesting. The coarse, consistent. Cloth mask, a little bit lower RNA copy number. Surgical mask, not too impressive, actually. KN95, yes, that looked a little bit better. Now, here, the N95 was much better. We're seeing, going from this 390 down to 47, so almost a log drop there. Then when they just did the combined, you see similar trends for the different RNA copy number reduction.

VR: Daniel, these GMs are basically viral RNA loads, right?

DG: Yes, it's geometric mean of the RNA copy number.

VR: Right, OK.

DG: Sort of interesting. It looks like N95 is coming out on top, but you're seeing most of the N95 effectiveness for the coarse fraction. Yes, it's helping, but there's overlap when you look at the fine EBA. There's actually overlap almost with everyone. The KN95 was doing a little bit better. The fine EBA, the GM, geometric mean, went from 5,600 down to 330 with the KN95, from 930 down to 51 with the N95 when you look at surgical mask, 180 to 60 with the fine, cloth mask 310 to 41.

VR: This looks good, right? I wonder, if there's still, you're going from 1,400 to 47, say, total EBA for N95, 47, is that still enough to infect someone? If so, at what frequency? You would like to know how much infectivity is being withheld, but on top of that, you need to know how much virus you need to infect someone. We don't have that number, so I'm still left a little unhappy. These look good, but I don't think they're still giving us real-world information.

DG: Yes, that's what you want. These are numbers, but then, is there a certain threshold? Did you get below that threshold? If you're still above the threshold, you're still above the threshold, yes.

VR: The advantage of this study is that you get people for an hour, you do the study and they're gone, right?

DG: Yes.

VR: That's really nice. The problem, if you want to do a real-world study, you have to tell people to mask for the next month, right, and see what happens?

DG: Yes.

VR: Then all is lost because you don't know what people are doing.

DG: Yes. Like the Bangladeshi study there, where you introduce masks or not, you see, oh, they did reduce transmission. Here is some nice, I'll say, particle science that looks like N95 is

the best. KN95s look pretty good. Surgical masks, cloth masks, not so good for source control. We're all wearing these surgical masks thinking, "Oh, I'm keeping my patients safe." I look at this data, and not particularly supportive of that practice.

VR: Isn't that what surgeons wear?

DG: Yes, but you know what? Remember the history of that was Columbia and it was bacterial wound infections.

VR: Right.

DG: Yes, a different physics. That's actually what got us in trouble. That was the 100-year-ago study with the Serratia where people gargled with Serratia, and then they showed it went six feet, and then they started wearing surgical masks. Yes, if you gargle with bacteria and put a surgical mask on, it'll keep you from spraying that into a wound, but is that really what we're after? All right. I think I mentioned last week that, for COVID passive vaccination, we have Pemgarda. There's now an infusion center locator, pemgarda.com. Still trying to get all that to work out.

Then moving into COVID early viral phase, not a lot of new here, just reinforcing. First week, that's the viral replication phase. We've got effective antivirals, Paxlovid, remdesivir, molnupiravir, some situations, convalescent plasma. This is the time when you're most likely to spread it to the others. All the isolation guidance. Week Number 2, that's when you move into the inflammatory phase, steroids, anticoagulation, pulmonary support, remdesivir, maybe if we're early enough, possibly a role of immune modulation. Then the meat of today, the late phase PASC Long COVID.

A couple of things to talk about here. The article, “Early Use of Oral Antiviral Drugs and the Risk of Post COVID-19 Syndrome: A Systematic Review and Network Meta-analysis,” was recently published in the *Journal of Infection*. Here, the investigators looked at nine observational studies containing 866,066 patients, with nirmatrelvir, ritonavir, and molnupiravir were evaluated in eight and two studies respectively, with both drugs evaluated in one study. This meta-analysis showed that early oral antiviral drugs reduced post COVID conditions by 23%.

This meta-analysis showed that nirmatrelvir-ritonavir may perform better than molnupiravir at reducing this risk. They've got some nice forest plots where you can really go through all the studies. There's one outlier, this Durstenfeld 2023. That's the only one that really looks like it's going in the wrong direction. There's a Chuang 2023, which, just on the line there, but a number of other studies really showing this about 20%, 25% reduction.

All right, the article, “Long COVID Autonomic Syndrome in Working Age and Workability Impairment,” published in *Scientific Reports*. These are results from a prospective observational study conducted during the second wave of the pandemic in Italy. Forty-five patients hospitalized for COVID-19 were enrolled at the time of their hospital discharge, that's T0, and then they followed them for six months.

Autonomic symptoms and workability were assessed by the COMPASS31 and the Workability Index Questionnaires at T0, at T1,T3, and then six months after hospital discharge, and

compared these to retrospectively collected for a period preceding SARS-CoV-2. Clinical exam and standing tests were also performed at a one-month and then six-months discharge. One in three working age people developed a new autonomic syndrome that was still evidenced six months after the acute infection resolution. Pretty impressive. Now, this COMPASS31, what's that?

That's the Composite Autonomic Symptom Score 31. It's a scale that measures neurodegenerative system symptoms through 31 patient-reported questions. I'm going to leave a link in there, but orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, pupils. Basically, the higher the score. There's a link I'll leave in for people to look at that. This is something I think once you start looking and start talking to people, it's actually pretty common when people have COVID severe enough to end up in the hospital, that you see this ongoing autonomic dysfunction.

Why do we care? Why do we keep spending time talking about Long COVID? According to the Centers for Disease Control and Prevention, 5.3% of Americans currently have Long COVID, with a significant proportion of those experiencing disability from the condition. I'm going to leave a link to that number. That's a lot. You do the math on that, you're talking about millions of Americans. You're talking about 20 million if you really buy that number. Even if you think it's a little high, you're still talking about millions. The National Academy of Science, Engineering, and Medicine presented a report with a number of conclusions about Long COVID diagnoses, symptoms, and impact on daily function.

Really, it's complicated here. They included more than 200 symptoms, and they're falling into this, you don't necessarily need a positive COVID-19 test, if you have the clinical diagnosis, that that can be used to make this Long COVID diagnosis. What is this all about? This is really meant to guide the Social Security Administration, and really going to help government groups look at how they address this going forward.

All right, as promised, a little shorter than our usual, and I will say no one is safe until everyone is safe. We are in the middle of our Floating Doctors fundraiser, May, June, and July.

It was actually right before our recording I was on the line with Jolene and Ben LaBrot, just talking about just the tremendous work that Floating Doctors continues to do down in Panama. Your donations during this period of time, we're going to double them up to a maximum donation of $20,000 to help them just continue to do the tremendous work.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Rob writes, "Within a few hours of listening to *TWiV* 1118, I found out my 82-year-old mom had COVID. Apparently, they called the urgent care and were told that COVID is like the flu now. People have had vaccines and infections, and they don't give out Paxlovid anymore until the disease progresses and becomes severe. I've heard this story a bunch of times from other letters and Daniel, but I never thought it would happen to me or my mom.

I set my parents straight with all the information provided in the show note links, and my dad made an angry in-person visit to the urgent care, where he was quickly given the requested prescription. Thanks for all the information you provide and your great work. We really need to do something about these Paxlovid-denying doctors, though. This is ridiculous."

DG: No, Rob, I appreciate your email. Your email is going to help us just keep reminding people Paxlovid keeps people out of the hospital, it keeps people from dying, and now we're seeing more and more studies suggesting that it can reduce your risk of getting Long COVID. It's just this whole idea that providers are failing to treat. They've got a diagnosis in front of them, they've got evidence-based interventions, and I've got to tell you, a lot of the stuff doctors do is not evidence-based. Here's an opportunity to make a difference, and yes, we'll just keep ringing the bell, sounding the horn, whatever the expression is.

VR: Jonathan writes, "Thank you for all your work in public communications and volunteer work. I like your quotes at the start of the shows. My father-in-law tested positive for COVID for the first time yesterday. I've been pushing for him to start Paxlovid, but he got pushback from his nephew, who's an ER doc. He is 84. His mobility has declined significantly and uses a walker due to some Parkinsonism symptoms. His last booster was now about nine months ago. The ER doctor said there are side effects and drug interactions that Paxlovid might have.

I fully admit I know very little, but thought that if he is to start Paxlovid, he should start right away. I thought that perhaps he can pause some of his medicines for the Parkinsonism symptoms and the side effects, while not trivial, are preferred to any chance of disease progression. He's in Colorado. Should we push for exploring COVID further, given his vaccination status and age?"

DG: It's really tough. People still die from COVID. We've talked about the fact that sometimes they die in the first 30 days, and this is a gentleman who's 84 years old, who is at risk of progressing and ending up in the hospital, and by then you've missed your window. Also, the six-month mortality is increased for people that don't get access to treatment during that first week. Just, oh, there's medicine interactions. You can look them up. You can make an educated decision about, risk, benefit. You don't just throw up your hands and say, "Oh, medicine interactions, drug interactions, side effects."

As we've talked about many times, the biggest side effect is not getting Paxlovid, ending up in the hospital, dying, getting Long COVID. The possible side effects of not treatment in many cases, particularly a high-risk individual like this, really makes you want to do the lift to figure out what to do here.

VR: RoNell writes, "What is the latest up-to-date medical advice regarding daily prophylactic penicillin VK, for someone who has been on it for 48 years, 250 mg Pen VK 2X daily? The medical experts who helped me through rheumatic fever, three open-heart surgeries, and ultimately, a pacemaker, always told me it was vital to take it twice daily for the rest of my life. The only exception is when I visit the dentist and use amoxicillin. Recently, my longtime electrophysiologist of 30 years retired, and I was reassigned to a new doctor. Now I'm being told daily prophylactic is no longer recommended.

I'm aware of the latest information on the gut microbiome and its effects on the immune system. Is this the reason why? I don't want to be susceptible to infections by stopping, especially after years of indoctrination that it's required. Please help settle this for me. Side note, I take warfarin daily as well, which always complicates future medical interventions. Thank you to you and Vincent for sharing your expertise with the world."

DG: Thank you. I was quickly searching and found there was an article, “Secondary Antibiotic Prophylaxis for Latent Rheumatic Heart Disease,” an interesting title. I'm not sure latent is the right word here. There are parts of the world where I go, where some of us practice, where we still see a significant amount of rheumatic heart disease. This is, you got a strep throat infection perhaps, and then there's an immune response, ends up doing damage to the heart. For instance, this was a study where they looked at children, adolescents in Uganda.

They get their echocardiogram at baseline, and then they go on and they put them on the antibiotics. Interesting enough, and maybe this is why people use the word latent, is they follow them a couple of years later, and the kids that got this daily antibiotic did better. Now, the challenge, though, is the scenario you put in front of us is a little bit like how long do you stay on that penicillin? Do you stay on it for 40 years? I'm going to say we like to give people broad strokes, things to think about. It would be worth your time sitting down with an infectious disease physician and looking for what's right for you, just doing what you've been doing for 48 years, try to figure out what's right for you.

VR: All right. This next one, Daniel, is purely for fun. Lisa writes, "I love Noah Kahan, and the line, 'Doc told me to travel, but there's COVID on the planes,' is oh so effing fabulous. Also, his line, 'So I forgot my medication, fell into a manic high, spent my savings at a Lulu, now I'm suffering in style,' from his song, “Growing Sideways.” Four years in, and this peds NP is still listening to your fabulous updates each Saturday morning. Thanks for all you do. Lisa, from the crazy (not-in-a-good-way) state of Florida."

[laughter]

DG: OK.

VR: Mike writes, "Thanks for your continued weekly helpful updates on *TWiV*. This week you touched on SARS-CoV-2 wastewater viral activities level and were discussing the significance of numerical changes in the viral activity level, but I don't think you and Racaniello ended up having time to fully explain what the levels mean. In case you want to provide more clarification on your next update, the CDC's website, and it provides a link, explains that 'the value associated with the wastewater viral activity level is the number of standard deviations above the baseline transformed to the linear scale.' Sincerely, Mike." You remember, Danny, we were trying to figure out what the Y-axis meant.

DG: Yes, I remember this, and I'm sure Mike was sitting there going, "Guys, guys, it's the number of standard deviations above the baseline transformed to the linear scale."

VR: Oh, yes, we should have known. That's actually right.

DG: No, Mike, I appreciate you sending this in. That's great.

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

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

[music]

[00:31:48] [END OF AUDIO]