This Week in Virology

TWiV 1042 Clinical Update

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

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VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1,042, recorded on September 6, 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: What's new in infectious diseases, Daniel?

DG: Stay tuned and we're going to go through it. Let's start with the quotation. A sad week. I don't know how many of our listeners are aware that Jimmy Buffett has left us, has died in the last week. I have a quotation from Jimmy Buffett. I am a huge fan of Jimmy Buffett. "I have always looked at life as a voyage, mostly wonderful, sometimes frightening. In my family and friends, I have discovered treasure more valuable than gold." I just thought that was really a nice quotation. That goes out to not only family, friends, but all our *TWiV* friends who have joined us in the last few years. Thank you for being here.

Let's start off with mpox, a situation that Vincent and I were discussing last week. There was a news piece, "Mpox: China's Health Authorities Fight Surge in Cases of Unknown Origin," published in *the BMJ*. What is happening with mpox? We talked a bit about all these dire predictions about what might happen in the U.S. A lot of times when a public health response is effective, we don't notice. You don't get any credit. You only get attention when you fail. Confirmed cases of viral infection, which primarily spreads through contact with infectious lesions, increased for mpox nearly fivefold to 491 on the Chinese mainland in July, according to the China's Center for Disease Control and Prevention.

Even though we call it the China CDC, they've got a P in there. That was up from 106 cases in June. No deaths were recorded so far. Four in five of the cases had no known origin, according to a post on the China CDC's website. A little quotation here, "The reported cases represent only a fraction of the actual numbers, a phenomenon common in almost all other countries." This is from the deputy director of the Stanley Ho Center for Emerging Infectious Diseases at the Chinese University of Hong Kong. Couple concerns. None of the three vaccines in

widespread use elsewhere for mpox prevention have been approved for use in China. That's a bit of a challenge. Also, there may not be a recognition of the at-risk populations.

VR: Daniel, I'm going to China in November. Do I have to do anything?

DG: No, you don't. I don't think this is going to be a problem for you, Vincent. All right. RSV, have people seen the advertisements? The vaccines are now available. Actually, I was talking to one of my neighbors earlier today. His parents have actually gotten their vaccines at a local pharmacy actually. He was touting how nice an experience it was for them. As we've discussed, the to-adult-over-age-60 vaccines are now approved, licensed, shared decision-making for higher-risk individuals. Shall we discuss timing? When are we encouraging the high-risk individuals to do this?

The nice thing about these RSV vaccines is their efficacy is for a 90% reduction in medically attended lower respiratory tract infection with RSV. We're already seeing durability out to two years. This isn't something you need to wait. The recommendation is, as soon as you can get that appointment, run in and get it. Maybe right after the Jewish holidays, when my parents head back to this part of Long Island, they will get their appointment scheduled. I want to just put this right up front. Call this a public service message. We all need to be on board with this.

I want to mention the article, "Analysis of Seasonal Variation of Antibiotic Prescribing for a Respiratory Tract Diagnosis in Primary Care Practices," published in *Antimicrobial Stewardship & Healthcare Epidemiology*. Unfortunately, this is an article that serves as a reminder that as we head into winter, when the temperature drops, the number of inappropriate antibiotic scripts goes up. Let's try to not participate in that.

COVID, what is going on with COVID? Just a reminder that people can have more than one thing at the same time. That can be a bad thing. With the article, "Prevalence and Associated Outcomes of Co-infection Between SARS-CoV-2 and Influenza: A Systemic Review and Meta-analysis," published in *IJID*. Now, with home testing, we're often stuck with a yes or no on COVID, but we're not getting this information about co-infection. A lot of people may think, oh, my test is positive, I've had COVID, they're trying to decide whether or not to get treatment. You may get a little bit push left or right, depending on whether or not you have something else going on.

For instance, here, what if you also have influenza? Here, they looked at folks who had influenza and COVID at the same time, comparing those patients with COVID-19 only. A co-infection had an increased risk of ICU admission, 2.2. Increased risk, the odds ratio for mechanical ventilation, 2.73. The odds ratio for death, 2.92. Almost three times more likely to die if you have both SARS-CoV-2 and influenza. Now, this is an interesting one, and maybe it serves as a stepping off to discuss a little bit about what's going to be on people's mind the next couple weeks here.

Actually, it's going to be in the news a lot, I expect, this week. In the COVID active vaccination immunity section, we have the article, "Comparison of Bivalent and Monovalent mRNA Vaccine Boosters," published in *CID*. Just to start with the abstract. This is a cohort study that was conducted in Hong Kong, where both the bivalent and the monovalent formulations of

the BNT162b2, that's the Pfizer BioNTech boosters, were available. What they're looking at is they're actually comparing mortality, hospitalization. Here, they report no significant differences in the mortality or hospitalization between those who received the bivalent or the monovalent as second boosters.

Basically, bivalent, monovalent mRNA boosters appeared equally protective against clinical outcomes when one was looking at disease, not just the positive PCR test. They have a table we can actually look through and see, about 1,622 folks decided to do the bivalent, 1,622 decided to do the monovalent as the fourth dose. They look at all-cause mortality or hospitalization, respiratory-related hospitalization, basically comparing these across. This is encouraging data, and that moves us right into boosters are coming later this month. Actually, COVID-19 booster shots are expected as early as next week.

We're recording this Wednesday, but this will drop Saturday, and that will be true. First, the FDA is expected to authorize or approve the shots, which they've signaled they're about to do. They need to do this soon because the CDC's independent panel of advisors is going to meet on September 12, next Tuesday. Then the CDC director will sign off, will get recommendations on who should be getting those shots. Here, going to talk a little bit, timing does matter. We've talked about the fact that we're expecting this to give some kind of a boost for, let's say, four months.

That boost, there will be contraction of those neutralizing antibodies that we keep mentioning. If you rush out and get it immediately, let's say the end of next week, the clock's already ticking on that contraction. A lot of us are recommending end of October, early November as a great time to be getting both your flu and your COVID shots. As we've mentioned, it probably doesn't matter which arm. You can get them both at the same time. I usually pop both into a person's same arm, and then we move forward. Early viral upper respiratory, just a refresher.

People are testing positive. A lot of people are testing positive. Keep seeing those numbers rise. Number one, still Paxlovid. Number two, remdesivir. Number three, molnupiravir. Convalescent plasma, only for a specific subset. Immunocompromised with no other options. We are avoiding doing harmful things. Early inflammatory phase, we unfortunately are still seeing folks - and this tends to be the profile - that first week they did not receive treatment, they're starting to have problems requiring hospitalization during that second week.

They become hypoxic. Saturations drop to less than 94%. That's when steroids, we jump in with dexamethasone 6 milligrams a day times six days. I will leave a note into the systemic review and a meta-analysis and *OFID*, that *OFID* that that is based upon. Anticoagulation recommendations from American Society of Hematology, I'll leave in a link for those. Pulmonary support, a lot of subtleties there but starting with nasal cannula and then escalating. Remdesivir, this is now five days if we're after seven, we've ended up here. It's that day eight, nine, or 10, is a five-day versus a three-day first week, and immune modulation in certain circumstances.

Here's a big challenge. People, it's early, they get COVID. A lot of folks are not thinking they're going to die. They're not thinking they're going to end up in the hospital, but they're worried about Long COVID. Is there any way right up front that maybe we can predict who's at highest

risk? We have the article, "Acute Blood Biomarker Profiles Predict Cognitive Deficits 6 and 12 Months after COVID-19 Hospitalization," published in *Nature Medicine*. These are the results of a prospective cohort study of 1,837 adults hospitalized with COVID-19.

The investigators use data from a large prospective longitudinal cohort study, the post-hospitalization COVID-19 study, that's the PHOSP-COVID study. I don't know if people are following the acronyms. This was designed to discover patterns of association between biomarkers measured on admission to hospital for COVID-19 and post-acute cognitive deficits. They're going to be measuring at six and 12 months. They're actually using a formal Montreal cognitive assessment score to assess cognitive function. I'm going to leave a link into a copy of this test.

Maybe some people are familiar, maybe they had this done, but this is where you connect letters with a line, like A to B to C. You draw a cube, you draw a clock, you name some animals, you remember stuff, you pay attention. It takes about 15 minutes, it's not the hardest test to do. There's a lot here, they have a lot of nice figures. There's a huge amount of data. The findings the authors highlight is there is a correlation between certain blood tests on hospital admission with cognitive issues at six and 12 months. The most predictive was having an elevated fibrinogen level and a low CRP.

Even more predictive as we put these together and create a fibrinogen/CRP ratio. Also, elevated D-dimer was associated with cognitive issues. We can also create a D-dimer/CRP ratio. These two dimensions were robust across secondary analysis. They do a secondary analysis in a separate large-scale electronic health record. We see really the D-dimer is really specific to this COVID19 and the six- and 12-month cognitive issue. Really worth looking at, what do we do? I guess that's the big thing. Is there any way we can target these individuals early maybe for a closer follow up, maybe as we get more evidence-based therapeutics.

VR: What do you think about the CRP, D-dimer business, Dan? What's the mechanism that's really telling us? It could be just an association, right?

DG: Yes, it's interesting. There's a lot in this paper where they actually speculate about what's going on. There is this idea that fibrinogen and the D-dimers which are going to be the split products of the coagulation, but also the inflammatory cascade, may be telling us something about the degree and the nature of the inflammation that is being triggered during that second week requiring hospitalization. There may even be something here about permeability of the blood-brain barrier, allowing certain pathology to begin early in disease.

Lots of speculation, lots of really interesting ideas. D-dimers are not just for clotting. They're part of the inflammatory cascade, same with fibrinogen. I know on some of the other shows have been a lot of coverage of complements, so I'd love to see some studies on that potentially playing a role. Here is another, a couple more here to finish us off in the Long COVID section. The article, "Temporal Changes in Fecal Microbiota of Patients Infected with COVID-19: A Longitudinal Cohort," published in *BMC Infectious Diseases*.

These results of a monocentric - that sounds fancy but it just means they did it in one center - monocentric longitudinal observational study to describe the gut microbiota profile in COVID-19 patients, and compared this to a pre-existing cohort of ventilated non-COVID-19

patients. The investigators included patients admitted for COVID-19 on the medicine ward. These are 43 folks not on a ventilator. Or folks in the ICU, with 14 of those on ventilators with a positive SARS-CoV-2 RT-PCR assay in a respiratory track sample.

16s metagenomics was performed on rectal swabs from these 57 COVID-19 patients. Thirty-five with one, 22 with multiple stool collections. Nineteen non-COVID-19 ICU control patients were also enrolled, among which 14 developed ventilator-associated pneumonia, so we have this pneumonia group. Five remained without infection, so a different control group. They're doing these SARS-CoV-2, they say viral loads, but we all know they mean RNA copy number, in fecal samples measured by qPCR.

They noted that the microbiota composition became distinct between the COVID-19 and the non-COVID-19 groups. The fecal microbiota COVID-19 patients was characterized by increased *Bacteroides*, and the pneumonia group by *Prevotella*. The COVID-19 presented significant effects on the microbiota composition in this study. Moreover, as they describe, patients in the ICU harbored increased *Campylobacter* and decreased butyrate-producing bacteria such as less *Lachnospiraceae,* less *Roseburieae,* low *Faecalibacterium.*

VR: Daniel, what do you think, do you think these microbiome changes predate COVID or are a consequence of COVID?

DG: I think they're actually triggered, because as they're following these, and 22 of these folks have multiple, so you're able to see this composition becoming distinct over time. It is interesting. I think we've talked a little bit about this. I'm starting to get more and more patients with feedback on using the Bifidobacterium probiotics who are suffering from cognitive issues with Long COVID. Hard to sort out how much is placebo effect versus therapeutics, but seeing a lot of people, I'm thinking I'm going to help their gut microbiome and they're coming back with improved cognitive function.

Call me curious, but certainly need a lot more work to better understand this. The last one, and I think this is just a reminder for everyone out there about the fact that the journey does not end when the person is clapped out of the door. We have the article, "Long-term Survival after Intensive Care for COVID-19: A Nationwide Cohort Study of More Than 8,000 Patients," published in *Annals of Intensive Care*.

Among the 7,390 patients with complete 360-day mortality data, remember, these are the people that survive that hospital admission, 24% of them died within the next 30 days, 28.8% within 90 days, and it was up to almost 30% over that first year. The 360-day mortality rate for folks that survived the ICU care for COVID-19, 27.1% for the female patients, 31.0% for the male patients. Pretty--

VR: That's very striking, isn't it?

DG: People have probably heard how upset I would get if they're clapping people out. I'm like, this is, for so many people, just the beginning of this journey. A lot of these people, here as we see, about a third of them will not make it through this next year. You can't just clap them out. Now is the time when you've got to start saying, how can I help these people transition? How can I make sure they're on the right medicines? How can I do everything I can to make

sure that all the resources we put into getting them through this ICU experience doesn't just result in them dying in the next 360 days?

VR: Daniel, what's the main cause of death? Cardiovascular things?

DG: It is, yes. This study, I don't have the specific of these 8,000 patients, but for a lot of them that's what it is. As I've been closing for a long time, no one is safe until everyone is safe. We all wish we were done with the pandemic, and a lot of us who wish we were done are being rudely reminded that things are still going on, whether it be COVID, whether it be RSV, whether it be other issues.

We are continuing to do our Floating Doctors fundraiser for August and now September and October. They desperately need your help. They're really struggling financially. The money you send us, we're hoping to get up to a doubling of your money to a maximum donation of $20,000 to help Floating Doctors continue to do the great work that they do down in Panama.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Barb writes, "Would you provide the studies you're referring to for six-day course of dexamethasone for hypoxic inpatient? Our guidelines still specify 10 days. Thank you." Barb is a hospitalist.

DG: Yes, Barb. Thanks for bringing that up. I've brought this up several times, time to update the order set. I think I was saying earlier last week when I was talking with one of my hospitalist colleagues, Dr. Parnell, who used to borrow my kayak and now he's got children, is much too busy to kayak. When will we update those order sets? I think at this point, the inertia is there and the 10 days may just stay. We may have to manually change our duration.

I discussed the article back earlier this year, so early this year, 2023, which was the article, "Optimal Duration of Systemic Corticosteroids in Coronavirus Disease 2019 Treatment: A Systematic Review and Meta-analysis," published in *Open-Form Infectious Diseases*. As people may remember, these were the results of over 13,000 hospitalized COVID patients, seven RCTs, 20 observational studies, no benefit beyond the six days of treatment. Now, you just start getting into all the side effects without the benefit. I'll leave a link in our show notes, or maybe Vincent, someone will leave a link in for us.

VR: J writes, "Currently undergoing rabies post-exposure prophylaxis in my family, which led me to do some searching online about how long we'll have protection. From what I found, it sounds like rabies PrEP, pre-exposure, affords very long-lasting protection, while PEP may provide six to 24 months. As PrEP is two shots, maybe a booster after three months, and PEP is four shots plus immunoglobulin. I would love it if you would explain the immunology behind the lower durability of the PEP regimen. The only thing I can think of is that the ig interferes with the full response. PS, lest I leave the wrong impression, we will move forward following CDC recommendations. I'm just curious about the immunology underlying the interventions."

DG: Let's get everyone up to speed on this, because this is really an interesting topic. You go ahead, like me, and you get yourself your rabies vaccines. This is great. You got your rabies vaccines. Like me, you're out there petting all those dogs who may or may not be rabid. Lo and behold, so far this hasn't happened, you get bitten. You have one of those high-risk exposures, break of the skin, dog runs off, you don't know, maybe that dog was rabid. Let's

say you're in India where we see, what, 100,000 rabies cases a year. I've heard these estimates, which I can't believe the number's that high, but that's the number that's been suggested.

What do I do? Oh, I've been vaccinated, it all should be OK, but it's not. Here's the interesting binary. If you've been vaccinated, you don't need the immunoglobulin, you just get a post-exposure vaccine series. If you have not been vaccinated, then you're going to get that immunoglobulin right up front, and you're going to get shots afterwards. What's the immunology here? The immunology is that when you get bitten, this is great, I love rabies, just from virology, not from the human side of it, but when you get bitten, that virus initially is not connected to a nerve.

It's not migrating through a nerve. It's in the surrounding tissue. There is a window period when that virus can be neutralized and cleared before it makes contact with a nerve. Once it makes contact with a nerve, it's going to be migrating to the central nervous system at a certain rate per day. The idea is if a person has not been vaccinated, you want to immediately flood the area with the immunoglobulin. If they've been vaccinated ahead of time, the idea is they're going to be starting to respond, and they're going to be able to provide their own local immunoglobulins in that area.

VR: Charles writes, "I'm 71 years old. I've had all COVID vaccinations except for the last bivalent one. I had COVID February, 2023, mild symptoms for a week. I had AFib in 2018 that was treated with an ablation. About five months after I was ablated, it was discovered I had multiple pulmonary embolisms in both left and right lung areas. Some were old, some were newer. I was put on Xarelto and told I will be on it for life.

A recent echocardiogram shows I have moderate mitral, bicuspid, and tricuspid valve regurgitation. I've read that COVID can exacerbate this condition. I've also read that the vaccine can also impact the heart, but not as frequently as COVID does. Since the vaccine appears to be to provide a diminishing protection against infection while not adding any additional benefit to T cell function, I wonder if I should get the next round of COVID vaccinations."

DG: This is a great discussion. It's good that you have both Vincent and I on board here to give you that perspective. The first thing is to always ask what are you going to think that booster might provide for you? You're in your 70s, you have what sounds like a number of cardiac issues, valvular issues, the atrial fibrillation. I don't know if there's other medical issues going on. You're an individual with a non-zero risk of progression should you get infected with SARS-CoV-2, should you get COVID-19. The durability of those three, four shots for preventing disease looks to be durable.

That is the reassuring message. Now, a booster for maybe three to four months might get you some temporary, let's say four-month decrease in your risk of getting infection. I'm going to call it SPF2 or something. Instead of being there for 15, maybe you have to be there for 30 minutes. Still want to be making smart decisions. Is it really going to impact that 90% that you've got going? I think we have to be honest about what we promise there. I don't think that the vaccine itself relative to getting COVID is going to be a health risk, these vaccines are incredibly safe.

This is not as important as those first three shots. The other side that ties directly in here is you're on one of these direct oral anticoagulations, one of the medicines that is metabolized in a way that Paxlovid might have an interference. Another thing that's probably really important I'm going to say, I know you're asking about vaccines, is talk to your providers about what happens? What's the plan? What's my plan should I get an infection? Do I risk to stop that medicine, that Eliquis for five, six days? I think that's going to be the most important thing. Vincent, any?

VR: I think that's the right advice. Paxlovid is a game changer and can prevent some of these other issues that he's worried about.

Don writes, "As an old (Vincent's age) country doc in Kansas, I was intrigued by stumbling onto a PBS special concerning epipharyngeal abrasive therapy. A short internet search indicates that there are some who feel it not only may be a viable adjunctive treatment for Long COVID, but multiple other maladies that are not well understood.

Since you are one who seems to evaluate literature with more than average astuteness, I would love to hear your opinion. As a function of having been around for a while in medicine, I predict we will see an amazing amount of epipharyngitis in many patients we scope, which would leave us with a conundrum on whom to treat and how aggressively."

DG: I have to say, this is something I'm not familiar with. I'm going to put this in my list of things to investigate, and maybe in the future if there's some interesting stuff here, I will share.

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

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

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