This Week in Virology

TWiV 947 Clinical Update

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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 947, recorded on October 19, 2022. 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: Daniel, I am in Washington, DC, at IDWeek. Today, I went to a session on monkeypox. A representative from CDC said they no longer recommend using a needle to unroof lesions because there are too many accidents.

DG: [laughs] OK. I think, yes, we know why.

VR: Yes. Before we hand it over to you. Let me remind everyone that if you would like to support our work here at MicrobeTV and wear a T-shirt with a spike protein of SARS-CoV-2 on it, please go over to vaccinated.us, pick out one of their cool Spike t-shirts. When you go to check out, use the promo code MicrobeTV, and they will donate their profits to our science communication work. Thanks very much to Matt at vaccinated.us. OK, Daniel.

DG: All right. I will start with my quotation, "For I found myself embarrassed with so many doubts and errors that it seemed to me that the effort to instruct myself had no effect other than the increasing discovery of my own ignorance." That's René Descartes. This is IDWeek when a lot of people gather together, and we move forward, and we realize how many things we've been doing wrong, how many things we can do better. It's a great, great time for us to, well, I think, be humble and learn.

All right. Well, let's get right into it. First, polio keep reminding everyone, get your polio vaccines. Don't check your serology. I'm still getting questions about that, "Can I just check my serologies?" No. If you haven't gotten your polio vaccine, get your polio vaccine. All right. Influenza, as I promise, let me start with the article, “Prediction of Upcoming Global Infection Burden of Influenza Seasons After Relaxation of Public Health and Social Measures

During the COVID-19 Pandemic: A Modeling Study.*"* This was published in *The Lancet Global Health*. We are getting better at predicting the weather. [chuckles]

Perhaps we are getting a bit better at predicting the impact of upcoming influenza season. Lots of ways of predicting the upcoming flu season. I'm going to start with a little bit of history here. I know people are, "Dr. Griffin, why are you so doom and gloom about the upcoming winter?" Well, as a bit of interesting history, the CDC's attempts to forecast the upcoming flu season began, I'm going to say, in 2013 with the Predict The Influenza Season Challenge. This was a competition that encouraged outside academic and private industry researchers to forecast the 2013-14 flu season.

Each flu season after, the CDC's influenza division collaborated with external researchers on flu forecasting. The CDC has provided forecasting teams data, relevant public health forecasting targets and forecast accuracy metrics while teams submit their forecasts which are based on a variety of methods and data sources each week. I'm going to leave a link in our show notes for that.

The original competition was a competition with a cash prize, and I'm going to read from the 2013 announcement. The registrant who most successfully predicts the timing, peak and intensity of the 2013-2014 flu season using social media data, and they actually mentioned Twitter, internet search, web surveys, will receive an award of $75,000 and CDC recognition. I thought that was interesting.

This modeling study that I'm going to leave a link to in *The Lancet Global Health* is introducing new variables from the COVID-19 with waning immunity, secondary to the lack of influenza recently as well as the dropping of much of the public health and social mitigation measures, these non-pharmaceutical interventions that we've been discussed.

This study along with what we saw in the southern hemisphere is predictive of a significant influenza season. I will say we are already seeing this, our urgent cares, our hospitals, the CDC flu tracking. We're already seeing an exponential rise in flu cases. The season is already here, so what to do. If you are higher risk or holding an event or organizing a gathering with high-risk people in attendance, remember all we learned from COVID-19, ventilation, outdoors is better than indoors, hygiene, vaccination and early treatment. And I'll add that getting that flu jab isn't just about you.

VR: Daniel, did anyone win that prize?

DG: I don't know. [laughs] That'd be interesting. We should bring them on, right?

VR: Yes. I have a feeling no one did.

DG: [laughs] All right. Monkeypox. Monkeypox is not a gay disease or an African disease. It is an infectious disease. Numbers are still trending down. I think they'll keep trending down particularly if people are not poking themselves with needles as they unroof those lesions. I started patting myself on the back the other day talking with one of my patients who is a member of the high-risk community. He's like, "Dr. Griffin, summer's over. What did you expect?" [laughs] It is funny. We talked about how the behavior got better. Well, the days of summer love are over, so we will see what happens going forward.

For now, remember, if you don't test for it, you will not diagnose it, and you can do that with the swabs. You don't have to do that with a sharp needle. When we do see cases, remember, STOMP TPOXX, the trial to understand the role of tecovirimat in this disease. All right, COVID, right to it nice and quickly. Just the first I will throw out here, this is a news item, maybe. The Biden administration announced that the COVID-19 Public Health Emergency will continue through January 11, 2023. The public health emergency first declared in January 2020 and renewed every 90 days since.

The declaration, it's actually important. It enabled the emergency authorization of COVID vaccines, testing, treatments for free. It expanded Medicaid coverage to millions of people, many of whom will lose this coverage once the emergency ends. It temporarily opened up telehealth access for Medicare recipients. We do hear we're going to get 60 days' notice before the public health emergency might end, but I have to say a lot of these measures - I'm particularly going to harp on the telehealth access - has been tremendous.

Really, a lot of data suggesting that this is a very effective way of reaching a lot of individuals. You leave the hospital. You've been seen by the doctor every day. Suddenly, you're out there in the world, and you're told you just went from being sick enough to be in a hospital, I'd like to have you come see me next week in the office. A lot of them can't make it, but the ability to check in with them in the home, make sure they're doing OK, run through the medicines, make sure that transition to the outpatient setting went well. These are tremendous things. Hopefully, we can maintain a lot of this going forward.

All right, children, COVID and other vulnerable populations. Children are at risk from COVID. When I was on the Local Channel 12 news station with Elizabeth Hashagen, I shouldn't say local anymore. It's now in like seven areas. It's like the whole tri-state area, but I was asked about the *MMWR,* "Adverse Childhood Experiences During the COVID-19 Pandemic and Associations with Poor Mental Health and Suicidal Behaviors among High School Students - Adolescent Behaviors and Experience Survey United States, January through June, 2021." Really disturbing. None of this is surprising.

Perhaps people remember when I questioned some approaches to the pandemic and our priorities, when at risk to my Irish ancestry, I suggested things like perhaps we should close the bars and open the schools rather than the other way around. As the authors point out, social and educational disruptions during the COVID-19 pandemic have significantly - I put that in exacerbated concerns about adolescents' mental health and suicidal behavior. Looking at the data from this survey, really, not surprising but shocking at the level, 37% of the U.S. high school students reported poor mental health. OK, 20% considering and 9% attempting suicide in the preceding year. Really devastating. Hopefully, we learned something there.

All right. The pre-exposure period, transmission testing. I keep reinforcing: This is when you come up with a plan. You don't wait until you test positive. You want to have a plan ahead of time. All right, COVID, active vaccination. Never miss an opportunity to vaccinate. Vaccinated people still get infected. They are just less likely to die or have severe disease. I'm going to talk a little bit here about the whole nasal vaccine discussion. I want to put this whole nasal vaccine discussion in context. I don't know, Vincent, how much you've followed this, but lots

of superlative, scary ideas about how U.S. biosecurity is on the line if we are not the first to develop a nasal vaccine that stops transmission.

We, [laughs] Vincent's shaking his head for those of you that don't know. We hear that India, Russia, and Iran have authorized nasal vaccines. I would be delighted if more money goes into research, and if a chunk is given to scientists investigating nasal vaccines that stopped transmission, but a couple reality checks here for people that are seeing this in social media. People who get that Hobbesian natural infection with SARS-CoV-2, who get COVID-19 acquired through the nasal and respiratory root, guess what? They get re-infected.

We see re-infections in some cases as early as one month after, so understanding mucosal immunity is still in its infancy, and yes, it needs more funding, but let's not mix our apples with oranges here. People are calling for nasal-administered vaccines that are going to produce such a robust mucosal immunity that they block transmission. The nasally administered vaccines licensed in India, Russia, and Iran are just systemic immunity-inducing vaccines given by a spray instead of a needle.

Did FluMist turn out to be a game-changer for influenza vaccines? Did the world end when one company invented FluMist? When vaccines are introduced, when vaccines get better, no country is going to hide the science and let the rest of the world suffer. I think there's a lot of superlatives here. I don't feel like the end is near and our national biosecurity is on the line, and do ask that important question, is it a nasal administered vaccine or is it a nasal transmission blocking mucosal immunity inducing vaccine?

VR: A few thoughts, Daniel. The problem here is that, even if you had a nasal vaccine that worked really well to induce, say, antibodies that block infection, those high levels would decline within a few months and you would get infected and you would transmit again. A good example is the polio vaccine, the oral polio vaccine, which is used to stop outbreaks because it stops transmission for a few months after it's administered, but beyond that, antibody levels decline. You can get infected in the gut and until the memory response kicks in, you're able to transmit. That's basic immunology and no vaccine is going to be able to get around that folks. Now, maybe if you could block transmission for a couple of months, let's say, Daniel, we could humanize everybody in the U.S. at the same time, then you could stop transmission, but what's the likelihood of that happening?

DG: I think this is a pretty high bar that people are asking for. It is a new frontier of science, and we will move forward. I just think a lot of superlatives here. Let's bring things back down to earth. All right, the article, “Severe COVID-19 Outcomes after Full Vaccination of Primary Schedule and Initial Boosters: Pooled Analysis of National Prospective Cohort Studies of 30 Million Individuals in England, Northern Ireland, Scotland, and Wales,” was published in *The Lancet*. I'm going to put my glasses on because I have some figures we're going to walk everyone through. If people can actually, if they have the chance to go through this article while we talk, I think this is worth it. There are some really important bits of data here or datum that have been compiled so that we have the data.

Between December 8, 2020, and February 28, 2022, 16,208,600 individuals completed their primary vaccine schedule and 13,836,390 individuals received a booster dose. Between this period of time, 0.4% of the primary vaccine group, 0.2% of those who received the booster

had severe COVID-19 outcomes. The risk of severe COVID-19 outcomes was reduced after receiving the booster. The rate change 8.8 events per 1,000 to 7.6 events per 1,000 person-years. Little bit of a difference there, but let's put this in context. This is a reduction of 1.2 events per 1,000 person-years, so a number needed to treat or vaccinate of about 1,000.

Older adults, those that are elderly-elderly even particularly more so greater than or equal to 80 versus those in the 18 to 49 adjusted relative risk of 3.6, those with comorbidity, so greater or equal to 5 versus none. 9.5 adjusted relative risk. Being male, 1.23, a little bit worse, and those with certain underlying health conditions, in particular individuals receiving immunosuppressants increased risk 5.8. Those with chronic kidney disease, so I'd like to point that out, 3.7, all remained at high risk despite that initial booster.

I'm going to recommend that people actually look at the - there's a really nice figure and it really gets at who we're talking about, who we're targeting when we encourage boosters, and we do encourage boosters in certain contexts. There's this wonderful Figure 1. I'm assuming Vincent's had a chance to glance at it, but a couple things that stand out. One, I thought it was really interesting when you just look at everything together, this greater than or equal to 20 weeks after a second dose. We start to see an adjusted rate ratio increase.

Age is a big factor in looking who's at risk. Move through ethnicities, number of risk groups. The number of comorbidities, the more certainly starts to add up. Then the number of previous PCR tests, not sure what to make of that, but I think there's really a lot in here. It really asks this discussion. Boy, if I'm elderly-elderly as Paul Offit has said, getting that booster, whether it's the bivalent or whether we had stuck with the old, you really start to see a lot of bang for your buck. I don't know, Vincent, if you had any comments on this complicated?

VR: This is from when vaccinations started and through February, 2022. We don't have Omicron at that point, correct, but we do?

DG: Omicron, I'm thinking about time when Omicron came in.

VR: Maybe that's the earliest date for Omicron. This is mainly pre-Omicron date.

DG: Yes, it is mainly. Yes, definitely say that.

VR: I still think it's interesting to look at the effect, as you said, of age and other conditions when it's all together in the same graph because often you read a paper and you get bits here and it's hard to compile them, but this does that in a very nice way so I like this.

DG: All right. Evusheld, we keep plugging Evusheld. I will tell people there's a really nice article hot off the press, so we'll be talking about Evusheld a little bit more next week. I continue to bemoan its lack of use, but let's move right into the COVID early viral upper respiratory nonhypoxic phase, the time of viral replication, and went through trying to put a lot of the data together. I have this vision that people will be sitting there at IDWeek and Saturday morning drinking their coffee listening to the clinical update, taking notes.

The big thing, number one. What is the number one recommended treatment? Forget about what you see in social media. Forget about rebound. Paxlovid. If you are high-risk individual during that first three to five days, we have a number of excellent studies. 89% to 88% reduction in the EPIC-HR study published in the *New England Journal of Medicine*. Unvaccinated. We have the high-risk patient progression to hospitalization or death from Clalit Health Services in Israel, showing a 73% to 79% reduction in those endpoints in mostly immune individuals. We have reduction in progression of hospitalization or death in the EPIC research.

We have growing data, growing experience that this really prevents progression. As we talked about, the COVID rebound, that week two, we've been calling this the early inflammatory phase or the cytokine storm phase for over two years now, and now we have very good data that, yes, this represents an immune response and not a second period of viral application that would benefit from additional antivirals. It's not that easy to get someone on Paxlovid. I know they have this idea that folks are just going to show up at the pharmacy and this test and treat in the same place, but there are a number drug interactions. I was on a call today with our urgent care providers about the tri-state area and most of us will sit down and we'll leave links to this. We'll go to the COVID-19 drug interaction checker and we'll run through the medicines with the individual. We also need to look at kidney functions. This is why we went to medical school, so that we can go ahead, we can work ourselves through these challenges, but we can make a difference.

Number two, I do bemoan the limited access to what is an incredibly effective drug if used at the right time, and that's remdesivir used in the first seven days. This is a three-day, early IV approach, 87% reduction of progression if given in the first five to seven days, that's our *New England Journal of Medicine* study. Early remdesivir in solid organ transplant patients, 88% reduction in progressing to hospitalization. Then we've also talked about an 84% reduction in high-risk folks, three-day course during the Omicron season, so really tremendous data on remdesivir.

Number three, and this is an inferior because we do have some head-to-head comparison, bebtelovimab, this is for adult and pediatric patients down to 12 years of age. We have limited efficacy data here. We're hoping we carry over from the prior monoclonals, but we do have that retrospective cohort study of greater than 3,600 patients that we've talked about where the bebtelovimab 1.4% progressed versus 1.2 in Paxlovid, 0.2% died in the bebtelovimab, zero deaths in Paxlovid. I know which group I would like to be in. Molnupiravir last and least with only that 30% reduction in progression, so less impressive, but again, no renal, no drug issues. But be careful if you're used in an individual of childbearing age who potentially could get pregnant, get that negative pregnancy test, not authorized for those under 18.

Hopefully, important here, avoid doing harm, avoid those steroids. Overall progression of severe disease and hospitalization, and one study increased sixfold, mortality increased 35%. Another study showing hospital admission adjusted odds ratio 2.5, elevated cardiac risk, elevated risk of pulmonary embolism, and elevated adjusted odds of mortality of 3.5. You are not just doing something innocuous, you are doing something harmful if you give steroids in that first week and avoid those antibiotics. Multiple studies looking at

doxycycline, multiple studies looking at azithromycin, no meaningful effect on the clinical course, and you are feeding into the antimicrobial resistance.

Yesterday I was in the ER, I was consultant on an older woman who was admitted and her daughter was there and I was getting the story. The story was this woman was diagnosed, came down with acute COVID-19. The primary care doc suggested that they start the woman on Paxlovid. The daughter was not comfortable with that. She had heard all this stuff about Paxlovid. She had a long discussion, finally she was able to get the doctor to give her mother steroids and a Z-Pak, and now her mother is in the hospital on day 12 of the illness on oxygen.

VR: Not a *TWiV* listener, I guess.

DG: Not a *TWiV* listener. I hope not a *TWiV* listener. Hopefully one that will become a *TWiV* listener and then this will not happen again. All right, COVID, the early inflammatory, lower respiratory hypoxic phase, as I just described, a woman who progressed to that, coincident with following administration of steroids and antibiotics during that first week instead of something that would've reduced that risk by 90%, something that increases that perhaps sixfold.

Now is the time when this hypoxic woman might end up with steroids appropriately. This is when we talk about anticoagulation. We're probably already past the remdesivir window, past day 10, going to require pulmonary support. Some cases, we're still using immune modulators and perhaps a nice silver lining to the pandemic was suggested by the article, "Successful Immunomodulators for Treatment of COVID-19 Have Opened the Pathway for Comparative Trials," published in *CMI*.

Here the authors suggest, and I'm on board with the hopeful aspect here, that the success of immune modulation in the early inflammatory phase of COVID-19, that rebound, that second week, with steroids, baricitinib and tocilizumab, may be something that allows us to move forward and start looking at immune modulation in a lot of other situations.

All right, I will wrap us up with Long COVID, the late phase. I'm going to try to keep these under an hour, maybe even down at half an hour, that's our goal again.

A link to the *BMJ* paper, "Long COVID, an Update for Primary Care." Really a great resource for these growing number of individuals who we're trying to take care of. We're still waiting for more evidence to help us in this arena. It's nice to get an understanding, the different groups and a lot of the different things that are being tried out there. 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 a small amount, every little bit helps us continue to do our work. Here we are in October, wrapping up our three-month fundraiser. We're Floating Doctors. We'll have to throw in some wraps so they're actually wrapping it up, but we're trying to get up to that level where we can make a potential donation of $40,000, so help us reach that goal.

VR: Speaking of listening to *TWiV*, Daniel, I had lunch today at the Unconventional Diner. Outstanding. If you ever go there, it's right in the convention center on the outside. I wondered if it would be any good and it's actually quite good. Anyway, I'm sitting at the counter, the guy next to me, and he looks at me and he says, "You know, I never listened to *TWiV*, but I think I will now." I guess because I was eating at that diner, he thought he should listen, but anyway, this is a shout out to Brett in case Brett starts listening.

DG: Listening to *TWiV*. He's got it now.

VR: The funny thing is tomorrow I'm going to record a *TWiV* with Jeff Taubenberger at NIH. Brett turns out to have trained with him at NIH. It's a small world.

DG: It is a small world.

VR: All right, onto your questions for Daniel. You can send yours to daniel@microbe.tv. Jerry writes, "I developed cellulitis in my right leg, not diabetic, after IV Ceftriaxone was not working as fast as my physician wanted. I was put on ZYVOX caplets, which resolved it quickly and I just finished last Thursday. I've been told that in addition to the normal antibiotic side effects and MAOI issues, this particular medicine can play havoc with your immune system. I'm due for my booster and I'm in the class of people who should get it. I'm concerned, however, that my immune system is not currently up to the challenge. What would your recommendation be on timing? I'm doubly dosed with the initial vaccine. I've had two previous boosters. I've already had my flu shot in September along with my first dose of SHINGRIX. I would've gotten my COVID booster at the same time, except my provider was not offering that one at that time. Thank you for your help."

DG: Now, this is a great question. Linezolid, actually one of my favorite. It's a great MRSA medication, oral bioavailability is excellent. It's now generic. If you work this right, you can actually get it affordably. It usually takes a few weeks before we start to see this cumulative impact, so really at about two to three weeks is when we start seeing the marrow suppressive impact. Usually, and here we are at IDWeek, so people are up on the recommendations. ID to society recommendations, about five days in general for that cellulitis. Five, seven, short course Linezolid. I don't think there's going to be much of a problem if you waited a couple weeks just to be on the safe side. I think that's reasonable, but I wouldn't suggest you need to wait much beyond that.

VR: Amy writes, "Given the upcoming cold and flu and COVID season, I started wondering if faced with a swab that returns positive for COVID and influenza, do I treat that patient with Paxlovid and Tamiflu at the same time? Gosh, I feel bad for their GI tract if that's the case. What treatment guidelines address this?"

DG: That is the recommendation. Yes, the Paxlovid, the Tamiflu pill. The nice thing, they'll be on it for the five days, they'll get that metallic taste in their mouth. You may recommend they try some strong hard candy to help with that. We're going to see a lot of this. Actually, Australia had a lot of bad experience with the twindemic as people have started to refer to this. The flurona, you can get more than one thing at the same time and you could treat more than one thing, and should, at the same time.

VR: James writes, "Just listened to your latest update on COVID rebound. I thought I would pass this along to you. I know that Pfizer has been pushing for a second course and the FDA is balking at this, rightly so. Now Pfizer is putting together this trial. There's also a 10-day course being sponsored by Pfizer also at the FDA request as well. Still not happy with Fauci taking a second course in spite of the current EUA." James provides a link to that clinical trial. "Based on the CID paper you mentioned, not sure if this is even necessary and wouldn't even provide answers to more pertinent questions. Love Dr. Griffin quoting Ford on learning retirement. Let's have more time to learn things."

DG: [laughs] I think we got to do the science, and sometimes we do the science because we want to know the answers. Sometimes we do the science because there's a vacuum there. Without addressing that vacuum people are going to do stuff. That's what's going on. People are getting second courses of Paxlovid. I actually have heard of some fairly famous prominent individuals that have gone ahead and done that as mentioned. We need to know the answer.

It is interesting, we looked with remdesivir, 10 versus five, and now we're down to three in the first week. More actually was not better with remdesivir. Understanding the biology of this disease would lead me to think more is not better with the Paxlovid, but yes, let's, let's do the science. Yes, sure. Pfizer at some point is going to be selling this drug commercially. They would love to be able to sell more pills. Yes, let's lead this with the science.

VR: Chris writes, "How common is severe COVID in infants up to 6 months of age?"

DG: Fortunately, it is not common. It’s one of these tough things. Children, in general, are quite resilient. No, this unfortunately as we saw particularly last winter, that zero to 4 years, that zero to 6, was actually one of the highest impacted relative. Fortunately, we're talking about rare, uncommon events.

VR: Lastly, Clark writes, "My spouse and I are physicians in San Francisco for patients at increased risk for complications of flu. We wondered if there are any known significant downsides to their receiving two flu vaccinations this season, and what the optimal timing of them or spacing between them might be. Profound thanks for the best COVID infectious disease information podcast on the web.

DG: Again, it would be great. We do need the science on this. There are a few of us who are winging it based upon our immunology sense. One of the things, and I know this has come up in the past, is when you get that influenza vaccine your protection against symptomatic influenza does wane over the few months. It's about a 10% to 12% decrease per month going forward. You start running the numbers and you say, "OK, so I get my flu shot early October and then I go November, December, January, February, it's four months out. Would it make sense to do a second shot?"

It seems like it would make sense. I know there's people out there who do it, myself included, but we should do the science, particularly in higher-risk populations. Not just look at symptomatic influenza, but also look at the risk of hospitalization, severe disease. What's really important, I'm sort of plug here, is when people get influenza, their risks for the next

30 days of getting admitted for a cardiovascular issue for having other issues does go up. It's important to look at the big picture in those studies as well.

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

DG: Oh, thank you. Everyone be safe.

[00:34:25] [END OF AUDIO]