This Week in Virology

TWiV 1046 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]

From MicrobeTV, this is *TWiV, This Week in Virology,* Episode 1046, recorded on September 21, 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: Daniel, I went to my doc today and we got to talking about COVID and he said, "Yes, rebound is a thing, but it's really rare."

[laughter]

I can't escape it.

DG: Oh my gosh. OK, kill me now. All right, we'll talk about that but let's start off with a quotation. I actually was listening to one of the other *TWiV*s and, Vincent, you mentioned the book *Fever! The Hunt for a New Killer Virus*. Also, one of my favorites. Oh, look at that.

VR: This is the 1970 copy that I have had for years.

DG: That's great. I was given a copy by one of the characters in the book.

VR: Yes, you gave me a picture of the autograph inside it.

DG: Yes, so here we go. "In these times, the predictability of viruses creates a situation which is as delicate as a hand grenade with the pin pulled. The only answer is constant vigilance." People seem to have forgotten that. I think the current updated version is, the only answer is to put our head in the sand. [laughs]

VR: Exactly right.

DG: All right, well, let's take our head out of the sand for a moment. We'll start with flu RSV. Actually, really this is a wastewater. Flu and RSV all in one with the *MMWR,* "Wastewater

Surveillance Data as a Compliment to Emergency Department Visit Data for Tracking Incidents of Influenza A," that's the epidemic, "and Respiratory Syncytial Virus - Wisconsin, August, 2022 through March, 2023." Really what we're seeing here is it's all in the figures and so people should take a little time.

Basically, there's a positive correlation between the two surveillance systems. The wastewater surveillance basically shows that numbers start to go up, and we actually get a little bit of a warning. Wastewater goes up for flu, and then we start to see ED visits for flu. The wastewater starts to go up for RSV, and then we see the ED visits go up for RSV. It's really a nice early warning system. I was talking to our urgent care doctors this week about how it would be really nice if we check our weather, we check our news. For our employment, it might be nice to get the alert. By the way, wastewater surveillance has risen above such and such a threshold. Get prepared for the next few weeks when we'll see flu or RSV.

VR: Are we going to get those reports or are they going to just keep them?

DG: You actually have to go on, you've got to do the labor. Someone needs to make an app. It should be on the phone of all, well, I'm going to say all providers, urgent care, primary care, infectious disease, and then instead of just checking the weather and tracking the hurricanes out in the Pacific or the Atlantic, I guess.

VR: Oh, we should be on all *TWiV* podcasters so we can say with the weather, here's what's going on in the sewage, right?

DG: Yes. You guys stop talking about the weather. Start talking about this wastewater. [laughs]

VR: I'm all for it. Somebody write the app. All it has to do is pull the data.

DG: Yes. You'll be like, "It is now 22 degrees. RSV levels have passed the 200, you know."

VR: We have to give it a good name, right?

DG: A really cool name. Maybe people can write in. Maybe there's some people out there that want to create an app with the wastewater viral concentrations. Then you could actually see it starting to graph up and you can look, "Oh, look, human metapneumovirus." Somehow it's got to be linked to the data. All right, well, last week we talked a bit about flu, RSV and updated COVID vaccines and the messaging around the new Wild to Mild campaign. Now, how are we going to communicate? Well, apparently this is Vincent's favorite thing, we are going to have a chatbot reach out to people and encourage them to get vaccinated.

The article, "Chatbot-delivered Online Intervention to Promote Seasonal Influenza Vaccination During the COVID-19 Pandemic, a Randomized Clinical Trial," published in *JAMA Network Open*. These are the results of a nonblinded parallel-group randomized clinical trial conducted between December 1, 2021 and July 31, 2022 in Hong Kong, China. Eligible participants were 65 years or older, had Cantonese and/or Mandarin speaking skills. This is a Mandarin/Cantonese-speaking chatbot were community dwelling, had Hong Kong residency, were smartphone users, had not yet received their seasonal influenza vaccine, their SIV, for the 2021 through 2022 influenza season.

VR: All right, Daniel, we can't use SIV for that abbreviation.

DG: Isn't that a problem? I saw that. I was like, "Oh my gosh." You have to be careful with these three letter acronyms. "Have you gotten your SIV yet?" "No."

[laughter]

Participants were recruited through random telephone calls, and those who completed the baseline telephone survey were randomized to receive the intervention; get called by the chatbot or to be in the control group. In the intervention group, a simplified rule-based chatbot first assessed the participant's SOC. Let's see what the SOC stands for. What was the SOC? Am I even seeing what the SOC -

That's a problem with all these three letter acronyms. Basically, a chatbot is going to tailor online health promotion messages, and they're going to do this every two weeks for four sessions. What did they find? Well, they recruited about 400 so 396 participants, about 70 years. You got to be over 65. Sixty-three percent were females. They randomized them one-to-one, 198 in the intervention, 198 in the controlled. They showed that the seasonal influenza vaccine uptake rate was higher in those that got called by the chatbot, so 50% versus 35%.

VR: States of change. That's what SOC is.

DG: The chatbot is improving the rate of change. After we get our chatbots to encourage everyone to get their flu vaccine, maybe also chatbots tell people to get their COVID vaccine. What is going on with COVID? I think just like I talked about, we need an app where people can know what's about to come from the wastewater data. You can actually go on, I'm going to leave a link, you can go on covid.cdc.gov, you can look at the COVID tracker. You can look at what's going on with new admissions per week, and you can actually see that we are still in the midst of a steep rise.

We have more weekly COVID-19 hospitalization admissions since we had in early March of 2023. Also, if you look at this data, you start to get a sense of when we see these rises. We see an early, we see a plateau, and then it's really our January when we tend to historically see these peaks. Actually, the biggest peak was 2021 as far as hospital admissions, interesting enough. All right, well, I wanted to start this article with a reminder of the early days. It takes a while sometimes to get the data, but the article, “Temporal Assessment of Disparities in California COVID-19 Mortality by Industry: A Population based Retrospective Cohort Study,” published in *Annals of Epidemiology*.

Now here, the investigators used a population based retrospective cohort study approach. They identified COVID-19 deaths that occurred between January 2020 and May 2022 among the California working population age 18 through 64, using death certificates. They used the current population survey to drive estimates for working age Californians at risk of COVID-19 mortality.

A couple things you're seeing, we're not looking at everyone, we're looking at this 18 through 64. What they're really trying to look at is what was the mortality by industry. They're going to look at the different waves of the pandemic, but in all the waves of the pandemic, you can

see that healthcare is one of the highest risk industries. Here we're seeing an increase risk 2.49. Other service industries also up there, 2.89, manufacturing about twice the risk; transportation also elevated, 2.64; retail a little bit less than 2, so 1.9, and really much higher than professional, scientific, technical industry, where we're seeing the lowest rates.

Not only will I leave a link to this for people to take a look at this, but I also want to leave a link to a project called Lost on the Frontline. This is really recording the almost 4,000 U.S. healthcare workers that died in the first year of the COVID-19 pandemic. It just has a photo, has a little bit about them, just turning those statistics into real people. I think a lot of us have forgotten how bad it was in those early days as people say things like, oh, it's just the flu, et cetera, et cetera. I think we really need to realize just how incredibly powerful these vaccines are, how effective these medications are in transforming it from those early days.

VR: Can you imagine if we had had Paxlovid from the start, how much different it would've been?

DG: Not only would it be different, but I think it would be different now. Because we'll talk about a little bit later, but when you were saying, OK, 20% of my patients are going to end up in the hospital, and you could drop that from 20 to two right in front of you, I think it would've helped people. Because now we're talking about, maybe taking 6% and dropping that down to two or three. It's not quite real-time feedback. It would've been great in the early days to have that reinforced. Ventilation transmission. Now this is exciting stuff, Vince, and I hope you're as excited as I am. People are excited [chuckles] both -

VR: Well, when you say that I have suspicions. Go ahead. [laughs]

DG: [laughs] For those following this, a CDC advisory committee has been updating its 2007 standards for infection control in hospitals this year. Now, couple things to comment: 2007 since the CDC has updated its standards for infection control in hospitals. That's one kind of comment. Boy, that's been a long time. The other is, this is just hospitals. They released basically a PowerPoint on what they've been thinking about discussing. The final form probably won't be out until November. A big change that I've talked about over time is there used to be this binary that was right in the middle of respiratory transmission. They've now changed that binary to being between air and touch.

As they consider transmission via air, they make a few comments. They point out, historically, the infection prevention community has categorized transmission of respiratory pathogens as droplet or airborne. We've talked about how this goes back to about 100 years ago. As they comment in their slide deck, while these epidemiological terms reflect observed patterns of short- versus long-distance transmission, respectively, the terms do not explicitly describe a continuum of respiratory pathogen transmission through in the air.

They go on to say, all pathogens that spread via the air preferentially transmit over short distances due to greater concentration of infectious particles in the air and near an infectious person.

However, each pathogen has a signature pattern observed transmission that extends variably across short to long distances and over time, reflecting unique characteristics of pathogen durability while suspended in the air and the required dose for causing an infection in a

susceptible host. Then they're going to suggest new air transmission-based precaution categories. I'm going to go through these because in a sense, we've talked about the fact that some people are already moving in this direction. I actually am excited about this update. It's very controversial. I'll discuss why.

One of the things I really like as we get into this, is they're moving away from droplet and airborne, things that have meaning outside of the transmission directives. People say, how can it not be airborne if it's transmitted through the air? Let's use terminology. These are the new draft transmission-based precautions to prevent transmission by air. I'm going to start with the highest level, extended air precautions. This is where it's recommended that an N95 respirator be used. They're also recommending that the person be in an airborne infection isolation room. That's the negative pressure room. They give example pathogens, tuberculosis, measles, varicella.

Then they have what I think we refer to at Columbia as enhanced droplet, what they're now calling novel air precautions. Where you wear an N95 respirator. You don't have to have the person in a negative pressure room, you just keep the door closed. Then routine air precautions, where you might wear a medical or surgical mask, you don't have to have them in a negative pressure room. Eye protection is recommended for the novel air precautions, possibly for extended air precautions. For the novel air precautions, that would be MERS**,** SARS-CoV-2, SARS-CoV-1, pandemic phase respiratory viruses. Now, routine air precautions just for coronavirus seasonal influenza.

VR: I don't like this novel in the middle of the two. I get extended, I get routine, but novel?

DG: Yes. Novel's odd. Novel repercussions. How long will it be novel? Should it be -

VR: Yes, it needs another word to put it in the middle there. I know what they're trying to do, but -

DG: It does need a better.

VR: I would like some words that give you a hint of mechanism.

DG: What are you going to suggest? Enhanced? Air precautions? I like enhanced.

VR: For the middle one?

DG: Routine, enhanced, extended?

VR: Enhanced would work if you want to stay with this. Yes.

DG: What a lot of people are concerned about. There was actually a letter to, I say Manny Cohen in my notes, but it's actually Mandy Cohen, Dr. Mandy Cohen, CDC/HICPAC's plan to weaken guidance for healthcare, respiratory protection and infection control. I'll leave a link into it. They put out this PowerPoint. They're asking for feedback and input. Some of the things people didn't like is some of the articles that were referenced in the deck here seemed to suggest that maybe the medical surgical face masks are pretty good and almost as good as N95s. That's not what I'm seeing in the updated draft of the transmission-based precautions.

They also talk about how those N95s can tire you out, they can give you acne or, I think it's called maskne, stuff like that. I do like the fact that this old binary in the middle of respiratory, which goes back to over 100 years, is finally being addressed, finally being updated. People are also saying, hey, by the way, if you're going to do this, you should get people who are expert in these different areas, moving away from this five-micron thing that people have talked about for over 100 years. All right, I actually like this, Vincent. I'm optimistic that in November we're going to have an updated, improved, bit of guidance.

Because right now, some of the hospitals, they put airborne, they put the big red signs up, and then the door's sitting there half open and the person's sitting in a regular room next to a neighbor. Yes. Let's be honest with what we're actually doing.

All right, COVID active vaccination. I was talking with our Optum pediatricians this week and reviewing what is new with RSV, but also what's new with COVID vaccine guidance. I'll leave a link in here to updated CDC page, September 15. In a sense, things have gotten a little bit easier for just about everyone but the pediatricians. The CDC now recommends, we've talked about different levels of recommendation, updated COVID-19 vaccines for really everyone 6 months and up.

Really aged 5 years and up you get, one is the recommendation. We've talked about how the level of recommendation is increased for folks who are higher risk coming from other groups. Still for those kids 6 months to 4 years of age, you're going to be getting an updated vaccine with Pfizer, it's going to be three doses on a schedule, with Moderna it's going to be two doses on the schedule. One of the questions that came up last time is one of the comments put forth by Dr. Mandy Cohen. "The more people who get the shots, the bigger difference it can make in how many Americans are sick, and the ability of our healthcare system to handle influxes of patients."

This is this whole question of, am I doing something for other people when I get a vaccine? The more people that get vaccinated, does that really affect what's going on around us? How do we figure that out? Well, there's a couple ideas of how we might try to do some science here. We can do some modeling. I'm going to reference the article, “Modeling the Impact of a High-uptake Bivalent Booster Scenario on the COVID-19 Burden and Healthcare Costs in New York City,” published in *The Lancet Regional Health*. Here's the challenge. As we read in the supplementary materials, we performed a literature review to derive the estimates of vaccine effectiveness following each dose of vaccine against infection, symptomatic disease, and severe disease for all variants in this model.

This is tough because do we really know what the effectiveness of the new updated vaccine is against infection, symptomatic, and severe disease for all variants above prior infection, prior vaccination in many cases or both? Searching around, I found this article, “Can High COVID-19 Vaccination Rates in Adults Help Protect Unvaccinated Children? Evidence from a Unique Mass Vaccination Campaign, Schwaz, Austria, March 2021,” published in *Eurosurveillance*. Here they use this unique opportunity that was presented after the government of Austria supplied 100,000 extra doses of the Comirnaty vaccine to rapidly mass vaccinate the entire adult population over the age of 16 of Schwaz.

After the first campaign weekend in March 2021, around 70% of the adult population of Schwaz had received their first dose. In contrast, the rest of the country had a very low vaccination coverage first dose of only around 10% at that time. Now, of note, they're only vaccinating those over the age of 16 as the vaccines were not approved for younger ages until 28 May, 2021. This local mass vaccination campaign created a situation in which we have really high coverage of the adults, and then we have an unvaccinated 16 and under. Then we can compare that to surrounding folks and they're going to observe them for three months.

They're going to observe them until the end of May when the kids can actually get access. They observed a reduction in daily COVID cases of 57.4%. OK, that's fine. We got all these folks getting vaccinated. What about potentially a benefit for the kids? For children below 16, they saw, we'll call it a bystander-observed reduction in daily COVID cases of 42.8%.

VR: That's convincing as long as there are no issues with this way of studying it, which is an interesting way, right?

DG: Yes.

VR: As long as those kids are not vaccinated. They only vaccinated over the age of 16. As long as that's correct. Who knows?

[laughter]

Maybe some of those kids snuck in and got vaccinated. I just -

DG: Oh, my gosh. It's Austria. This is where if you've been pickpocketed and show up to get your wallet and it's three minutes past 7:00, they won't hand it to you until the next day. OK. No, there are some challenges. I like this because this is actually bystander effect. Remember, it's only three months. That's what they're arguing with the boosters. Three to four months we get everyone vaccinated. Maybe there'll be a bystander effect.

VR: Here's the thing, folks. It's not because it's sterilizing immunity in the adults. It's reducing the amount of shedding and that reduces the transmission. Stop saying sterilizing, OK?

DG: [laughs] I don't want to be sterilized. You want to be sterilized? No.

VR: No, I don't. It's not sterilizing. All you need is a reduction in shedding. Don't you agree, Daniel, with that?

DG: That's the goal. Yes. The goal is - Yes.

VR: It's transient because antibodies don't last at high levels forever. It's transient. It's the same thing we're trying to do with this new vaccine this fall is give you a couple of months of reduced shedding, right?

DG: Yes. Hopefully, this will pan out. Hopefully, there'll be a personal benefit and maybe there'll be a societal benefit as well.

VR: The question is, did CDC head know this data when she made that statement?

DG: I'm sure Dr. Cohen knew this data, but [laughs], all right. Let's move to the COVID early viral phase. I'm going to start with a little bit of an anecdote. Hopefully, people will find this educational, really edutaining, I think is what we like to say. I get a call on Sunday morning from a primary care doc about a patient in their 90s, tested positive. They want to know, should they go ahead with the Paxlovid? They've heard about this rebound. We have a little bit of a conversation. I reach out to the gentleman in the 90s. First thing is, this gentleman did an at-home COVID test and it was reportedly positive. I asked about it, "Oh, I had my housekeeper read it. They told me it was positive. There was a line."

I was like, "Was there one line? Was there two lines?" "I don't know." [laughs] All right, let's start by repeating that test. We repeat the test. There was one line, yes, the control line, not the positive test line. That's one of the first thing. Let's judge, let's talk to our patients. If you need to have them send us a photo, if you need to jump on a FaceTime or a telehealth, whatever it is. If someone is using those home tests, you may even want to observe them. Watch that they get a good sample, watch that they do the test properly. Because we're making a big decision. We're about to maybe spend $800 or $900 on a medication. We're potentially going to be adjusting, maybe stopping or adjusting other medicines to make that happen.

That's one of the first things, is make sure you spend the time to get the diagnosis correct. The next thing is there is a challenge with adjusting the medication. This provider I'm talking to a bit hesitant to use the Paxlovid because they were concerned. They told me straight they had a patient on diltiazem high dose they stopped the diltiazem and that person then ended up having issues and I asked them, "So, you just stopped the diltiazem? Did you look this up? How did you do this? This is really a plug for something I do all the time. Take the time, go onto your computer, use the Liverpool COVID-19 drug interaction checker. Go through the medicines. Let's say diltiazem comes up as a possible drug interaction.

They'll go ahead and there's a whole little blurb. They'll tell you that diltiazem is metabolized by the CYP 3A4, the CYP 2D6, that there's probably going to be an interaction they'll recommend not stopping diltiazem, but a dose reduction of 50%. Really, it's all out there to help you manage these drug-drug interactions. The next thing I want to, just going to have to keep saying this a million times, there is no such thing as Paxlovid rebound. Twenty percent of high-risk patients will feel better and then they will feel worse during that second week. That is whether you treat them or not. The big difference during that second week is whether or not they end up in a hospital. Let's talk about another article.

The article, “Nirmatrelvir/Ritonavir Use and Hospitalization or Death in a Previously Uninfected Nonhospitalized High-Risk Population with COVID-19: A Matched Cohort Study,” published in *JID*. Here are the results of a matched cohort design where they're going to look at individuals prescribed Paxlovid within three days of a COVID diagnosis compared with untreated controls. Oh my gosh, among 7,615 individuals prescribed Paxlovid and 62,000 controls, these are people who did not get treated, the risk of hospitalization and death was, oh my gosh, lower among the folks that got Paxlovid versus untreated controls. The difference was significant for those over 60 as well as those less than 60. Interesting for asymptomatic and symptomatic persons.

They're actually seeing benefit. Asymptomatic folks are actually ending up getting hospitalized. Significant benefit was observed among unvaccinated and vaccinated individuals. Those with and those without a booster. I want to put this in context. We were talking early on, what if Paxlovid had been here in the early days? In the early days, about 20% of folks ended up in the hospital. High-risk people, it was even higher. A high-risk person may be someone with a 40% risk of ending up in the hospital. These are uninfected, but many of these folks are now vaccinated. In the control group with 62,000, we saw 3,468 hospitalizations or death combined endpoint, or about 6% progressing to this endpoint. In the treated group, this drops to 243, only about 3%.

Number one, as we've been saying, we do recommend Paxlovid; number two, remdesivir; three, molnupiravir; four, convalescent plasma for certain select group and avoid doing those harmful things. As we've discussed, early steroids can increase your risk of progression, basically turning off the immune system when you need it most. Second week, we've been talking about this forever, the cytokine storm. What you can do is turn this from wild into mild with Paxlovid, molnupiravir, remdesivir. If they end up here, we're looking at treating those patients with steroids, anticoagulation, pulmonary support, maybe remdesivir and immune modulation. I'm going to finish this off with an article that another group published.

Hopefully, our group will publish our article soon. The article, “Vaccination after Developing Long COVID: Impact on Clinical Presentation, Viral Persistence and Immune Responses,” recently published in the *International Journal of Infectious Diseases*. Now there's growing evidence of a preventative and therapeutic benefit for vaccination in terms of Long COVID, but what about mechanism? They're going to try to get at that a little. These are the results of a prospective observational cohort study that evaluated the number of PCCs, that's post-COVID condition symptoms, affected organ systems, and psychological well-being scores before and after patients with post-COVID conditions received COVID-19 vaccination.

They simultaneously evaluated biomarkers of systemic inflammation, levels of plasma cytokines and chemokines. They measured blood, plasma, and intracellular level of SARS-CoV-2 antigens, which is interesting, and immuno reactivity to SARS-CoV-2 antigenes in blood. We'll start off with the numbers. These are not huge numbers. Actually, I'll tell you from our study, it's hard to recruit for these studies. Of the 83 participants included in the study, 44 had not yet received a COVID-19 vaccine at the inclusion visit, these are unvaccinated, while the remaining 39 had already received one or two doses. Of the 44 unvaccinated participants, 39 were also evaluated. After one, it was 23, or 2, that was 16 vaccine doses. They also performed a cross-sectional analysis comparing all unvaccinated participants with those having received one or two vaccine doses. Not exactly the study design I was hoping for, right? Ideally, what I want is all unvaccinated people with PASC or post-COVID conditions and then a one to one. Half of them get the vaccine, half of them get that saline shot, and then we go measuring stuff at different time points. Some limitations here in design, just to point that out. Now, what they do find within the limitations outlined here is that COVID-19 vaccination was associated with a decreased number of post-COVID condition symptoms.

Pre-vaccination, 6.56; post-vaccination, 3.92; affected organ systems, we see 3.19 dropping down to 1.89; and we see increases in the World Health Organizatio- 5, Well-Being Index scores, pre-vaccination, 42.7 going up to 56. Now, patients with post-COVID conditions, it's where it gets into the molecular. They also had significantly decreased levels of several pro-

inflammatory plasma cytokines, chemokines, including soluble CD40L, GRO-Alpha, macrophage inflammatory proteins, so MIP-1Alpha, Interleukin-12P40, G-CSF, M-CSF, IL-1 beta, and stem cell factor.

Now, this was interesting. They report that SARS-CoV-2 S1 antigen persisted in the blood of PCC participants, mostly in non-classical monocytes, regardless of participants receiving vaccination. This last one is interesting. The investigators say, "How did they do this?" They tell us that they measured concentrations of soluble SARS-CoV-2 spike and nucleocapsid proteins using a special kit. They also actually did intracellular staining.

VR: All right, so there's a reduction in long PCC symptoms with vaccination. I'm curious as to whether subsequent doses would further reduce it, because the other day Paul Offit said after three boosters, three doses of vaccine, the effect on Long COVID is much diminished. That needs to be redone with currently circulating variants and the new vaccines, right?

DG: Yes. I'm going to agree with Paul, based upon some of the research I've seen here. We saw, and I'm just going to give numbers, a 40% people improved with the first shot, we pick up another 20% with the second shot, we pick up less than 5% with the third shot, and then we really see 1% or less after that. Really diminishing returns. Big bang with the first, OK with the second. Do we keep throwing people with Long COVID? We go, "Let's throw the updated vaccine. Maybe now, with new variants, we need to repeat those interventions." All right, I will close out here with no one is safe until everyone is safe.

Thank you, everyone, who's been going to parasiteswithoutborders.com and clicking Donate. We want to get up to $10,000. If we can raise $10,000 in August, September, and October, we're going to double that and give a potential maximum donation of $20,000 to Floating Doctors down there in Panama. One of the doctors from there is up visiting at the moment. They're struggling. Everything you can do, thank you.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Dave writes, "Thanks so much for all your advice on *TWiV*. I have numerous friends who are trying to get advance Paxlovid prescriptions filled, so they can take it early as advised in case they test positive while traveling. They're all elderly and definitely fall into high risk categories. Most are getting denied or told useless advice like, "Call me if you test positive in Hungary." Could you possibly update your COVID advice document with a few lines on Paxlovid travel guidance? It would be useful to have an authority to point to, since the CDC has been woefully silent on the issue. Most docs seem barely aware that the EUA restrictions are no longer in effect. Unfortunately, among the cruise ship set, this will probably lead to some preventable deaths."

DG: Yes, Dave, thanks for writing in. It's interesting. We've talked about this several times, and even the fact that we're not even using this off label. We're just prescribing it in advance. You're traveling, here's your treatment. Only take it if you test positive. I do, yes. Oh, if you test positive, and you're in Hungary, how are you supposed to get your Paxlovid if you're out on a cruise ship? These are some high risk individuals who we just talked about that recent study is 6%. Let's say, try to do the math in my head, 1 in 15, high risk person you could calculate, oh, you got a 1 in 15 chance of progressing to hospitalization. We can reduce that 90%.

One of the emails I recently got from a listener in Maine is that a lot of the Paxlovid prescriptions that are still sitting on shelves are still packaged in the EUA boxes, and the pharmacists feel like, "Oh, but if it's packaged in the EUA box, I have to follow the EUA." Not sure where that came from. It is a fully licensed, you can use it, and you're not even using an off-label here. If you look at the EUA, the EUA does not say that you need to have a confirmed positive test. The EUA was updated. Basically, we are prescribing Paxlovid for the treatment of acute COVID. We just might be sending the script in before the test comes positive, before the indication arises. Also, actually, we do have a listener, and I think we are going to be updating those COVID treatment summaries. If our listener wants to help us, there are going to be nice graphics and stuff, so we'll get those updated.

VR: Jen writes, "My husband, 7-year-old and I have been very COVID cautious, but we're about to have a lot of potential exposure on an early October trip to Japan with 45 members of our extended family, mainly because there will be no way to avoid indoor dining for all or most meals. We're trying to decide how to time our vaccines with this trip, and I'm separately agonizing over whether to go at all since I'll be 30 weeks pregnant at the time. Here are my questions: One, and we'll take these one at a time, as you've discussed, it's a little early to get COVID and flu shots. Ordinarily, we wouldn't rush out for boosters, given our trust in our primary vaccine series.

“Our main goal is to prevent me, the pregnant person, from contracting COVID from this trip. We are hoping to capitalize on the early protection from infection that a booster might offer. Would you recommend that we get these shots now in advance of our early October trip, since we will have way more exposure than we want, or save the protection for later in the season? I would be 28-to-29 weeks at the time of a pre-trip booster."

DG: Yes. This is a good question, right? Because, Vincent, I've been thinking about this lately. Normally, I do my flu shot in early November, end of October, because I'm thinking Thanksgiving, end of December holidays. Now you and I are going to be attending a bunch of conferences, first up in Boston, then out in Chicago. I'm starting to think, maybe if I'm going to get myself boosted for the flu protection, maybe if I'm going to get this new vaccine, maybe I want to time it two weeks before that. The challenge, right? You're understanding the science here. We're only thinking a three to four-month boost above that, enduring protection from the vaccine. I think what you're starting to bring up is reasonable. We think you really get up about two weeks after that shot. Really, it ramps up. That's our peak. Then it goes down maybe 15%, 20% per month after that.

VR: All right. She says, "Next, updated vaccines have been slow to arrive in Seattle. We may not be able to get one until a week before the trip. Is it worth it, or should we wait till we get back?

DG: A week before the trip, as I - it'll be ramping up. I think that's reasonable. Yes.

VR: OK, so here comes Paxlovid. Since I'm pregnant, I hope to get a Paxlovid prescription in advance of our trip, although I'm having a hard time finding a provider who recommends Paxlovid during pregnancy at all, much less as an advance prescription, but I'm also considering not going on the trip because of possible risks to the baby. My midwives have said they're seeing placenta damage when parents contract COVID, but they don't have info

on whether vaccination or Paxlovid mitigates that risk. Does research exist on the impact of Paxlovid or a primary vaccine series on the outcomes for a baby if a parent contracts COVID?

DG: You're listening to a provider who recommends Paxlovid during pregnancy. I should mention that the OBGYN Professional Society recommends Paxlovid during pregnancy. The CDC, we all recommend those of us keeping up on the science and literature, recommend Paxlovid during pregnancy. It is a high-risk state. Paxlovid has the ability to reduce your chance of severe disease. It also has the advantage of protecting the unborn child, protecting you from an early delivery, preterm delivery. There is research on the primary vaccine series and Paxlovid protecting you and your baby.

VR: All right, Rick writes: “From your discussion on correctly using the SARS-CoV-2 rapid antigen test, I see this worst case scenario: Day zero start to feel symptoms. Day one, first rapid test, negative. Day three, second test, negative. Day five, third test, positive; contact my Kaiser PCP, orders Paxlovid. Day six or seven start Paxlovid. Am I too late to catch any active virus? Is starting Paxlovid this late in the replication cycle better than nothing?

DG: Yes, it's really interesting. If you look at the data. If you got to start within the first three days 87% reduction, no, 89% reduction in progression in the first study. We started like, day five it's 87, you start day six, I'm not thinking suddenly you fall off a cliff. Ideally if you describe this worst case scenario on day five, when you test positive, hopefully your Kaiser PCP gets that Paxlovid to you same day and you get going, better than nothing. Ideally, let's get a little bit shorter.

VR: All right, Anonymous writes, "I'm an old, retired pediatrician, followed your podcast for years. A question has come up in my family with respect to initial immunization of their 2-year-old daughter, who through misinformation has been unimmunized against COVID. She's expecting a new sibling momentarily and her mother, who has been immunized but not recently, and also has presumably acquired COVID as well, they wish to start her immunizations ASAP. Should she receive the complete series of the new vaccine or one of the older versions? If she receives the new Moderna version just released, does she get two shots? She's in daycare. What advice to give her parents about exposure to the new infant? What about exposure to her great-grandmother, who is 85 and on Xarelto?”

DG: OK, so great, thank you for asking. I'm not sure why anonymous, but you're Doctor Anonymous. In a sense, I was saying it's been made quite a bit simpler. When I was talking to the pediatricians the other night this 6 month to 5 years, that's really the high-risk group. They don't come into this world necessarily with any pre-existing immunity. Maybe mom has some degree of transfer of immunity.

By the time you're 6 months to 4, when you're 2 years old these are the kids that we saw a disproportionate number requiring medical attention for their acute COVID. For the Moderna, it's a two-shot series. They would now get the updated vaccine. If it was Pfizer, it would be three shots. Again, they would get the updated vaccine. That would be the advice in this go ahead, get those immunizations ASAP. The two shots of Moderna would be a fine approach. As we talked about, it might not only protect the little one, but there may be some bystander protection for that great grandmother who's 85.

VR: All right, two more questions. We have a lot today because we're getting a lot of questions, Daniel. I guess it's COVID season.

DG: [laughing] OK.

VR: Michael writes, "I've had a few friends who have had COVID turn negative by lateral flow and then turn positive during rebound. I know rebound is not a thing after Paxlovid, but why would the assay turn positive again?"

DG: This is something that we have seen for a really long time. Those antigen tests are actually picking up protein intracellular. You're not picking up from the mucus, you're actually picking it up. During that inflammatory phase, you can often get significant shedding of the intranasal cells. If you were to actually quantify this with PCR, you're not back up there in the millions, tens of millions that you saw early on. You are picking up a little bit of positivity. That should not be confused with viral rebound. That is not viral rebound. That is the cytokine storm second week. That's the early inflammatory phase. What I tell people is once you test positive and you had COVID, stop testing.

VR: All right, last one is from Wendy: “Twenty-seven weeks pregnant, healthy 30-year-old without any complications. As a virology Ph.D., I'm well aware of the importance of vaccination, want maximum protection for my baby, therefore, I want to get updated COVID vaccine, flu shot, newly approved RSV and Tdap vaccines. My OB only provides Tdap. She says I can get them from local pharmacy. I asked her about how should I schedule it. She only says she can give the Tdap vaccine on my 37th to 38th week latest. Others I better have at least four weeks intervals apart. What would be your suggestion for the timeline? I'm thinking getting COVID flu week 29, getting RSV week 33 Tdap, week 37. Does that sound OK?

DG: That does, that sounds great. I should point out. The RSV vaccine on week 33 is going to protect your child. I'm thinking about timing. It's actually perfect timing. It's going to protect them during this upcoming RSV season.

VR: All right, second question. “I don't have RSV vaccine ready in a nearby pharmacy for pregnant women. They only have the one for 60 plus people. I believe the FDA already approved it for pregnant women based on your update. Has the CDC approved it? Do you know when RSV will be ready in the pharmacy for pregnant women? Do you know if there are any side effects related to pregnancy I should be aware of?

DG: Yes, so it's the same actual, so there's two approved RSV vaccines for the over 61 of them is also approved and recommended for pregnant women. That's sort of a packaging challenge maybe, unless they only are carrying one of the two and maybe they're carrying the one. Side effects, no. Actually, this was incredibly well tolerated. As mentioned, healthy kids end up in the hospital. I think it's 2%. One in 50 kids will end up in the hospital at highest risk is when your child's going to be born. That's just hospitalization. Forget about the 300 children that die every winter. Forget about the thousands and thousands that end up needing to see the pediatrician, suffering through the misery of RSV.

VR: “Third question, I always have a fever and whole-body pain every time I take a COVID shot. However, I'm allergic to acetaminophen so I can't take Tylenol. I used to take ibuprofen, but I'm pregnant so it's not an option with the baby in my body. I can't let my body

temperature go high. What other pregnancy-safe medicine you recommend me to prepare for the booster? My OB said I could probably take baby aspirin, but I'm not sure if I'm allergic since I have never taken it before.

DG: Yes, you always can use non-pharmacological ways of cooling yourself. I feel like we underutilize this. We're quick to grab the pills. A cool moist cloth on the forehead, maybe your partner can help with that. It's fine to use different things to help with the temperature. Because that's the biggest thing. You're pregnant. We really don't want that body temperature going up. We want to keep you cool and comfortable, drinking plenty of fluid, staying well hydrated. I think taking advantage of non-pharmacological cooling approaches.

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

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

[music]

[00:49:10] [END OF AUDIO]