This Week in Virology

TWiV 1036 Clinical Update

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Guest: Daniel Griffin

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

[music]

VR: From MicrobeTV, this is *TWiV, This Week in Virology,* Episode 1,036, recorded on August 17, 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, cases of COVID still going up in the New York area?

DG: They actually definitely are. The cases, the percent positivity, the hospitalizations, it's all on the way up. It's not going down.

VR: It's interesting. It's August. What do you think? Are they going to continue to rise through the winter or are they going to go down and then go back up again in the winter? What's going on here?

DG: I love predicting the future.

[laughter]

DG: No, I think people always say it's the hardest thing to predict. Maybe that was just Yogi Berra. Actually, we should have some sense in our specialty. The weatherman is wrong a lot, but they're not always wrong. We would expect it to go up, go down a little bit. Then we'll see our major surge December, January because this is a respiratory pathogen and it is influenced by human behavior.

It's been really hot lately as people may have been aware. A lot of people are indoors. You go somewhere to eat at a restaurant. No one's sitting outside, right? They're all packed inside. A lot of vacations. There's a lot of behavioral things that are going on. Don't worry. There are some people that are blaming it on the newest variant, but I will always-

VR: Nonsense.

DG: - attribute -

VR: Human behavior.

DG: - things to human behavior.

VR: What about flu? Does flu go up in August?

DG: It really doesn't. Part of it is you need a background level. Flu is fascinating. Usually, there are new variants that come out of certain parts of the world and we get - well, it would be - Then once they get in a certain level, then it is again behavior, right? We see surges sometimes right around Thanksgiving, right around the end of December. Maybe sometimes the surge happens in the spring. There are really a lot of human behavioral events that affect when we see the surges of respiratory pathogens.

VR: Now, I'm just trying to get people to understand that COVID isn't behaving any differently from any other respiratory infection.

DG: No, it's going to take a while before it settles. There's such a background that whenever you bring people indoors and close together, you see these rises. All right. Well, let's start with our quotation. "Success consists of getting up just one more time than you fall," and that's attributed to Oliver Goldsmith, an Anglo-Irish writer.

VR: That's really good. [laughs] That's really good.

DG: All right. Well, we'll start with dengue. Actually, you got to keep following this. I think this morning, I heard we were up to 11 dengue cases down there in Florida. I don't know how many people follow outbreak news today. Vincent, you actually sent me this when we were only at 10. We will see where we end. Now, you no longer need to leave the U.S. if you want to get leprosy, dengue, malaria. It's all here.

I also wanted to share an article. Actually, this is an article I ended up discussing on rounds this morning. It's this whole idea that people have, and I understand, "Listen, I'm healthy, so do I need to really worry about things? If I have a healthy baby or a grandchild, do they really have to worry about RSV? Isn't RSV something that sick people get, other people get?" Well, does RSV make perfectly healthy infants sick enough to end up in the hospital, sick enough to end up in the ICU?

Well, the article, “Infants Admitted to U.S. Intensive Care Units for RSV Infection During the 2022 Seasonal Peak,” was recently published in *JAMA Network Open*. These are results of a study designed to evaluate the characteristics and outcomes of RSV-related critical illness in U.S. infants during peak 2022 RSV transmission. The way they set this up is the first 15 to 20 consecutive eligible infants from each site were included for a target sample size of 600.

Among the 600 infants, the median age was 2.6 months; 71.1%, the vast majority, were full-term; 81.2% had no underlying medical conditions. I just want to point that out. These are healthy, full-term infants. That is what makes up the bulk of these tens of thousands of RSV admissions. Now, how do they do? They're in the hospital for a few days. Well, they're not just in the hospital for a few days.

Overall, a quarter, so 23.8%, required mechanical ventilation, so one in four. Many of the infants that were not intubated required high-flow nasal cannula. That was 40.5%, almost half, right? Now, we're up to 65%. We had a number of individuals requiring the bilevel-positive airway pressure. That was a quarter. Continuous positive airway pressure, 8.7%. I just want to point out, we don't hospitalize infants easily.

We don't really want them to have the trauma of being in the hospital. These individuals are being admitted to end up on a ventilator, to end up on high-flow nasal cannula, to end up with BiPAP or CPAP. Now, four of the infants, so that's 0.7%, actually required extracorporeal membrane oxygenation, that's ECMO, and a couple of kids. Only looking at 600. Two of them died. How long were they in the hospital? They were in for an average of about five days, so a range of 4 to 10 as far as the interquartile range.

VR: Daniel, the monoclonal that we discussed would be useful to have given these children, right?

DG: This is, I think, huge. People are like, "Who should get it?" Everyone should get it. I did listen to the Paul Offit episode about Beyfortus or nirsevimab. You can't say, "Oh, but my child is healthy. They'll be fine. This is that." Don't wait till after the test to start studying. We can reduce the risk of these healthy kids ending up in the hospital, ending up in the ICU, but it's about 90% reduction. Maybe it's even more once you roll it out and you can actually protect the community.

Six-hundred dollars a shot and it's just a shot, almost like a vaccine shot, tremendous, potentially benefit to doing this. All right, I just want to get that across. RSV this year can be completely different than every other year.

All right, moving into COVID, the article, "Long-Term Risk of Death and Readmission after Hospital Admission with COVID-19 among Older Adults: Retrospective Cohort Study," published in *the BMJ*. Here, they looked at 883,394 Medicare fee-for-service beneficiaries aged 65 or older. That's pretty old, Vincent, right? 65.

VR: It's incredibly old. Unbelievable.

DG: [laughs] Discharged alive after an index hospital admission with COVID-19 between the first of March 2020 and the 31st of August 2022. [laughs]

VR: Sorry, Daniel, you can only be discharged alive, right?

DG: [laughs] I like that. These are ancient individuals being discharged alive. No, we do joke about the celestial discharge. These are people who survived that hospital admission were discharged, not to the morgue.

VR: If you die, do they still consider that a discharge?

DG: Yes, it's a celestial discharge.

VR: Oh, OK. I'm sorry. I didn't realize it.

DG: [laughs] Vincent, even if you die in the hospital, we will still discharge you.

VR: Still discharge me? OK.

DG: Yes. They compared this to 56,409 historical controls that have been discharged alive after a hospital admission with influenza, first of March 2018 and 31 August 2019. Now, we're joking a little, but I have to say, this is an issue that people probably know gets me quite upset. I feel like we need to keep focusing on this because there was this whole idea that, "Oh, if you survive that hospital admission, it's all good, right?"

There were all these clap-outs that people are leaving. I'm like, "Yes, this is fine. Can you stop clapping? Let's try to make sure that someone's going to take care of these people. Because once you get out of the hospital, bad things can potentially happen," and they did. A significant number of these patients would die in the next few weeks, get readmitted, develop Long COVID, so just beginning the months of challenges that were before them.

Many being clapped out would not have the right medications at their pharmacies. They wouldn't have a follow-up appointment to make sure this was really a safe discharge. Many times late in the evenings after day in the hospital, I would be doing these telehealth visits with these patients after discharge, only to find out that they had not gotten the proper discharge medicines. Maybe what was prescribed was too expensive. They couldn't afford it, so they weren't taking the medicine. Sometimes this was financial issues.

A lot of times, as we know, during the pandemic, they really had trouble accessing their primary care doctors, and many were really struggling. Here, the investigators are going to compare the COVID-19 cohort to the influenza cohort. Despite the COVID-19 cohort being, in general, a healthier group, lower comorbidity burden, the COVID-19 cohort had a higher cumulative incidence of all-cause death at 30 days. These are folks that got discharged. Ready for this? 10.9% would die in the next 30 days of people discharged from the hospital versus 3.9% for influenza.

Now, when they were followed out to 90 days, 15.5% had died. At 180 days, 19.1%. The COVID-19 cohort also experienced a higher risk of hospital readmission at 30 days. That was 16%. At 90 days, a quarter of them, 24.1%, had been readmitted. Now, there was some good news I want to point out. Things did get better over the study period. The 30-day risk of death for patients discharged after COVID-19 admission did decrease from 17.9% to 7.2% over the study period.

VR: Just a reminder, these are people over 65 years of age, right?

DG: Yes. This is not all-comers **,** right? As we know in the early days, we had people in their 30s, 40s, 50s getting admitted to hospital. Some of them ending up in the ICU. This is specifically looking at those 65 and over. We're looking at a specific subset.

VR: Do you think the majority of these didn't start any antiviral medication soon enough?

DG: Well, if you look at the dates, we're looking here March 2020. It's early days, didn't really know what we were doing, didn't have a lot of great tools of anything. Unfortunately, we had tools that were not helpful. One of our listeners was asking for an updated, "How do we treat

COVID?" Hopefully, they're taking notes, but we're going to go through not only a recap, but we have actually what I think is a big update here.

As you mentioned, what about antiviral? Person tests positive, right? We can test with those rapids. If you get a positive, we usually are not testing that first day, you're feeling crummy. It's that next day. If that's negative, you want to repeat it in 48 hours. If it's positive, it's positive. Really great specificity here. As we know, the sensitivity, if we want to get what we want with those rapid antigens, you've got to test that next day. You've got to test 48 hours later.

Now, we're in the 90%. In some cases, now, we're having better access to PCR. Now, we've made the diagnosis. You've got symptoms. This isn't just a positive test in an asymptomatic individual. This is someone who has COVID-19, the disease, confirmed by the positive test. Number one recommended therapy is Paxlovid, right? It's about a 90% reduction in the risk of progression. We're seeing that consistent in unvaccinated, in vaccinated, et cetera, et cetera. As we've talked about before, some medication interactions.

Look at that Liverpool drug interaction checker to see what you can do. I had a gentleman yesterday. We were going through. No Cialis for 10 days. You may not want to use your Cialis for the next 10 days. Also, no statins for the next 10 days. You want to navigate those drug-drug interactions. Occasionally, you're going to be reaching out to a colleague to find out how you can safely manage these. The other we've talked about quite a bit is renal, right?

The article, "Safety Profile and Clinical and Virological Outcomes of Nirmatrelvir-Ritonavir Treatment in Patients With Advanced Chronic Kidney Disease and Coronavirus Disease 2019 (COVID-19)," published in *CID*. As we've mentioned several times, currently, nirmatrelvir, ritonavir, think of nirma, Paxlovid is currently not recommended in patients with an estimated GFR less than 30. Once we get less than 60, we actually drop the dose to a renal dose.

Here, we have the results of a prospective, single-arm, interventional trial that recruited patients with eGFRs less than 30 and those on dialysis. Primary outcomes included safety profile, adverse serious events, events leading to drug discontinuation. They looked at disease symptoms, virological outcomes by serial severe acute respiratory syndrome coronavirus-2 PCR tests, rapid antigen tests. Virological and symptomatic rebound were also recorded.

Now, 59, so 69.4% of the 85 participants, had stage 5 chronic kidney disease and were on dialysis. 94% completed the full treatment course. 9.4% and 5.9% had adverse events. These were comparable between those above and below, less than or greater than that 30 cutoff. The viral load significantly decreased on days five, 15, and 30 for everybody. The reduction was consistent in the subgroup with the GFR less than 30.

Ten patients had a virological rebound, which was transient, and I will point out asymptomatic. I just want to go through. We're going to leave a link to this article because I think every practicing provider who sees COVID patients should have this. What's in this is basically how they did the dosing, right? GFR is greater than 60, normal dosing, the nirmatrelvir, 300 milligrams, so two of the 150s, plus one of the ritonavir, 100 milligrams twice a day. Do that for five days.

Now, as per the package insert, licensing, if your GFR is 30-60, you're going to drop that down to nirmatrelvir, 150 milligrams, and ritonavir, 100 milligrams. One of each, twice a day, five days. Now, here is the variation. What if they are less than 30 but not on dialysis? Then they go ahead on that first day and get the nirmatrelvir, 300 milligrams, the ritonavir, 100 milligrams once on that first day. Then for days two to five, they do 150 milligrams of the nirmatrelvir, 100 milligrams of ritonavir, right? You're taking one of each once a day.

It's not a big difference, right? You went from the nirmatrelvir 150, 100 twice a day. Now, you're less than 30 and you're just doing it daily to finish off those five days. Then they actually have dialysis dosing, which they actually go through, which varies based upon body weight. If the body weight is greater than 40 kilograms, then you're going to do it just like the less-than-30. If the body weight is less than 40, you're just going to do the one pill, one pill once a day for the full five days.

All right, so I will mention that that would be off-label, by the way, so just to mention that. It's nice to know that this high-risk population potentially has an approach that is evidence-based. Number two, remdesivir. Remember, we're talking here about the first seven days, the first week. This is approved all the way down to 28 days of age. People at risk of progression to severe disease, we can do a three-day, early IV approach.

Number three, molnupiravir. Remember, that's Thor's hammer. Twice a day, five days, maybe about a 30% reduction, so better than doing nothing. Four, convalescent plasma. Remember, this is an early treatment option focused on the immunocompromised COVID-19 patients at high risk for progression to severe disease with no other treatment options. Interesting to think about that. Then as we like to say over and over again, let's not do harmful things and useless things.

Along these lines, I want to share the article, “The STOP COVID 2 Study: Fluvoxamine vs Placebo for Outpatients With Symptomatic COVID-19, a Fully Remote Randomized Controlled Trial,” published in *Open Forum Infectious Diseases*. These are the results of a randomized, double-blind, placebo-controlled, fully-remote, multi-site clinical trial that evaluated whether fluvoxamine prevents clinical deterioration in higher-risk outpatients with COVID-19.

Now, between December 2020 and May 2021, non-hospitalized U.S. and Canadian participants with confirmed symptomatic infection received fluvoxamine 50 milligrams on day one, then 100 milligrams twice daily thereafter, or placebo for 15 days. I think that was a saline squirt. Just mentioned that for you, Vincent. That pill that you thought was the other. The primary modified intent-to-treat population included participants who started the intervention within seven days of symptom onset with a baseline oxygen saturation greater than or equal to 92%, right? This is that first-week, non-hypoxic viral replication stage.

The primary outcome was clinical deterioration within 15 days of randomization defined as having both one, shortness of breath, and then two, oxygen saturations dropping less than 92%. Now, a total of 547 participants were randomized, met the criteria, 272 in fluvoxamine, 275 in placebo, the Data Safety Monitoring Board recommending stopping early for futility. I just want to point out that clinical deterioration occurred in about 5% of folks in the fluvoxamine group and about 5% of participants in the placebo group. The trial did not find

fluvoxamine to be efficacious in preventing clinical deterioration in unvaccinated outpatients with symptomatic COVID-19.

All right, so you've avoided doing harmful things. You've done the best you can, but a certain percent of individuals will still progress to the second week to the early inflammatory, lower respiratory hypoxic phase, the cytokine storm. Some people will feel a little bit better before they start to feel worse. Number one, steroids at the right time in the right patients. This is after the first week. This is in those patients with oxygen saturations resting on room air of less than 94%.

Updated, let's make sure we're making current up-to-date recommendations. Dexamethasone, 6 milligrams a day, times six days. Not 10 days. That's old. That's out of date. If you're still saying 10, you're not keeping up on the literature. If they feel better, then you don't continue it after discharge. In some individuals, it will be shorter. Ten days is not better than six. Now, are we doing anything other than helping our patients survive, helping them stay out of the ICU? Are there any long-term benefits to targeting the right patients with the right dose at the right time?

The article, "The Effect of Corticosteroids, Antibiotics, and Anticoagulants on the Development of Post-COVID-19 Syndrome in COVID-19 Hospitalized Patients 6 Months After Discharge: A Retrospective Follow-Up Study, was published in *Clinical and Experimental Medicine*. This study employed two distinct databases. The Medisch Spectrum Twente (MST) clinical database, going forward, comprising electronic health records of COVID-19 patients hospitalized at MST and post-COVID cohort database, which contain follow-up information on the same patients.

These databases were integrated to establish the relationship between the administration of corticosteroids, antibiotics, or anticoagulants during hospitalization, and the occurrence of post-COVID-19 syndrome after a six-month interval following discharge. Now, a total of 123 patients who are hospitalized due to COVID-19 were included in this study. Among these patients, 26.8% developed post-COVID-19 syndrome, which persisted even six months after hospital discharge.

Multivariate analysis revealed that patients who received treatment with corticosteroids had a significantly lower likelihood odds ratio of 0.32 of developing post-COVID-19 syndrome, so a 68% reduction in getting on COVID getting steroids into these folks. Now, they did report a trend toward a protective effect of anticoagulants and a trend for patients treated with antibiotics having an increased risk of developing COVID-19 syndrome, but just a trend. Small N of only 123. Nice to see that in such a small number, there was already a statistically significant 68% reduction of Long COVID in folks that got the steroids at the right time.

All right, number two, anticoagulation. We have really good guidance from professional organizations, and also really outlining what were the studies, on whom were they done, and how we translate those into our patients. Number three, a lot on pulmonary support. Number four, remdesivir. If we're still within the first days from symptom onset, if we're not on a ventilator, here, we're talking about five days versus three.

Always important in our consults to be pointing out, we're in the first seven days. I'm recommending three days. We're past that. We're starting to get into the early inflammatory phase but still in the window of benefit. There, we're recommending five days. Now, we have a bit of guidance to help us make decisions about our high-risk, really compromised individuals. Basically, with remdesivir, the product insert says we can go right ahead even if they're on dialysis, so great option.

Number five, immune modulation. Tocilizumab. In some cases, baricitinib. Data is looking like a 30-day outcome, pretty similar. Independent of which of those two options you go with, tocilizumab might be a little more frequently used here in the States. Remember avoiding those unnecessary antibiotics and unproven therapies, so really make that decision. Does every patient with a viral pneumonia need to get a dose of antibiotics in the ER? Probably not.

All right, and moving into Long COVID. The *MMWR*, "Long COVID and Significant Activity Limitation Among Adults, by Age - United States, June 1-13, 2022, to June 7-19, 2023," was published August 11. Start with a little background here. This is a retrospective cohort study among eight large integrated U.S. health systems that found that SARS-CoV-2 infection was associated with a 4% increase in healthcare utilization over the six months following positive SARS-CoV-2 test results.

Further along, COVID, as we know, can have this significant impact on quality of life, functional status, inability to work. Well, what is this study, this report at? In this report, the CDC analyzed data from the Census Bureau's home Household Pulse Survey, HPS. Now, the HPS is a, as they say, rapidly-deployed, cross-sectional, national survey with a two-week on, two-week off collection and dissemination approach designed to measure the social and economic effects of COVID-19 on U.S. households.

Long-COVID questions were added to this survey, beginning June 1, 2022. Respondents reported previous COVID-19 diagnosis. Basically, have you ever tested positive for COVID-19 or are told by a doctor or healthcare provider that you had COVID-19 and current Long COVID via an online survey? Beginning September 14, 2022, participants were asked about significant activity limitations from Long COVID, reduced ability to carry out day-to-day activities compared with the time before COVID-19.

Now, important to really understand the methods there. The prevalence among Long COVID based upon this methodology, this approach among all U.S. adults decreased from 7.5% during June 1 through 13, 2022 to 6%, during June 7 through 19, 2023. From June 1 through the 13th, 2022, through January 4 through 16, 2023, prevalence decreased 0.28% per survey cycle, but then it actually remained stable.

Now, the statistically significant rates have declined, only occurred in adults younger than 60 years of age. The over 60, it was stable. Now, among adults reporting previous COVID-19, Long-COVID prevalence decreased from 18.9% to 11% during the study period. Prevalence decreased 1.16% per survey cycle and then remained stable. One of the challenges here, and I've talked to a lot of people about this, is these are surveys. What is the background of people having issues? How much of this is coming from COVID?

It's always going to be a challenge for us to keep track or to ever really put a number on how many people have post-COVID issues, but some things are a little bit more solid. What about diabetes? You really don't answer on a survey that you have diabetes when you don't. It is a little bit harder, more objective.

The article, “Incidence of Diabetes Following COVID-19 Vaccination and SARS-CoV-2 Infection in Hong Kong: A Population-Based Cohort Study,” published in *PLOS Medicine*. These are the results of a population-based cohort study.

Individuals without known diabetes were identified from an electronic health database in Hong Kong. They found that upon a median follow-up of 384 to 386 days, a little over a year, there was no evidence of increased risk of diabetes following vaccination with the CoronaVac or the BNT162b2. Upon a median follow-up of 164 days, SARS-CoV-2 infection was associated with a significantly higher risk of incident diabetes, 9.04, so a hazard ratio of 1.225, mainly type 2 diabetes regardless of the predominant circulating variants. The number needed to harm at six months was 406. For every 406 cases, we were seeing one additional diabetes case.

VR: Daniel, does this mean these are in the unvaccinated people or in the vaccinated people who got infected?

DG: It's an excellent question. The first part was they basically were saying, "Is there a higher risk in people who got vaccinated?" The main increase in diabetes is people who were unvaccinated when they were actually infected.

VR: Good, OK. Vaccines work.

DG: Well, I think this next one really hits this, which I really think is great. What about really pinning down and saying, "Can getting vaccinated protect you against diabetes?" No one wants diabetes, right? As a response to this last article, we have a preprint, “Diabetes Following SARS-CoV-2 Infection: Incidence, Persistence, and Implications of COVID-19 Vaccination. A Cohort Study of Fifteen Million People,” posted as a preprint on *medRxiv*.

Usually, we're moving away from preprints, but these are the results of the convalescent study out of the UK. I feel all right discussing a preprint coming out of this group. As far as background, they mention that most studies describe a cumulative relative risk for infection versus no infection one to two years post-SARS-CoV-2 of 1.2 to 2.6. Four studies found no association with type 1 diabetes.

Most of our studies are looking at type 2. As they comment, all of these studies lack the power to compare diabetes relative risk by type, severity, and vaccination status. Here, they're going to study diabetes incidence following COVID-19 diagnosis in pre-vaccination, so that's January 2020 to December 2021. They're going to look at vaccinated. They're going to look at 11,822,640. They're going to look at unvaccinated, 2,851,183. In the pre-vaccination cohort, type 2 diabetes instance after COVID-19 was 3.01 in weeks one through four and then 1.24 in weeks 53 through 102.

Now, the adjusted hazard ratios were higher in unvaccinated. That was 4.86 compared to vaccinated, 1.42, so about three times as high in the unvaccinated. Incidence was higher in

hospitalized than non-hospitalized. The type 2 diabetes persisted for four months after COVID-19, about 73% of those diagnosed. They mentioned in their study that patterns were similar for type 1 diabetes, although excess incidence did not persist beyond a year post-COVID-19. Good news here. It appears that vaccination is associated with a lower risk of developing diabetes should you get COVID-19.

All right, and I will wrap it up there. As I've been saying for a while, no one is safe until everyone is safe. Pause the recording right here. Go to parasiteswithoutborders.com and click Donate. Even a small amount helps. Right now, we're doing our Floating Doctors fundraiser where, during August, September, and October, we double your donations up to potential maximum donation of $20,000. I was actually just speaking to a colleague of mine who was just down in Panama last week and they're struggling. These are tough times down there. These are tough times financially. Your donations will really allow us to support the fantastic work they do down there in Central America.

VR: It's time for your questions for Daniel. You can send them to Daniel@Microbe.TV. Sharon writes, "When someone gets the pneumonia vaccine shot, can it help with severity of COVID pneumonia if you should get that during a bout with COVID-19?"

DG: OK, yes, I get that. The first time, I was trying to figure out if we were going to give people the vaccine while they had COVID-19. This is a great question because on rounds today, we were talking again about this whole silly notion that you can only have one thing at one time, sort of Occam's razor. I was joking that none of my patients with pneumonia are allowed to have AFib because they already have pneumonia. How can you have two things?

As we well know, a certain percent. It's probably about 10% or 15%, so 85%, 90% do not, but 10% to 15% of individuals that get hospitalized with COVID also have a bacterial process. We've talked about how you can use the ferritin-procalcitonin ratio. We use blood cultures. We use chest imaging. We use clinical exam, a number of things to sort out who these folks are. If you have had the proper pneumonia vaccine, this is going to protect you against that pneumococcal pneumonia should you end up with the COVID-19 pneumonia.

VR: Portia writes, "I have a question for Daniel about Paxlovid. When I caught COVID in January, it was not an issue to get mine since I'm over 65, but just last week, my two-year-old grandson and my son and daughter-in-law also got COVID and Flu B at the same time. I suppose because of their ages, no Paxlovid was available to them. My grandson was only getting Tamiflu and Tylenol. My question is, why not? Is there a reason not to take it if you are a healthy young adult or a child before getting COVID? Do you think the recommendation will change over time?"

DG: Yes, so we're just getting experience. By that, meaning millions of people have gotten Paxlovid. We're getting a lot of experience pretty quickly. Now, with rising case numbers, we're getting even more experience with Paxlovid. We'll learn more about Paxlovid. Right now, we know compelling evidence that Paxlovid prevents progression in the acute period of time. That's really the indication. Will Paxlovid prevent some degree of inflammation? Will it benefit Long COVID? Will it have other benefits? We're going to learn those things over time. Depending upon what we learn, it will impact our prescribing.

VR: Currently, what is the age recommendation for Paxlovid?

DG: If you use age alone, it's 50, but then you can look and basically say, "Do people have comorbidities?" It's interesting. People with learning disabilities, people with heart disease. There are other indications other than just age, but 50 is the age, which is actually probably younger than most people realize.

VR: Is there any reason to think that that might go all the way down to a two-year-old one day?

DG: We'll have to see. We have to learn. These are medicines. These are foreign agents we're putting into people. You want to know the safety profile and you want to know that you're actually getting that benefit. I know people will mention names who take another round of Paxlovid during week two when they no longer have any ongoing and they say, "Well, what's the harm?" Every time you take a medicine, you're potentially taking a risk of having an issue.

VR: Susan writes, "I'm a 74-year-old woman on CellCept for interstitial lung disease caused by anti-synthetase syndrome. I've been pretty stable for years, have had every COVID vaccine available as well as Evusheld. I have not gotten COVID because I take every precaution. I'm planning on a week in Paris in October, a lifelong dream. When there, I would mask inside. I keep waiting for it to be safer to go, but at 74, there's not that many years left. On the other hand, with an uptick in cases, I don't want to be foolish and end up losing the years left to me. Any advice, Daniel? Thank you for your updates during the pandemic. It meant so much to know there was somewhere that the information on COVID was based on science."

DG: Yes. No, Susan, thank you for writing. Yes, you certainly sound like an individual who is at higher risk of a bad outcome. You've done a lot of the things that you can do. We were joking a little bit when we were recording *This Week in Parasitism* with poor Christina, who is suffering through COVID. She is suffering through it. She's pretty miserable. She made the mistake of flying up to Norway. It was a small plane. It was hot. She just felt like even though the mask was in her pocket that wearing it would be a bit oppressive. Now, she's suffering the consequences of that.

Proper, tight-fitting masks in indoor spaces continue to be a wise thing. When you go to Paris, you're going to want to go to the Louvre. You're going to want to go see some of the Monets. Maybe you'll even want to see the Van Goghs. Yes, continuing to make these smart decisions. It's going to be October. There's definitely the ability in Paris to eat out in these cafes, so making the decision to eat outdoors rather than inside a crowded restaurant. Continue to make smart decisions and then a discussion about whether you and other medicines you're on would allow you to safely take Paxlovid.

VR: If that were the case, you could take it with her, right?

DG: Yes. People are doing that now and that's -

VR: Ellen writes, "My grandson is 10 months old, received his first COVID vaccination in June. The family has been extraordinarily careful and no one has become infected yet. However, the five-year-old with two vaccinations and a booster will start kindergarten in two weeks, going to school for the first time. I'm wondering whether the 10-month-old should get his

second shot before kindergarten starts, not quite three months after the first one, or wait for the new booster that might prove more efficacious in terms of durability and prevention of infection."

DG: Yes, this is a great and very timely question, right? We are expecting the next round of shots to come out right after September 15th is what I understand. Part of it is, I understand they're almost available, but then there's some licensing and approval process. We are hoping that the newest booster - we are hoping because we don't have the data yet. I actually like to have the data instead of just someone saying, "Trust me." I've bought used cars in the past.

We are hoping that the new boosters will provide not only the 90% durable reduction in risk of severe disease but maybe several months of some reduced risk of even infection. You're in this little window. We're kind of getting near the end of August. It's only a few weeks to wait. It is a judgment call. I probably would say, talk to your pediatrician, but also getting to that three months as we've talked about a little bit of a delay to really get a true boost out of that next shot. Allow the germinal center maturation to occur. Makes sense. We're probably sort of weighing in here for you on the end of September.

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

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

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