This Week in Virology

TWiV 1124 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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

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From MicrobeTV, this is T*WiV*, *This Week in Virology,* Episode 1124, recorded on June 20, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: How was my sit-in last week? OK, Daniel?

DG: The sit-in, whose name shall remain unmentioned, did a great job. They had these wonderful new glasses on. I think the makeup artist gave them a treatment or something because they were looking quite good.

VR: All right. We don't mess around here at MicrobeTV. All right. What's on the bow tie today, Daniel?

DG: Oh, this is the plague actually, Yersinia pestis.

VR: OK.

DG: All right. Let's jump into it. We had a little technical delay there, and I got to get to a sailboat race.

VR: Sorry.

[laughter]

DG: Fine, Vincent. All right. Here we go. “Let us speak, though we show all our faults and weaknesses, for it is a sign of strength to be weak, to know it, and out with it - not in a set way and ostentatiously, though, but incidentally and without premeditation.” That's by Herman Melville.

VR: Did you read *Moby-Dick*, Daniel?

DG: We were doing a beach walk this last weekend, and the whole subject came up of name your five favorite books. *Great Gatsby*. I live in East Egg. My daughter's named Daisy Sabrina, so who knows? I love *Catcher in the Rye*. Are you ready for this? The first 128 pages of *Moby-Dick*. After that, it drags.

VR: It does drag a bit. Yes.

DG: Yes. I love the first 128 pages. That that's a masterpiece.

VR: All right.

DG: All right. Let's get right into it. We're going to go right into COVID. You missed this last week, but we have an interesting issue going on with Puerto Rico. Look at that. It's yellow. A lot of COVID deaths going on [crosstalk] -

VR: Which means -

DG: This is a map of the United States--

VR: Four to 5%.

DG: Yes. Four to 5.9% of all the deaths in Puerto Rico right now are due to COVID. That's a lot.

VR: Do we know what's going on?

DG: I'm not sure I know exactly. Looking at wastewater, we've been tracking for a while what's been going on with the West. This trend is actually continuing. We're up now to our wastewater viral activity level of four, really heading back up, actually, to what we've seen in the past as things start to rise.

VR: Is this accompanied by increase in cases also, Daniel?

DG: We are seeing an increased number of cases out in Hawaii and California. We're actually seeing this correspond. All right. Well, a couple of papers I want to talk about today. The first one to my dismay, the study, "Comparison of Two Methods for Sterilization of Filtering Facepiece Respirators Worn for Extended Periods During the COVID-19 Pandemic: An Experimental Laboratory Study," published in the *American Journal of Infection Control*.

I don't know if you all remember during the pandemic when we, healthcare workers, were wearing N95s for extended periods of time and the hospitals would offer to sterilize these so we could just keep using them over and over again. I certainly remember. I had my numbered brown paper bags, and I would rotate through. That was my idea. It's sterilizing in a super-hot car. Now, here these investigators looked at filtering facepiece respirators, FFRs. I've never really heard them referred to that before, but they collected these from three hospitals after extended use up to 15 or 30 days of use. They assessed the physical characteristics and filtration levels of worn FFRs before sterilization.

Respirators that achieved at least 94% filtration of aerosol particles, nasal clips still attached, had no tears, had preserved elastic bands, had no dirt, they were then randomized to receive or not receive cleaning before being submitted to hydrogen peroxide plasma gas sterilization.

Maybe give people a sense. Those plastic bands, they were not really lasting on my mask, so I actually got elastic and a stapling replacement elastic. Yes, my N95s were not in really the best shape.

As we read here, they go ahead and they collect 1,055 of these respirators. Over 85% of them exhibited secured nose clips, preserved strap elasticity, and no tears. Good so far. However, 78% of the samples basically were filthy, contained dirt. They really only had 19.6% eligible to actually even undergo the sterilization.

Now, after the sterilization, none of the FFRs in either group, the respirators in either group, achieved that minimum filtration, that greater than 95%. About 72% without cleaning, 80% with cleaning had filtration in this 90 to 93.9%. Not the end of the world. As I pointed out, most of these were dirty and could not even be sterilized. People are wearing these filthy, damaged things. They bring them and say, I just want to get it sterilized. They basically say, that thing is too dirty for us even to do that. You might want to toss that at this point.

VR: Basically, we need to just use new masks periodically, right?

DG: Yes. We need to have a better supply chain for our personal protective equipment when it comes to respirators. All right. COVID active vaccination. A little bit of an update here. The FDA updates advised manufacturers of COVID-19 vaccines 2024/2025 formula. If feasible, use the KP.2 strain of JN.1 lineage. Maybe the KP.2 variant? I don't know. Have we lost our battle with strain, Vincent? Should we just give up?

VR: I would call them variants, but -

DG: Yes, they're still variants. Here's what we read. Based on the totality of the evidence on June 6, 2024, the FDA initially advised the manufacturers of the licensed and authorized COVID-19 vaccines that the COVID-19 vaccines 2024, 2025, so basically upcoming fall-winter for use in the United States beginning in fall 2024, should be monovalent JN.1 vaccines.

Now, the FDA has continued to monitor the circulating variants of SARS-CoV-2 based on the most current available data, along with the recent rise in cases of COVID-19 in areas of the country, which we just mentioned. The agency has further determined that the preferred JN.1 lineage for the COVID-19 vaccines is the KP.2 variant, if feasible. This change is intended to ensure that the COVID-19 formulations more closely match the circulating SARS-CoV-2 variants, and the FDA has communicated this change to the manufacturers of the licensed and authorized COVID-19 vaccines. The agency does not anticipate that a change to KP.2 will delay the availability of vaccines for the United States.

There's some interesting stuff here to think about. Here we are in June, so July, August, September, two to three months lead time. Who needs so much lead time? A lot of this is actually Novavax because the mRNA vaccines don't need quite as much. I think we have to be thinking about that as far as our national, public health plans going forward. Novavax says, don't worry, we're going to be there on time.

All right. Oh, Pemgarda. I should talk about Pemgarda. Just a couple little things. You can get this. You can get it into patients. This is that passive vaccination that monoclonal antibody

that protects you. It's a pre-exposure prophylactic. 4,500 milligrams, so 4.5 grams of this stuff. You run it in IV. It's Q3 months.

All right. COVID early viral phase, really just repeating, beating on the drum over and over. We have our NIH and our IDS guidelines, early effective antiviral therapy. Paxlovid, remdesivir, molnupiravir, some situations, convalescent plasma. Remember when we had those monoclonal antibodies for treatment, not just prevention, but for treatment of acute COVID-19 with reductions in progression of about 90%, high 80s? Those were dark days when so many people and companies really stepped up to develop tests and really create access for these life-saving therapies. These pop-up infusion centers all across the country.

This week we have the article, "Real-World Effectiveness of Sotrovimab for the Treatment of SARS-CoV-2 Infection During Omicron BA.2 and BA.5 Subvariant Predominance: A Systematic Literature Review." This was published in I*nfection*. If our listeners remember when the BA.2 and the BA.5 variants became predominant, we had these lab-based in vitro neutralization assays, and they said, oh, we're just seeing a decrease in neutralization here, better toss out that sotrovimab. We had a little bit of a talk about, I don't know, what about FC-mediated effects? I know it's challenging to test those, but maybe this stuff still actually works. You hate to throw it out. Unfortunately, in many places, this was the end of sotrovimab. Here, as we read, some patients were still getting sotrovimab. Let's see what we find out.

Here, the authors identified 14 studies where there were heterogeneous in terms of study design, population, endpoints, and definitions, so mixing and matching here. They end up including over 1.7 million high-risk patients with COVID-19, of whom approximately 41,000 received the sotrovimab during the BA.2, BA.5 predominance. Now, four studies compared the effectiveness of sotrovimab with untreated or no monoclonal antibody treatment controls to compare the sotrovimab with other treatments, and three single-arm studies compared outcomes during BA.2 and or BA.5 versus BA.1. Five studies descriptively reported rates of clinical outcomes in patients treated with sotrovimab. Lots of stuff here.

Pulling it together, during BA.2, a lower risk of all-cause hospitalization or mortality was reported across studies with sotrovimab versus untreated cohorts. Compared with other treatments, sotrovimab was associated with a lower or similar to-— lower than molnupiravir, similar to Paxlovid risk of COVID-19-related hospitalization or mortality. There was no significant difference in outcomes between the BA.1, BA.2, BA.5 periods.

Really a lesson here for the next time we want to use monoclonals. It looks like despite that in vivo drop in in vitro neutralization assay stuff, and I was tossing this in the trash, it actually looks like we were still seeing an effectiveness on par with Paxlovid, which is about 85%, 90%.

VR: This is fantastic, right?

DG: Fantastic that we were still having effectiveness, but not fantastic that we threw it all in the trash.

VR: As you say, we were basing it on in vitro neutralization, and many people, including us here, said, wait, FC-mediated functions are clearly important, but they weren't considered. This is a great example now going forward that you have to look at the clinical efficacy. You can say, oh, the FC-mediated assays are too hard. Fine. Let's just see if it works in patients.

DG: Yes, which is not that-— Just follow. OK, we have this many people. They're coming in. Are we suddenly seeing like all these people end up straight in the hospital or are we still seeing this 90%? We do this clinically. We treat people for urinary tract infections and then, hey, are you doing OK? We start to notice, hey, something's going on here, and maybe we have resistance things to help us. We could actually have kept using this apparently for quite a while.

VR: We're not going to start using this again, I presume?

DG: I don't think we are at this point. We now have Paxlovid. There was an overlap there, except I don't know how many people are using Paxlovid. But no, I think this is going to be word to the wise for the next time around.

VR: Pem - What is it?

DG: Pemgardia. Pemgarda.

VR: Think of Harry Potter. Pemgarda is based on neutralization right now, right?

DG: Which is really interesting. It's one of those, if you get the neutralization, that's great, good to go. If you lose neutralization, that doesn't mean you have to throw away the drug, I guess, is what we're saying here.

VR: I think that lesson here should be held for Pemgarda for sure.

DG: Yes. Even when they start to say, oh, we're seeing issues with our in vitro, pseudovirus, a lot of that's what they're doing, neutralization, we say, are we starting to see all these people end up at the hospital? Are we getting breakthrough? Yes.

VR: Daniel, this is a problem when you don't really have a correlative protection for SARS-CoV-2.

DG: Yes. All right. COVID, the early inflammatory week. Steroids at the right time in the right patient at the right dose. This is after that first week. Folks in the hospital, we have some anticoagulation guidelines, pulmonary support, remdesivir, immune modulation. As we've been pointing out for the last few years, it is during that second week, during the inflammatory phase, that we see patients develop the hypoxemia and complications that tend to lead to hospitalization.

In the famous words, first, I just had a cold, then I got COVID, or better, but first, I experienced the viral replication phase, and then I got hit with that cytokine storm. Who am I quoting? We won't mention. This week, we have the article, “Hospital Nurse Staffing Variation and COVID-19 Deaths: A Cross-Sectional Study,” published in the *International Journal of Nursing Studies*. Here, these investigators performed a cross-sectional study of 87,936 Medicare beneficiaries hospitalized with COVID-19 and discharged, alive or dead, between April 1 and December 31, 2020 in 237 general acute care hospitals in New York and Illinois.

Now, Vincent, I've noticed that people take issue if I oversimplify study design or method terminology, but I will continue with the caveat that if you want a further in-depth

explanation, this may not be the place. I want to make sure our listeners have a basic comfort with how the studies were conducted, but study design and analysis, I will admit, is a complex, specialized field. I just want to say here that when we read that they are doing a cross-sectional study, this tells us that they're looking at a population at a single point in time. That gives us an initial insight into possible limitations such as, well, what time? What point in time? What period of the pandemic?

Now, here, measures of hospital nursing resources, patient RN, staffing ratios, proportion of bachelors, qualified RNs, nurse work environments, magnet nursing recognition in pre-pandemic period, and then during this April to June 2021 were used to predict in-hospital and 30-day mortality. The mean age of patients was 78 years. About half of them, 51%, were male. Twenty-three percent of patients admitted to the hospital with COVID-19 died during the hospitalization. In this study, they found that patients admitted with COVID-19 to hospitals with better nursing resources pre-pandemic and during the pandemic were significantly less likely to die.

We're always patting ourselves on the back as physicians, but here we're seeing a huge impact of the nurses. For example, each additional patient in the average nurse's workload pre-pandemic was associated with 20% higher odds of in-hospital mortality, 15% higher odds of 30-day mortality. Hospitals with greater proportions of BSN qualified RNs, better quality nurse work environments, and magnet recognition offered similar protective benefits to patients during the pandemic. If all hospitals in the study had superior nursing resources prior to or during the pandemic, models estimate many thousands of deaths among patients hospitalized with COVID-19 could have been avoided.

VR: Daniel, are these all nurses, including ICU and general floor nurses and so forth?

DG: Yes, so it's across the board. They didn't pull out. What is the difference? You can have your LPN, you can have your BSRN. You also can have better nursing ratios. I have to say, in California, it's mandated, like nurses have X number of patients that they care. That's the law. Here in New York, there's been a lot of strikes with - Basically, the nurses have said, stop asking us to take care of so many patients that it's not safe. Unfortunately, they have to go on strike to get the hospitals to create the right nursing to staff ratios. Yes, I'm making friends right now with all the hospital administrators, Vincent.

VR: It's about money, Daniel.

DG: Twenty percent higher odds of hospital mortality by giving them like too many patients. Yes.

VR: I'm not surprised.

DG: Yes. That's per extra patient that they do. None of this like, oh, we're going to make believe the patients aren't quite that sick. That way, we can give you extra patients. Let's be honest because this really matters. Excellent nursing care is critical as we see great evidence here to support that. All right.

COVID, the late phase past Long COVID. I think I have about three articles here. One, two, three, four, actually. We've got a bunch here. We're going to start off with the article,

“Endothelial Dysfunction and Persistent Inflammation in Severe Post-COVID-19 Patients: Implications for Gas Exchange,” recently published in *BMC Medicine*. Here the investigators studied 88 survivors of COVID-19-associated severe ARDS six months post-ICU discharge. I just want to point out that this is not a study of run-of-the-mill COVID-19, so we need to put this in the context. This is severe disease with ARDS. Of note, we think ARDS is caused by endothelial dysfunction, a resultant local injury to capillary membranes. Just, I was thinking about this, are we talking about COVID? Are we talking about ARDS? Just keep that in mind.

Now, assessments included clinical and functional evaluation, as well as plasma biomarkers of endothelial dysfunction, inflammation, and viral response. Additionally, an in vitro model using human umbilical vein endothelial cells explored the direct impact of post-COVID plasma on endothelial function. All right, so they've taken plasma from folks after COVID, and they're going to see what happens in that model.

Now, they found that post-COVID patients with impaired gas exchange demonstrated persistent endothelial inflammation marked by elevated ICAM-1, IL-8, CCL-2, ET1 plasma levels. Concurrently, systemic inflammation evidenced by NLRP3 overexpression, elevated levels of IL-6, soluble CD40L ligand, and C-reactive protein were associated with endothelial dysfunction biomarkers and increased in post-COVID patients in this group with impaired gas exchange. T-cell activation reflected in CD69 expression and persistently elevated levels of interferon beta further contributed to the sustained inflammation.

Then, as mentioned, they do that in vitro model, and the in vitro model confirmed that patient plasma with altered levels of soluble CD40 ligand and interferon beta proteins had the capacity to alter the endothelial function. They conclude with six months post-ICU discharge, survivors of COVID-19-associated ARDS exhibited sustained elevation and endothelial dysfunction biomarkers correlating with the severity of impaired gas exchange, NLRP3 inflammasome activity, and persistent T-cell activation indicating an ongoing inflammation contributing to persistent endothelial dysfunction potentially intensified by sustained immune response.

VR: I wonder how many of these patients would go on to develop PASC?

DG: Not only that. That's huge, right?

VR: Yes.

DG: The reason I guess this caught my eye is there's so much discussion of endothelial dysfunction as part of PASC. Be interesting to really look at this in people with PASC and people without PASC and see. Also, just look at this in ARDS from other causes, like how unique to COVID, how much is this ARDS?

VR: This kind of work is important because eventually we can try and interrupt this sustained inflammation, right?

DG: I think that's key. If you see this and you diagnose, you can say, OK, we've got this sustained endothelial dysfunction. Now, what's the therapeutic? How do we interrupt this? Yes. All right.

Now, another thing that folks worry about with happening in acute COVID, maybe linking to PASC, post-acute sequelae of COVID, is a reactivation of latent viruses. Let's run through the article, “Prevalence and Risk Factors of Cytomegalovirus Reactivation in Critically Ill Patients with COVID-19 Pneumonia,” published in *PLOS ONE.* Then I'll explain why I put it here in the PASC section.

These are the results of a retrospective cohort study conducted among adult patients who were admitted to ICU and screened for quantitative real-time PCR CMV viral load. It's really nucleic acid amplification testing, by the way, in a tertiary care hospital during the third wave of COVID-19 in Thailand. A total of 185 patients were studied, 71.9% in the non-CMV group, 28.1% in the CMV group. Of all, the mean age was 64.7; 54.6% were males.

Now, the CMV group had received a significantly higher median cumulative dose of corticosteroids than the non-CMV group. You ready for this: 301 versus 177 milligrams of dexamethasone. Remember that like six milligrams a day times 10 days, 60 milligrams. These are huge doses, much higher than the ones we recommend, even if you shorten it, which we often do to only six or seven days.

Other modalities of treatments for COVID-19, including antiviral drugs, anti-cytokine drugs, and hemoperfusion were not different between the two groups. The 90-day mortality rate for all patients was 29.1%, with a significant difference between the CMV and the non-CMV group. CMV group, 42.3%. That's huge, 24.1% non-CMV. Median length of stay was longer in the CMV group, 43 days versus 24. The CMV group had the detectable CMV DNA, and they saw this in plasma and BAL, and then they do this multivariate analysis. It's really the cumulative corticosteroid dose that really was associated with this CMV reactivation.

A couple of things I'll say here. This goes into the bucket of studies that show that activation of latent viruses, such as *herpesviridae*, can happen with acute COVID. There may be some mechanism here for folks with Long COVID. Some of the stuff I didn't really know was the corticosteroids driving the reactivation, or were people so sick with reactivation getting more steroids because of the degree of illness?

VR: The real question is whether CMV is participating in the pathogenesis, right?

DG: I think that's ultimately. Is it participating in the acute pathogenesis, and is it participating in Long COVID? There's evidence that people with PASC, people with Long COVID, tend to have these really high serology results or evidence that there was reactivation. There seems to be a correlation there.

VR: Also, if you have severe COVID and you're getting treated with a lot of steroids, as we saw here, this could also make CMV worse.

DG: Yes. Yes. Here you are with CMV DNA being detected, and you're on steroids that your body really can't respond.

VR: Yes.

DG: All right. Last couple for everyone. We've got the article, “Epidemiologic Features of Recovery from SARS-CoV-2 Infection,” recently published in *JAMA Network Open*. Here,

they're looking at what variables might impact or predict a person's time to recovery from an acute SARS-CoV-2 infection. They do a prospective look at a cohort of 4,708 participants and find that by 90 days post-infection, there actually were significant differences in mean recovery time according to socio-demographic, clinical, and lifestyle characteristics.

Now, particularly acute infection severity. We also see vaccination prior to infection being protective, shortening that time to recovery, depend which variant. Infection during the sixth Omicron variant versus first wave, but recovery was unfavorably associated with female sex and pre-pandemic clinical cardiovascular disease. They did not find, so no significant multivariable adjusted associations were observed for age. Educational attainment. All that school, Vincent, it ain't going to protect you. Smoking history, obesity, diabetes, chronic kidney disease, asthma, COPD, or elevated depressive symptoms.

VR: I don't understand this Omicron business. We've been saying for a long time, Omicron is not mild, and now they're countering it. I'm sure they're confounding issues here with their study.

DG: There's an interesting thing. It was like Omicron is not all the same. We saw different variants in the Omicron lineage where mortality went up, mortality went down. This whole like, oh, it's fine, it's Omicron, it's mild, that really has not stood the test of time.

VR: I would also like to know the age demographics here and also the status of immunity. I think all of those play into these outcomes, right?

DG: Yes. A couple of things we got is that vaccination was associated with a quicker recovery, but you saw the same thing for reinfections, the same patterns.

VR: Yes.

DG: All right. We're going to wrap it up with the article, "Reduced Olfactory Bulb Volume Accompanies Olfactory Dysfunction after Mild SARS-CoV-2 Infection. It's an open-access article published in *Scientific Reports*, and I'm going to put this in the more objective evidence that Long COVID is real, and particularly here, post-COVID olfactory dysfunction had objective changes associated with it.

In the study, 233 participants underwent MRI and neuropsychological testing, as well as a structured questionnaire for olfactory function. The study included 233 individuals recovered from mainly mild to moderate SARS-CoV-2 infections, and they found that participants with post-acute self-reported olfactory dysfunction had a significantly lower olfactory bulb volume than normally - they say, normally smelling individuals. I feel like they could word that differently, that individuals with normal smell. They don't need smelly people versus - Anyway. [laughs] Olfactory bulb volume at baseline predicted olfactometric scores at follow-up. This is actually an objective measure.

I will wrap it up there. Low and medium-income countries. Just try to keep people thinking about the entire world. No one is safe until everyone is safe. Hoping folks will pause the recording right here, go to parasiteswithoutborders.com, and click on Donate. Even a small amount helps. Every little bit helps us do our work, and we are now doing our Floating Doctors

fundraiser for May. A little bit more June and July. We'll double your donations up to a potential maximum donation of $20,000.

VR: When I was in Sweden, I did an interview with a physician who treats Long COVID patients, so that will be released over the next few weeks, and I think many listeners will find that interesting.

DG: Oh, I look forward to listening.

VR: It's time for your questions for Daniel. You can send yours to Daniel@micro.tv. Wendy writes, "I'm writing as a New Yorker planning a trip this summer to the Canadian provinces of Nova Scotia and New Brunswick. I'm 67, fully vaccinated, and boosted with the latest formula. Generally, in good health. Because I listen to Dr. Griffin, I'd like to be able to get Paxlovid if I need it during the trip. Naively, I thought Canada, sane people, good health system, no problem. Well, as it turns out, not so much according to the article from January 2024 linked below.

Paxlovid is sitting in stockpiles in Canada while physicians fail to prescribe it for all the same flawed reasons that Dr. Griffin debunks week after week, including doubts about its effectiveness in vaccinated individuals. The guidelines for prescribing it are also flawed. The drug is approved in Canada for adults at high risk of severe illness, but each province decides what this means, often based on a hodgepodge of criteria that can include age, vaccination status, how long since the person's last vaccine dose, and various medical conditions.

In some provinces like Ontario and Manitoba, just being older is enough, but in other provinces, including those I'll be visiting, the hodgepodge method applies, and it's not all clear to me that I'd be eligible. So if I were to contract COVID-19, I might have to go to Maine where it appears I'd be able to get a prescription. Also, I learned that Paxlovid has been free in Nova Scotia since 2022, but soon, only adults with immune deficiencies will have this benefit, no one else. Out-of-pocket price, by the way, is Canadian $1,288 or about $1,000 US at current exchange rates. Curious to hear Dr. Griffin's thoughts about this messy situation to the north."

DG: It's really tough, and there's something weird about COVID still. If you had urinary tract infection or you had the flu and you go to see a provider, you say, hey, I'm sick. I'm not doing well. Is there anything you can offer me? We don't have this weird, nope, nope, 90% of those urinary tract, they're going to get better on their own. Keep your fingers crossed. Or, oh, I'm sorry, the Tamiflu, I'm only giving it out to cousins of mine from Northern Ireland or something.

I really don't understand the madness. We did have compelling studies early on, randomized control trials, FDA approved drug, we now have hundreds of studies showing benefit, and it just keeps growing. Not only are we seeing benefit for acute COVID but a growing evidence that this can actually have impacts outside of that initial high-risk population. Impacts on Long COVID actually at this point, I think the evidence is really growing there to be thinking about using it in that context as well. We'll keep spreading the knowledge, the evidence, and hopefully, we'll see more evidence-based practice out there.

VR: Daniel, aren't there organizations like, I don't know, American Medical Association, that establish what physicians should be doing, or that does not exist?

DG: No. We link those articles in acute COVID. We link to the NIH and the ID Society of American guidelines, like these are the evidence-based guidelines. By the way, they recommend Paxlovid. Then, as mentioned, you can even, dare I suggest that people should stay up to date and maybe they just listen to this to stay up to date. We'll read the articles for you. You don't have to go through that painful mental rigor, but you got to stay up to date.

VR: Ellen writes, "On the recent *TWiV* on the lab leak hypothesis, Vincent remarked in passing that 10-to-20% of transmissions occur by super-spreader. I've been consoling myself with the assumption that the vast majority of transmission occur with an encounter with a super-spreader, which given the low level of COVID at the moment, has to be rather rare. How far off the mark am I?"

DG: I'm like the way you think about this. I understand your idea. It's like every time you roll the dice, what's the chance that that person I'm sitting across from in the restaurant is a super-spreader? There was evidence. There's this Pareto principle where it looks like in, at least with SARS-CoV-2, with COVID-19, most people who are getting COVID-19, there's a single individual who's given it to like 10 people where 80% of people have given it to zero or one. There really seems to be this -

There was that wonderful Colorado study where it was like, what was it? Ninety percent of the virus, of the RNA copies were in less than 10% of the people. Really, is something going on there. You got to think about it. It all evens out. I hear what you're saying. I remember early on, my wife wanted to know, we got to figure out who those super-spreaders are. I was like, no, we don't [laughs]. What if it's you?

VR: All right. Jeff writes, "I'm writing about the recent *Nature Communications* paper on Paxlovid in adolescence that you briefly discussed in the last clinical update. I was interested in what seemed to be a clinically significant benefit in using Paxlovid on otherwise healthy teenagers. As a pediatrician, we are all well accustomed to using licensed products beyond their strict FDA approvals because pediatric trials are often limited or lacking entirely, but we do want to see some evidence of benefits that outweigh the potential harms.

Up until now, when asked by my patients about using Paxlovid, the general response has been that we don't have good evidence that it improves outcomes in healthy children. My question is, does that statement still hold true, or are we starting to see good evidence that Paxlovid is beneficial in teenagers?"

DG: Jeff, we've been sharing that, and as we shared this in *Nature Communications* paper last week. One can argue about, oh, number needed to treat and how expensive is this, but if it came down to it, if my teenager at this point, my adolescent ended up - I guess I'm thinking of Barnaby. He's my only adolescent. He's 19. Everyone else is over 20. If they ended up with COVID at this point, I just don't see the downside.

We saw that there was benefit. You could argue about number needed to treat, growing evidence that this might reduce the risk of Long COVID, and boy, that's worth doing because Long COVID, you start asking, are we really saving money by leaving this stuff sitting on the shelves and then we've got this just growing number of folks with Long COVID? Still, one of Barnaby's friends, he can't smell. It's been like a couple years now and the kid lost his smell

due to COVID and ain't coming back. Would that have happened with Paxlovid? I think we have a growing amount of evidence, and we'll keep sharing it.

VR: Gail writes, "I asked my doctor if I should get another vaccine four months after the last one, and he shocked me by saying that developing data shows that the more COVID boosters one has, the greater the risk of immunosuppression and cancer. He said, when you add that data into their lack of effectiveness against COVID, he's discouraging patients from getting any additional shots, including those who would be at high risk from the disease. I was completely taken by surprise. Have you seen any data confirming a greater risk of immunosuppression and/or cancer as a result of getting COVID vaccines?

DG: I'm as shocked and surprised as you are. This is one of those situations that maybe we should be held to the standard, say, wow, that seems out of the mainstream and what I've been hearing. Are you quoting Fox News, or? Where are you getting this? Is this like your social media feed? Who do you follow? This is all that anti-science misinformation. It's not true. There's none of these crazy turbo cancers. None of this.

What is the other thing people worry about? Like overloading your immune system. They've got some name for that too. This is not true. We recommend, and actually, CDC recommends the vaccines and getting the boosters. We've shared data repeatedly, question of how long it lasts, but a 50-to-70% reduction in your risk of getting severe COVID by getting those updated shots. None of this is true.

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

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

[music]

[00:40:30] [END OF AUDIO]