This Week in Virology

TWiV 1134 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. From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1134, recorded on July 24, 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: What you got on your tie, Daniel?

DG: Today is my fungus bow tie. There's conidia, there's spores, all kinds of good fungal stuff.

VR: Nice. Excellent.

DG: Yes, I came down here to have my glass of water, and the one that was here was slimy, and I was thinking now I will end up not just having it on my bow tie.

VR: You have a *TWiV* mug, Daniel?

DG: I have several. That's usually how I start my day.

VR: OK, good.

DG: [laughs] All right let's jump right into it because I'm going to try to keep this short because we're recording on Wednesday night because, well probably when this drops, I may actually be done. We'll have to see. I'm starting a 200-mile sailing race that starts at the Statue of Liberty and then goes all the way out around Montauk. It's 105 miles open Atlantic before we then drop back into the Long Island Sound.

VR: How long is that going to take?

DG: That's the question isn't it? Last year we did it in 40 hours. Started off really fast and then got hit by a squall and then there was some doldrums. We'll see how it goes this year, fingers crossed.

VR: Good luck.

DG: Yes, thank you. All right so right into it with our quotation. I started thinking about Thomas Edison while I was listening to the last *TWiV* and things were being described as light bulb-like, incandescent light bulb-like, the part of the virus that would bind to the receptor. I

feel like Thomas Edison is - Well, he is talking about science or technology here when he says, "I have not failed. I've just found 10,000 ways that won't work." All right so we're going to get right into RSV.

VR: That means don't give up, right Daniel?

DG: Definitely means don't give up. I think it's also one of the things about science is negative results are helpful. It's important to know what doesn't work. It's great when you figure out what does work but it's really important to know as well what doesn't work. All right RSV we have more good news with, “Merck announces topline results for phase 2b/3 trial of” - I'm going to put my glasses on for this. It's not catchy, it's not catchy. “Clesrovimab, (MK1654), an investigational respiratory syncytial virus preventative monoclonal antibody for infants.”

Clesrovimab is another prophylactic monoclonal antibody designed to protect infants from RSV disease much like nirsevimab, easier to roll off the tongue. These top-line results are from a phase 2b/3 double-blind randomized placebo-controlled study to evaluate the safety and efficacy of Clesrovimab in healthy preterm and full-term infants.

The participants either get a single dose of the Clesrovimab or placebo. The primary endpoints include the incidence of participants with RSV-associated medically attended lower respiratory infection which apparently they call MALRI, five-letter acronym for that, and they follow them out to day 150 compared to placebo. Now we don't actually get the numbers. All we hear is that Clesrovimab met its primary safety and efficacy endpoint.

Be interesting to sort of see how this compares to what's currently out there, but I'm excited that, hopefully, we're going to have another option.

All right. COVID update. Not looking good. We've been talking for quite a while about Puerto Rico being greater than 8% of the deaths, of all deaths in Puerto Rico being due to COVID. Actually we're starting to see a little trouble down there in Maryland.

Maryland is now 2% to 4% of all the deaths that they're seeing are due to COVID. If you look at wastewater, this is not encouraging. The wastewater data is always a little bit old so a little bit behind, but we're really looking at some of these numbers way past last summer's wastewater viral activity peak and actually looking like they're headed right towards last winter's peak.

VR: Daniel, I'm looking at this pattern. December, which makes sense, right, the peak, but then there's a peak in September-ish. But this year's peak is now July, so it's a little earlier.

DG: It's still on the way up so I'm a little worried about where is it going to head. It's starting to rise a little bit earlier than it did last year. It's already above where it is. I have to say, my wife and I were talking about this, what exactly is going on? I don't really have a great explanation. Why are levels so high? The flu is one thing, right? Every winter flu's around maybe you get the flu. There's a period of time of a few months.

But what's going on with COVID? We had this huge peak in the winter. We've now settled into this pattern of surges, and now it's looking like a solid peak in the summer. And the activity never really goes down. I'm getting more and more annoyed with COVID, Vincent.

VR: It doesn't fall into any patterns yet except the winter. The winter and sometime in the mid to late summer it seems.

DG: Yes it does not seem to go away. All right. Right upfront I wanted to discuss the article, “Insights from an N3C RECOVER EHR-based Cohort Study Characterizing SARS-CoV-2 Reinfections and Long COVID,” right? A lot of us are just getting COVID over and over again, right? This article was published in *Communications Medicine*. I've often said that one case of COVID-19 doesn't always predict how the next case of COVID-19 will be. Now how accurate is that? Is there some degree of predictability?

We have lots of anecdotes that I've shared with the first infection is a week or two feeling crummy at home. Second infection severe enough to spend time with me in the hospital. Or a person survives the first infection and does not survive the second which is clearly different. Now at this point, many of our listeners have had their own experiences. They also have the experience of people close to them that they can bring to this topic. There's a lot of personal experience that people have out there.

Then there's also this study. These are results of an electronic health record study. We've got this cohort of over 3 million patients from the National COVID Cohort Collaborative. It's part of the NIH Researching COVID to Enhance Recovery Initiative. These investigators calculated summary statistics, effect sizes, we've got Kaplan-Meier curves really trying to better understand COVID-19 reinfections. Then one thing about this article, I actually like this. This is not something that I remember seeing so much in the past but they actually have a plain language summary.

I know people ask some sort of the deep dive *TWiVs*. Like, "Before you go all into the details, can you just give me a plain language summary of what's going on?" In addition to the abstract, they've got this plain language summary. Just to start there, they tell us that more than three years after the start of the COVID-19 pandemic, individuals are frequently reporting multiple COVID-19 infections. They report finding that individuals with severe initial infection are more likely to experience severe reinfection.

That some protein levels are lower leading to reinfection and then a lower proportion of individuals are diagnosed with Long COVID following reinfection than initial infection. Let's actually look at the data. There's a really nice table too. Vincent maybe you and I can walk through this. I truncated it a little because the bottom was you die during the first infection, which there's no reinfection after that.

VR: We don't need that. Yes.

DG: I'm not sure why they have that other than just to say, "Oh, this is the incidence of people that died during the first." In this table you've got four choices with regard to severity of initial infection. Mild, no medical issue; mild but you end up with an ED visit; moderate we end up in the hospital; then we've got our severe where you're on a ventilator or ECMO or ICU level care. Eighty-seven percent, these numbers seem reasonable, have a mild, you end up not even having to go to the ER. Then what happens, what's the severity of reinfection?

We see of those people, so you got to take 100%. If this was completely predictive, then the second time would be the same. We're almost thinking it's got to be a little better because

now you've had some memory, maybe there's even been some vaccines, you've got this infection. I'm thinking almost everyone's going to stay out of the hospital, but again we end up with about 13% of the folks actually having a more serious issue that second time.

Seven percent end up in the ED, 4% who are completely fine the first time ended up in the hospital. Then about 0.5% end up severe, ICU-level care.

VR: Some die.

DG: Yes, actually about 1% die the second time. You survived it, it was mild, wasn't a big deal the first time, and yes, about 1% die the second time. The next is you have mild. Mild but sick enough that you end up going to the ER. About 60% end up the next time mild, not even going to the ER. About 33% are that same. You end up in the ED, but 6.6% end up in the hospital. About 1% severe. And here 0.5% or so end up not surviving that second. Then the last two, more worrisome. Sick enough to end up in the hospital the first time.

Only about half those folks have mild the second time with 16% ending up in the ER. About a quarter of these folks ending up back in the hospital the second time, 2.4% in the ICU. And 3.6%, almost 4%, 1 in 25, that second time are not going to survive. Then the worst is the folks that had severe, people that were in the ICU, et cetera. In that case, 6% are not going to survive the reinfection, 8% are, again, going to have a severe. About a quarter of them are going to end up sick enough to be in the hospital.

VR: Basically, the more severe your first infection, the more severe the second is going to be.

DG: That is true. Yes. And just because you had a mild no-ED visit the first time, you may still die the second time. What about Long COVID? We covered the article last week in *The New England Journal of Medicine* where we read that with the initial pre-Delta variant in the unvaccinated first infection context, we were seeing about 10% of people develop Long COVID. This was down to 3.5% for current Omicron infections in the vaccinated.

Here we read that the largest proportion of Long COVID diagnoses occurred among individuals with the first reinfection in the Delta epic. They report the rate of Long COVID diagnoses have been, are you ready for this, increasing with each successive Omicron variant. Because we sort of thought, oh, it's Omicron, it's mild. No, Omicron seems to be changing a little bit. Actually, we're starting to see more and more Long COVID with each of these different Omicron variants.

All right. This is an interesting one. We're moving into testing now. Remember those rapid tests piled high, a dollar a test on someone's desk? We have the article, “Cost-effectiveness of COVID Rapid Diagnostic Tests for Patients with Severe Critical Illness in Low- and Middle-income Countries: A Modeling Study,” published in *PLOS Medicine*. Little context. These are those rapid diagnostic tests used for diagnosis of COVID. They're looking here at their use in low- and middle-income countries to inform treatment decisions. Really asking this question, is it cost-effective? Is it helpful?

Sort of thinking about this this morning, is this going to change management? I remember going through medical training, that was always the question when you wanted to order a test. It's like, OK, that's great, you're curious, you want to order this expensive test. In this

case, this particular test. Is it going to change management? Is it cost-effective? They included the side effects of corticosteroids, which really is the only available treatment for COVID in a lot of these places.

So what they're really saying is, is this helpful? Because, if the person has the flu, we might not want to give them steroids. If they've got COVID, it's the second week, they're hypoxic, there's compelling evidence that we can actually have better outcomes by doing that. They found that SARS-CoV-2 testing of patients with severe COVID-like illness, so that second-week hypoxemia, can actually be cost-effective in all low- and middle-income countries, though only in some circumstances.

A lot of this is impacted by what's the prevalence of influenza. What's the other thing going on? Lots of influenza, lots of opportunities to give steroids to people who don't need them and may actually be harmed by them, where if there's really not much influenza and it's all COVID anyway. But here's actually interesting. The authors point out one of their primary limitations. There's substantial uncertainty around some of the parameters just because there isn't as much data as they would like.

Also, there's this changing what is the current COVID mortality with standard of care. Then we're not actually really sure about the negative impact of steroids in people with severe influenza. Is it really harmful to be doing that?

VR: The use of steroids for COVID in these situations is in the second week, right? Not earlier.

DG: Yes, that's exactly. Here you're looking at using this WHO approach where severe COVID, we're talking about second week, cytokine storm, hypoxemia. That's where we have the good data that corticosteroids have about a 25% reduction in mortality. The interesting thing, we have these great studies, but what about in influenza? If someone's got that, severe influenza with hypoxemia, would they benefit from steroids or be harmed? The general thought is they'd be harmed. But as they point out, it'd be nice to have some better data on that.

VR: That would require some kind of a trial, no?

DG: Imagine that.

[laughter]

You have to do the science. All right. This is something I have to say. A lot of us, with all this COVID around are interested in. Durability. This is the article, “Durability of Protection Against COVID-19 through the Delta Surge for the Novavax Vaccine, the NVX-CoV2373 Vaccine.” This was published in the July 15 edition of *CID*. I'm going to get two of those right here in a row. We'll start with the background.

Now, the protein-based vaccines for COVID-19 are, in a lot of people's mind, a traditional vaccine platform with the impression that they might provide this long-lasting protection for non-severe acute respiratory syndrome, SARS-CoV-2 pathogens. They may complement messenger RNA vaccines as a booster dose. We've seen a lot of early efficacy. But what about this durability that we keep talking about? Here are the results of the PREVENT-19 vaccine trial, which used a blinded crossover design.

The original placebo arm received the Novavax, the NVX-CoV2373, after efficacy was established. We start off with placebo and vaccine, and then they say, "Hey, this works. All you placebo folks, you get to have access as well." I love this next line: “Using novel statistical methods that integrate surveillance data of circulating strains with post-crossover cases, we estimate a placebo-controlled vaccine efficacy and durability of Novavax against both pre-Delta and Delta strains of SARS-CoV-2.”

We'll have to get some mathematician on to discuss in detail these novel statistical methods. But what do the novel statisticians tell us? Vaccine efficacy against pre-Delta strains, variants, COVID-19, was 89% and 87% at zero and 90 days after two doses, respectively, with no evidence of waning. Vaccine efficacy against Delta was 88%, 82%, 77% at 40, 120, and 180, respectively. They say there was some evidence of waning, 88%, 82%, 77%. In sensitivity analysis, the estimated Delta vaccine efficacy at 120 days ranged from 66% to 89%.

There's this really rather extensive discussion section, but I have to say, ultimately, we're going to need those head-to-head monitoring studies to really clarify the durability issue relative to the mRNA vaccines. Definitely not seeing it drop down to that, less than 50% that we were seeing in some of those trials.

All right. We've also got the article, “Combined Protection of Vaccination and Nirmatrelvir-Ritonavir against Hospitalization in Adults with COVID-19,” in this same July 15 *CID*.

These are results of a retrospective analysis of patient records in Cosmos, a data set that at the time of this study, included electronic health record information for more than 160 million individual users of U.S. health systems that use EPIC electronic health record software. Among 731,349 patients with COVID-19 diagnosis in an outpatient setting that were eligible for nirmatrelvir or ritonavir, 24% were unvaccinated, 21.5% received two mRNA vaccines, 45% received three or more mRNA vaccines, 9% were characterized in this other vaccination category.

Basically, what they're going to do is they're going to go through and they're going to look at all these different individuals. We're going to get this really nice table where we get the adjusted hazard ratio for protection against progression to COVID-19 hospitalization. What are the differences? Vaccinated, not vaccinated, getting treatment, not getting treatment. We start off with the folks that are, say, unvaccinated, vaccinated, but no treatment. Our unvaccinated no treatment is going to be our baseline of one.

If we look at folks that get just two of the mRNA vaccines, we see about a 25% reduction in your risk of ending up in the hospital. Three mRNA vaccines, it's about a 50% reduction. Now interesting, if you compare that getting nirmatrelvir, you're actually seeing a little bit better about that same 50% reduction that you get with three vaccinations just by getting a course of the nirmatrelvir-ritonavir, the Paxlovid.

What if you get two mRNA? What if you get three? What if you do everything right, is what I'm going to say. You get your three doses, you get your full mRNA vaccination series, and you get your Paxlovid, now we've got a 75% reduction in your adjusted hazard ratio for ending up in the hospital.

VR: This should put to rest this idea that nirmatrelvir only works in unvaccinated people.

DG: Yes, I wish.

[laughter]

Yes, actually you could say, "Well, boy, in the unvaccinated, about a 50% reduction. In the vaccinated, about a 75% reduction." But it's all like, "Well, where was I before?" OK, it's about a 50% reduction in baseline risk for everyone. If you're unvaccinated, 50% reduction. If you're fully vaccinated, 50% more. Why not get that 50% reduction? I wouldn't want to end up in the hospital because as we keep talking about, you end up in the hospital, the more severe your disease, the more severe your disease the next time, the more your risk of bad outcomes, as well as Long COVID.

All right, so yes. Right in keeping, what are we recommended to do during the early phase, you test positive? We have the NIH treatment guidelines, we have the IDSA guidelines, and the data just keeps coming in. Number one, yes, Paxlovid. Number two, remdesivir. Number three, molnupiravir. We also have convalescent plasma in certain contexts. Yes, isolation guidance. You're feeling crummy, you don't feel great, you're already annoyed, but yes, you can give this to other people. So think about how you conduct yourself.

Then as we keep repeating, week two. This is the cytokine storm. This is when people might develop severe COVID. If you're sick enough, you end up in the hospital, you're hypoxic less than 94%, steroids, right time, right patient, anticoagulation guidelines. In some cases, pulmonary support to get through this period. Remdesivir if still in the first 10 days. And in some cases, we're still using immune modulation.

All right, this is going to wrap it up with us, the COVID late phase, past long COVID. The article, “Tracking Cognitive Trajectories in Older Survivors of COVID-19 Up to 2.5 Years Post-Infection,” published in *Nature Aging*. In this study, we have 1,245 COVID-19 survivors, 358 uninfected spouses, and they complete this 30-month follow-up. I was thinking about this, it sort of tells you when they must have gotten infected because they're following these folks for two and a half years. They were infected 30 months ago. What they're going to use to do cognitive status is something called the Telephone Interview for Cognitive Status 40, the TICS-40.

There's a bunch of these, like the TICS-30, the TICS-40, the MMSE. The TICS-40, it's on the telephone, and there's a bunch of questions you ask. Hey, what's today's date? What's your address? I want you to count backwards, listen to some words, you do some subtraction, response naming, some repetition. Who's the president? Who's the vice president? I don't know. I think they save that to the end just in case we get any emotion there. And delayed word list recall.

They use this test, and they tell us that the overall incidence of cognitive impairment was 19.1% among older COVID-19 survivors. So, one in five. Individuals with severe cases had a higher proportion of cognitive impairment than individuals with non-severe cases, so 40% versus about 15%. The controls give us this 40% versus 14.25%. Now, we're going to go through a table here, but more specifically, individuals with severe cases had a higher proportion of suspected dementia and mild cognitive impairment than individuals with non-severe cases.

Comparing there, you're seeing dementia about 12.5% versus less than 2%. Mild cognitive impairment, 27% versus 13%. Then, there is a baseline in controls. Let's look at Figure Number 1 because this is this cognitive trajectories of COVID-19 patients and controls during the 30-month period. There's a bunch of different panels. There's panel A, panel B. Really, panel C is what I like the most because, as we get older, there is going to be some decrease in our TICS-40 score.

We lose a few points where you follow us out for a couple of years, particularly when we're over the age of 70 or 80. You can see even the controls. They're going to lose about a point over 30 months. Then you look at the folks that have severe, and by about 12, 16 months out, they're already down like a couple points. And the non-severe COVID cases were really not that much different. It was a little bit of a decrease relative to controls.

VR: Everybody decreases with time.

DG: Yes, over time, we just were not quite as sharp. Getting a severe case of COVID, yes, we declined quite a bit quicker. All right. I will close us out with the no one is safe until everyone is safe, where I think this is probably going to be the last episode that drops while we're still doing our FIMRC, Foundation International Medical Relief of Children fundraiser. May, June, and July, we're going to double your donations. We're hoping to get up to a maximum donation of $20,000. Go to parasiteswithoutborders.com, click on the donate button, and help us support FIMRC.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. David writes, "On June 6th, I received my first HPV vaccination, Gardasil 9, half a mL, since I had never gotten it as a kid. However, when the person giving the injection pulled the needle out, I swear I felt a few drops of liquid drop on my arm. I don't remember anything like this ever happening before. Is it normal for a tiny amount of vaccine to be left in the needle and for this to happen or should I be worried that I didn't get the full dose and restart my schedule as if the first one never happened?"

DG: Yes. David, this definitely happens. I've definitely had this happen. The IM, the intramuscular, right, you're going to go in and, half a mL is quite a bit. Sometimes we actually will get a tiny amount, which will come back out. I've done thousands of vaccinations in my career. This happens. It's OK. You can move forward.

VR: A drop is 50 microliters. Which is point what? 0.05 mLs. No, that's even less, 0.1 mL would be 100 microliters, right?

DG: Yes.

VR: 0.05 would be 50 microliters. Am I doing that right, mL? A thousand microliters is an mL.

DG: Yes, 50, so this would be 0.05. Yes. So this is a small percent.

VR: Small amount. Toni writes, "Looking to pick your brain. I have an almost 20-month-old baby that unfortunately experienced COVID in utero around 14 weeks gestation and again at 13 months. The very same day he received his first Moderna vaccine his grandmother infected him along with the rest of the family. It was upsetting to say the least as we sacrificed a lot of

social gatherings over the holidays. My question, is there any meaningful benefit to give him his second dose of the COVID vaccine?

He's an otherwise healthy and very active baby boy with exposure to a school-attending six-year-old brother, double-vaxxed, dodged the infection seven months ago. Baby himself is not yet in daycare, but the plan is for him to start winter 2025. Full disclosure, I'm a family doc with a busy practice and have fallen off the wagon with keeping up with the latest pediatric recommendations. Thanks so much for your time and all that you do."

DG: In a sense, this, I'm going to say, is a little bit easier because we always run into this issue of a person gets one vaccine and now they're about to get the second one and it's whatever period of time at, and then they get COVID. And is that next exposure to COVID, is that that second dose? Or maybe they have two doses in an adult and now they get COVID. Does that really count as their third?

As you're describing, you get the COVID vaccine and then you immediately get infected the same day, I would sort of think of that counts as one exposure. Think of that as basically equivalent of getting that Moderna vaccination dose and then just follow the guidance as far as, whether it's two or three, vaccines going forward, boosters, et cetera. Yes, I would just consider this the one immunological event and then go forward with the vaccines.

VR: Janet writes, this is a question about Biden and COVID. "His doctor reported that he had taken his 10th dose of Paxlovid. I thought from you that five doses was all that was needed. My son with MS was prescribed five days times two, but we went with just the five days as he heard so many times from you that was all that was needed. Now, I'm wondering if it was a mistake to second guess the prescription from his MS clinic. He started a new immune suppressant drug a couple of months before."

DG: Janet, the 10th dose, the dose of Paxlovid, it's twice a day. There's three pills and there's sort of the old packaging. It was sort of like a yellow and a blue. I guess the yellow was the morning dose, of the three pills and then the blue was the evening. Tenth dose would be day one, two, day three, day four, and day five is going to be your ninth and then 10th dose. Five days. Now, more than five days have been studied and there was actually data presented by Pfizer and CROI where they said, "Well, let's look at people who are immunosuppressed."

This sort of applies directly. Let's compare head-to-head five versus 10 days. They really did not see that there was a benefit to the 10 days. You just get an extra five days of whatever that dysgeusia, that metallic bad taste in your mouth. So, no. The currently recommended is a five-day course.

VR: Jean writes, "Hi, Dr. Griffin. I live in Alabama and heard you've never been here. You should visit Huntsville, which is a great city in the scenic mountains of North Alabama. It's known for NASA's Marshall Space Flight Center, the HudsonAlpha Institute for Biotechnology and many technology sector companies. The Saturn V rocket was designed and built here in the '60s, giving Huntsville the name Rocket City. But I digress.

Here's my TWiV question. I received Novavax in October '23 and again March '24. Four months later, I'll be traveling during the summer COVID surge. Should I get another vaccine booster or wait until the fall when updated vaccines will be available?"

DG: All right. Yes, I've got to go to Alabama. Can you believe that? I've been to all 50 states except for Alabama. This makes me even want to go. Yes. Who is not? I'm still like that little boy fascinated by rockets and space. We expect that the updated vaccines will be available next month. Sort of a little bit of a challenging timing here. We're only a few weeks away, we think, from getting the next updated vaccine.

That's going to be the current recommendation is a few more weeks. Try not to get your COVID in the meantime. Then you'll have the opportunity to get your updated vaccine either end of August or sometime in the fall. Again, think about the timing of your exposures.

VR: J writes, "In her most recent Substack post, Dr. Jetelina, that's "Your Local Epidemiologist," stated that, quote, 'Evidence shows that Paxlovid works for a small subgroup of people medically vulnerable over 65, those who are not up to date on COVID vaccines. Unfortunately, Paxlovid is not as effective as we had hoped for everyone else. Evidence suggests that it doesn't protect against Long COVID, and it doesn't decrease the number of days you're sick if you're up to date on vaccines.'

This surprised and concerned me. As a 48-year-old with mild asthma but otherwise healthy, my plan with my doctor's input has been to use Paxlovid should I get COVID. I have come to trust Jetelina very much, but this comment makes me wonder if I should skip the Paxlovid if that situation comes to pass. I'm fully vaccinated with most recent dose Fall 2023. The contact of my question applies to folks who are fully vaccinated and not 65-plus and medically fragile.

I followed her link to the paper about Long COVID. It seemed only to address Pax as a treatment for Long COVID rather than a treatment for COVID, which might reduce the incidence of Long COVID. It also seems a bummer that it doesn't reduce the number of days one has symptoms. But I wonder if there are data that show statistical significance for (1), reducing severity of those symptoms, and, (2), reducing adverse outcomes like ER visits, hospital admission, or need for ventilator and other serious interventions, or death.

Is it really the case that only folks who are 65 plus and medically fragile should take Paxlovid based on their current data and understanding? Even under those conditions, an otherwise healthy 65-year-old would skip it, too."

DG: "We keep sharing repeatedly the data here, and it's evolved over time. There's hundreds of studies. It's a little disappointing that like, "Oh, it doesn't have any potential impact on Long COVID." We've shared a meta-analysis where they've looked at that, you look at a bunch of studies. There certainly is a growing amount of evidence that you drop that viral replication during that first week, you reduce the severity during that second week. Really, whatever your baseline risk is, we just share it at vaccinated individuals.

About 50% of their studies have actually suggested even more of a benefit in reducing ending up in the hospital, other outcomes. The data is here, the data keeps growing. Now, unfortunately, people who have Long COVID, and that was the study where they said, "OK, let's take people with Long COVID." This was the Stanford study that is now published. "Let's give them 15 days and see if it can treat Long COVID." Nothing compelling there that it's a good treatment.

Yes, growing amount of evidence that getting Paxlovid can reduce your risk of progression to severe disease, reduce your risk of ending up in the hospital. It may also reduce your risk of ending up with Long COVID. Though not necessarily statistically significant, there's a trend towards shorter period of time that you're feeling sick. Whether that's eight or 12 hours less of feeling sick, most of us would like to feel better a little bit more quickly if we've got COVID-19.

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

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

[pause 00:36:36]

[00:36:55] [END OF AUDIO]