This Week in Virology

TWiV 1078 Clinical Update

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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

[music]

VR: From MicrobeTV, this is *TWiV, This Week in Virology,* Episode 1078, recorded on January 11, 2024. I'm Vincent Racaniello. You're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: We're catching up on *One Piece*, Daniel.

DG: I was going to wonder if you were going to keep updating each time. I was actually watching a *One Piece* episode the other night as we were enjoying MB Ramen with the family at one of these local places. If we keep this up, maybe we will pass One Piece.

VR: Yes, we will. We will. Now, I'm looking at your tie, and I'm seeing viruses, right?

DG: Yes, so this is the homemade COVID bow tie. I have the matching COVID socks with COVID toes because are -

VR: You tie it yourself. Is that what you mean by homemade?

DG: No, actually, I have the fabric made. Then my daughter, Daisy, and my friend, Rupali Gupta, actually, they iron, they put in - there's a thickening fabric in here. It's cut to my dimensions, my specifications. Then, only then do I actually personally tie it.

VR: We have one here on the coat rack.

[laughter]

DG: I know. I leave one there with my vintage white ProHealth coat.[laughter] One time, I'll swap that out. I wanted to start with a couple of things. One is these couple of corrections and comments from our other shows. I don't know how many of our listeners also listen to *This Week in Parasitism* or the *ID Puscast*, but from the *This Week in Parasitism*, there are not yet one billion people living in Nigeria. I think we're only up to about a quarter billion. It's

another 75 years before we hit one billion. I would love to throw Dickson under the bus, but I think I'm the one that said there was a billion people living in Nigeria.

The other, I don't know if I had mentioned this on *TWiV*, but on the *ID Puscast*, Sara Dong and I were chatting about the New Year's sailing regatta victory. I got a text from my cousin, Peter Dates. Let me read that because I was very entertained. Apparently, he was getting on a flight to some ranch in Santa Barbara, California, and he said, "Daniel, there is no “I” in team. I prefer if you would say, 'My cousin, a regular *TWiV* listener, and I, won. It was my first win and my cousin's third win.'" [laughs] A little credit to our regular listener, Peter Dates. Actually, Peter Dates has contributed in the past.

We are right now in the middle of our MicrobeTV fundraiser, so this would be a great time for him and all his colleagues in finance to jump in with a donation to Parasites Without Borders that we will double and give to MicrobeTV. Right into our quotation. “I believe that unarmed truth and unconditional love will have the final word in reality. This is why right temporarily defeated is stronger than evil triumphant.” That's from MLK Jr.'s 1964 Nobel Peace Prize acceptance speech in Norway.

Now, measles, oh my gosh, back in the news again.

A cluster of measles cases in Philadelphia, what's Paul Offit doing down there? Is now up to eight children over the past - can you imagine, of all the towns and all the gin joints and whatever, and Paul Offit's town, a person who contracted measles outside the United States went to Children's Hospital of Philadelphia in early December, ended up exposing three people at the hospital. Paul, what are you guys doing down there? Ended up three folks tested positive for the measles virus. One of the people exposed attended a Philadelphia daycare. Days later, two children from the daycare were hospitalized with measles.

As I mentioned, this has widened to include eight people over the past month. This historically has been a success. Prior to the nation's measles vaccination program, about three to four million people got the virus every year and approximately four to five hundred died. We really dropped in this last 2023, 48 cases in the entire U.S. The last significant measles outbreak in the U.S. was in 2018, 2019. Where was it, Vincent? Can you guess?

VR: Disneyland?

DG: Rockland County, New York. [laughs] I'm going to just move up there. That's where all the good diseases are, but I'll leave a link into the City of Philadelphia Health Department for people to follow. Ninety-two percent of U.S. children have been vaccinated against measles, mumps, and rubella by age 2, according to the CDC, which means a growing percent, 8% of children, are not getting that protection. As we see, this is a horrible disease. Children can end up in the hospital. Remember on *This Week in Parasitism*, Dickson was asking questions about why only one person had been paralyzed with polio. If numbers move in the wrong direction, that one will turn into more.

As we see here, we're potentially exposed here with measles if we don't take advantage of the vaccine protection.

VR: The Disneyland outbreak was 2014. [chuckles]

DG: [laughs] I remember that one, actually, that created a little family conflict. I don't know if Vincent, but my oldest brother was not always up on the science, not always as embracing of the vaccines as an educated person should be. When he came to visit from California, there was a little bit of a discussion about his unvaccinated children hanging out with mine, which has since been addressed in a positive manner.

VR: Very good.

DG: Moving on to polio. I'm very curious your thoughts on this. Let's talk a little bit about this. The WHO recently pre-qualified the novel oral polio vaccine virus type 2. This is the novel, the nOPV2. We read this is the first time that this group has ever pre-qualified a vaccine that is being used under the emergency use listing. This was announced by the Global Polio Eradication Initiative. This is the interesting, and I hope you can weigh in on this. Estimates after three years of clinical usage suggest that the novel compared to the original OPV2 is 80% less likely to seed new variant polio outbreaks.

Then they go on to tell us that Nigeria was one of the countries hardest hit by the vaccine-derived poliovirus 2 outbreaks played a key role in the rollout of the novel OPV2. Over the past three years, use of the vaccine reduced Nigerian cases by 85%. That's where we're getting our number. Globally, 325 cases reported in 2023, which is down from 689 in 2022. What do you think about this? We've talked a bunch about this new vaccine, Vincent.

VR: The idea was originally that the new vaccine would not cause polio, right?

DG: Yes.

VR: We've since learned that it does, it can. The number I was recently given is, it's only five-fold better than its predecessor OPV2 in terms of not causing polio. You are the math guy. Is five-fold a -

DG: That's 80%, right? Eighty percent of that is five-fold.

VR: Five-fold, and when they first started giving it out, it was 150-fold. Then the more kids they gave it to, that number came down and down and down. I think if we continue to use this and they want to use it in a bigger way, I think it's going to be equivalent to OPV2. I don't think it's ethical to give kids a vaccine that will paralyze them. It's just not ethical. We don't do that in the U.S. I don't think we should be doing it in the rest of the world.

DG: This is a challenge we talked a little bit, you and I and Dickson and Christine Nala about. We are having all these concerns. It's anti-science, the vaccine hesitancy. Here we are actually seeing people develop polio from a vaccine-derived strain. It recombines in the gut. It doesn't matter how genetically stable we make either end of it. You and I, I think, are on the same page. We need to ante up. We need to find the funds. We need to make sure no one gets exposed to a vaccine-derived revertant polio virus that hasn't gotten the injectable polio to protect them from the paralysis.

Moving on to RSV. Put our hedged optimism here. It looks like maybe we were coming down, but there is some evidence that maybe there's a little bit of an uptick. Sometimes we've seen this in prior years where we peak, it goes down, and then we see a slightly later peak. Let's

just keep our eyes out. We still have very high RSV activity out there. The next is flu. We have not yet quite peaked. We're actually still on the way up. We're still seeing an increase in the number of positive specimens, still seeing an increase in the percent positive. Across the U.S., we talked before about North Dakota.

We didn't get any hate mail, Vincent. I can't believe that.

[laughter]

VR: Nobody listens.

DG: Apparently no one from North Dakota. We had talked about before it was white insufficient data. Now we have data and it is high, but lots of flu out there. Really most of the country is seeing high or very high levels, a few places where it's a little bit better, maybe Nebraska and Minnesota. No, in general, that pattern that we tend to see where the flu really moves up, but oh my, down there in the Southeast, just lots and lots of influenza.

Moving to COVID. Now, we'll have a little bit of a discussion here. I still pull those numbers off BNO. I think it's important to just take a deep breath and be honest about what's going on here.

Right now, we have lots and lots of COVID cases out there. The average number of cases is up another 10%. We have over 25,000 people in the hospital because of COVID. Forget about this with COVID. We are seeing people get COVID, get sick, get sick enough that they end up in the hospital. We have thousands of people in the ICU. I just want to point that out. Today, I was at one of our hospitals and just walking around, and just because people are saying, "Oh, yes, we see COVID, but it's not like people are ending up in the ICU." Yes, people are ending up in the ICU.

Last week, we had over 2,000 deaths, 2,000 individuals, 2,000 Americans died from COVID. This isn't died with COVID. This was COVID as the cause of death. That's quite a bar these days because there's so much else going on. I just want to point this out. One of my colleagues, a bright woman, infectious disease specialist, made the comment, "Oh, this new JN1 variant, it must be really bad," and I said, "You know -" Yes, Vincent, shake your head. Please do. I said, "The denominator has gone up, and when the denominator goes up, there will always be a variant," and we'll talk a little bit about this, "there'll always be a variant in December and January."

The numbers go up in December and January, so yes. What is happening across the country, and I intimated this before if we look at the wastewater, if we go back to last month, the wastewater, the limit only went up to about 1,200. They've actually increased that limit to 3,000, and the Northeast is actually approaching 3,000. The numbers are really going up, particularly in the Northeast.

VR: This 3,000 is copies per mil of sewage, right?

DG: Exactly. I like to point out, people are not drinking the sewage. This is a detector of what's coming out people's tails.

VR: Nobody is going to get COVID from sewage, right?

DG: Yes. That was the thing we talked about with polio. Polio, we say, is actually a disease of modern sanitation because it actually reduces the exposure to later in life. Yes, sewage and having these systems, this is a way of tracking what's going on. People are not getting COVID from sewage. Just because apparently, people need to have us say that. We're going to talk a little bit about variants this week because I think there was an interesting article. The article was, "The Death Rate of COVID-19 Infection in Different SARS-CoV-2 Variants was Related to C-reactive Protein Gene Polymorphisms," published in the *Nature* journal, *Scientific Reports*.

I think it's really timely with the discussion I had this week, but also after a question we had last week on the live stream about, is there some genetic basis to COVID-19 severity. In terms of background, prior investigations have identified the serum level of C-reactive protein, this is an inflammatory marker, as a significant independent risk factor for COVID-19. A link was found between serum CRP and genetic diversity within the CRP in earlier research. What they're going to do here in this study is they're going to examine whether single nucleotide polymorphisms - you change one of the single nucleotides, a little part of the genetic code that codes for the C-reactive protein, and they're going to find that a particular change was associated with COVID-19 mortality among various SARS-CoV-2 variants. They did genotyping and they found that certain polymorphisms in 2,023 deceased and 2,307 recovered patients were significantly different between the recovered and the deceased patients. In all of the three variants they examined, the COVID-19 mortality rates were associated with a particular genotype. More science to suggest polymorphisms within the CRP gene may relate to serum CRP levels and mortality in COVID-19 patients.

They do, they humbly suggest that a replication of these results is needed. I like that. One of the things that I found very interesting is that the risk correlation with different genotypes and death varied between different SARS-CoV-2 variants. I think a more subtle discussion when people talk about maybe this or that variant might have a difference. I do recommend people go look at this paper, look at Table 3. If for instance, you look at the Delta and you look at certain genotypes, you might see a small increase in correlation with death. For some genotypes, this might double when you compare it to Omicron BA.5.

To take a pun from "The Last of Us," one's risk of a bad outcome with COVID-19 can run in our genes. One of our listeners will know what pun I'm referring to, but really interesting to look at this. When people talk about different severities may be related to different variants, at least in this analysis, it depends who you are. I think it also, we should probably point out not every Omicron variant is exactly the same. Here, they're looking at Omicron BA.5. People now are talking about Omicron JN.1. So which Omicron are you even talking about?

VR: Daniel, this makes me think when I hear results, my first reaction is skepticism. It's rare that I'm not. It's a study that blows me away where I'm not skeptical, but this is one where I am skeptical. You look at the confidence intervals here, they are really big, right?

DG: Yes, they're huge. I look at the Delta GGRS1800947 and it's 6.8 up to 15.56. A lot of these are really overlapping. I think that's important. Is it really true? Is there really a statistical significant difference? Are the sampling sizes big enough with the number of genotypes? I

think this is interesting. Maybe this is in there with the gargling and aspirating your coffee and switching over to a vegetarian diet, but interesting work.

VR: It's interesting. It needs to be replicated, but more importantly, we need to understand what's going on. Are there plausible mechanisms that would make this make sense? I can't think of any right now, but I think you need to come up with some, you just can't say, "Here's this association." You have to move to the next point and say, "Here's what's going on," and I just don't see that.

DG: I think the idea, that's a good discussion, is that what gets people into trouble is not the viral replication in the first week. It's the inflammatory storm, the cytokine storm during that second week. One of the correlates of people doing poorly is an elevated CRP level. That's actually the people who benefit more from tocilizumab, benefit more from steroids. I think that the concept here is there might be different genotypes that are associated with more exuberant inflammatory response and more exuberant C-reactive protein production.

I agree with them. Let's see more. I'm not sure what clinically you're going to do with this. Are you going to genotype people and be like, "You really got to wear your mask. You're going to be the guy who gets in trouble. Ma'am, you'll be fine. You can get on that airplane without one." I don't know if it's really at that level yet.

VR: You don't know what future variants are going to do in terms of this, right? So this is historical.

DG: I like that too, is what's the hardest thing to predict is the future. You may have a great genotype for Omicron BA.5, what's the next genotype going to do? What's the next variant going to do? That's actually a great segue. A good time to talk about the fact that, here we are, it's January. Every January so far for the last few years, we have seen a rise in hospitalizations. We've seen a rise in deaths. I remember Boris Johnson, "Everything was great. All my policies in the UK were perfect. It's not a problem with everyone getting together in those crowded bars. It's the new variant."

VR: Of course. Blame it on the variant.

DG: We've been playing that game for a while, but I just want to point that this is a pattern. Actually, I'll leave in a link. You can go back to the CDC COVID dead data tracker and you can just see that in January of 2021, the hospitalization shoot up, in January of 2022, the hospitalization shoot up even higher, in January of 2024, where we are now, January of 2023. This is this pattern that we've been seeing. I just want to point that out when people - because this is one of those things where we say the three most dangerous words in medicine are in my experience because there's a confirmation bias.

The hospitalizations are going up, the media tells you there's a new variant. They tell you it's really severe, you see all these people in the hospital. It all fits together. This is why you need to step back and say, "No, the denominator is bigger than it's ever been. With a denominator this big, with that many infections, you can end up with more people in the hospital. With that many people in the hospital, you can end up with more people not surviving.

VR: Someone on the live stream last night said, this latest variant, I forget the number, "It's associated with cognitive issues and it's insomnia." I said, "Yes because the press is making people crazy.

[laughter]

DG: You might be right. I still get lots of questions from my colleagues about whether we should be recommending the new vaccine for COVID to high-risk patients such as those over the age of 60. Maybe better is the question regarding how much benefit there might be compared to just relying on the survivor immunity or immunity from the prior vaccine series. This week, we have the *Rapid communication,* "Early COVID-19 Vaccine Effectiveness of XBB.1.5 Vaccine against Hospitalization and Admission to Intensive Care, The Nether*lands,* 9 October to 5 December 2023," published in *Eurosurveillance*.

In the Netherlands, the 2023 seasonal COVID-19 vaccination campaign started on 2nd of October targeting persons age 60 years and older, healthcare workers, pregnant women, and medical risk groups. It used the monovalent XBB.1.5 Comirnaty vaccine, that's the Pfizer-BioNTech. All residents of the Netherlands age 60 years and older received a personal invitation for vaccination by post between 2 October and the end of November. Maybe that's what people need in the U.S. Did you get your personal invitation? I didn't get my personal. I'm not going. I'm not getting my vaccine. I haven't got my personal invitation yet.

Forty-eight point two percent of the residents age 60 and older had received the 2023 seasonal COVID-19 vaccination. A perfect opportunity to look and see what happens. They extracted hospitalizations with admission dates between 9 October and 5 December 2023 from the National Intensive Care Evaluation COVID-19 database. They did this extraction on the 11th of December to account for registration delay. The database contained around 55%, so the majority, of all COVID-19 hospitalizations during the study period in the Netherlands.

They calculate that the vaccine efficacy against hospitalization was 70.7%. Vaccine efficacy against ICU admission was estimated at 72.3. Then they break it down where they say the vaccine efficacy against hospitalization was slightly lower for the age group 60 to 74. That was about 68.3; 85 years and older, 66%, then for persons in the 75 to 84, that was about 74%, but not statistically significant. Just the difference. I have a few comments. We always and I appreciate you say that you always read studies with a bit of skepticism because you should. That's scientific training, is you want to you want to look at it critically. One, this is not an RCT.

There could be differences between the groups. I thought it was interesting, their first comment was it could be an overestimation of the efficacy because they refer to something as a healthy vaccine bias. You're feeling good, you're healthy, not a big deal for you to run out and get the vaccine. If you're someone using a walker, it's tough to get around. Going and getting the vaccine is a bit more of a lift or even the opposite. If you're higher risk, you're like, "I really should get the vaccine," where you might be lower risk or people love to perceive their risk as lower, so you say, "I don't really need that. I'm not as high risk as that other person."

You also might have an underestimate because if someone recently got infected and they've got that protection from the recent, they're not going to get their booster. So they're going

to have that. Just want to point that out. I think the other thing that I want to point out, in addition to recommending people go ahead, look at the article critically. This is really no matter what they want to call it, a booster shot on top of a very high primary vaccination rate in the Netherlands. The majority, it's like over 90% of folks in the Netherlands have been vaccinated.

If you break this down by age group, in the 80 and older, it's 92% in the 70 to 79, it's 93%. Go down to the 60s, it's 88%. Really high vaccination rates. This is really a boost for about half the population on top of that really high basal rate. Then you can even see it's concentrated. Percent vaccinated habitants is concentrated in different regions.

VR: So we don't know what virus infected these people, right?

DG: I was going to say it's SARS-CoV-2. You mean which variant?

VR: Yes, which variant? That's SARS-CoV-2. [laughter] Sorry. Yes, which variant? Because that would impact, and I suspect it is impacting these numbers. They're not bad, but, we're talking about hospitalization and ICU admission, so those are good numbers. I wonder if the very -

DG: We're in that window. That three- to four-month window when we expect to get the benefit. The match or mix match thereof between the variant and the efficacy is also important.

Moving on to the early viral phase. A start off with a call to action with the article, "SARS-CoV-2 Antiviral Prescribing Gaps Among Non-hospitalized High-risk Adults," published in *CID.* Here we read that within a multistate clinical cohort, SARS-CoV-2 antiviral prescribing patterns we evaluated from April 2022 through June 2023 among nonhospitalized SARS-CoV-2 infected patients with risk factors for severe COVID-19.

Among 3,247 adults, only 31.9% were prescribed an antiviral agent, mostly Paxlovid, a little bit of molnupiravir, less than 1% with remdesivir. Just this article's highlighting the need to identify and address what are the treatment barriers for people not getting the NIH-recommended treatment.

VR: Probably their doctors, right, Daniel?

DG: It's a combination. It's mostly their doctors, to be honest, because as we've talked about studies before, a lot of times people reach out to their providers and the provider does not recommend it because of misinformation. That's really a bit of a challenge. One of the authors, Shishi Luo, she actually emailed me right after I just finished reading this article and putting it in my notes and she emailed me and said, "Oh, and by the way, in addition to my publication, I also have a preprint." Shishi Luo is a mathematician with expertise in statistical modeling.

I will briefly mention a preprint. This is, in a lot of ways, a thought experiment we do on the show, but here was a formal, "Proportion of Hospitalizations Preventable with Increased Oral SARS-CoV-2 Antiviral Treatment Models." The percent of hospitalizations that could be avoided if people just followed those NIH guidelines and prescribed the antivirals. In this investigation, they estimated the proportion of hospitalizations that could have been averted

had all eligible high-risk adults with SARS-CoV-2 infection in a clinical cohort, been treated with an oral SARS-CoV-2 antiviral early in infection.

They're going to look at 3,037 patients with risk factors for progression. They're going to look at oral antiviral prescriptions, that number of 31.1%, which is what's out there, as we just talked about, for people actually getting treatment. Then they're going to look at what percent because even Paxlovid is not 100% of keeping people out. They're going to use a 3% of treated versus about 9% of untreated might end up in the hospital, basically saying if all patients had been treated, an estimated 63% of hospitalizations could have been prevented.

Really, again, when we talk about those thousands of people in the hospital, we talk about the over 2,000 people who die, just really doing some modeling. What kind of an impact could we have if we just use the recommended tools that we have? What are those tools? Number one, Vincent, what is number one?

VR: Oh, Paxlovid.

DG: What about the rebound? Oh, my gosh.

VR: Oh, yes.

DG: Unfortunately, I'm beginning to realize I have to recap this every week and I will say again, do not let your confirmation bias confuse you. I had a telehealth appointment today with a physician and he said, "Dr. Griffin, do you think I could be experiencing Paxlovid rebound?" I said, "Sir, just we'll start off with my comment. There is no such thing as Paxlovid rebound and let me explain." In my experience, because that was his thing. He's like, "Wow, I felt not so great and I felt a little better and now I feel not so great." I'm like, "Yes."

Straight from the CDC, “SARS-CoV-2 Rebound With and Without Use of COVID-19 Oral Antivirals.” To enhance understanding of rebound, the CDC reviewed SARS-CoV-2 rebound studies published during February 1, 2020, through November 29, 2023, including that article that the IDSA just put out in their newsletter again that was published back in November. No statistically significant difference in rebounds rates were identified. No hospitalizations or deaths were reported among outpatients who experienced "rebounds" because COVID-19 signs and symptoms were mild.

The potential for rebound should not deter clinicians from prescribing lifesaving antiviral treatments. We also have the other article that we talked about last time where they evaluated the double-blind placebo controlled trials. What are we seeing during that second week? We are seeing the early inflammatory phase of COVID, not a rebound of the viral phase. This is not the time when you need more antivirals. I will leave a link into a paper I published actually quite a while ago describing this. [chuckles] Actually, I think it was before Paxlovid was even a thing.

VR: Can we just purge rebound from the lexicon?

DG: I wonder if there's a way to do it. I think that that would probably, in the spirit of Paul Offit, words matter. We've got to get rid of that. There's no rebound. You are now having the early viral phase. You are now during that second week having the cytokine storm. I think

there was this question too, and we've talked a little bit about this. In addition to the acute, can Paxlovid prevent Long COVID, or PASC? Mixed results here with some studies suggesting we might decrease Long COVID, but not in all the studies, so I'll leave a link there. That's number one, Paxlovid. Number two, remdesivir, but as we've seen, not really being used a lot.

Number three, which is really second line, inferior, molnupiravir. After that, convalescent plasma for certain folks. We will move on to what about some other things. This is the article, fluvoxamine: *"Evaluating Fluvoxamine for the Outpatient Treatment of COVID-19: A Systematic Review and Meta-analysis,"* published in *Reviews in Medical Virology.* In total, we have nine RCTs, totaling 5,861 participants. I think, as I've talked about people before, look at the forest plots for hospitalizations, incidence of hospitalization based upon the different RCTs. You can really see, and we can go through this. If you look at fluvoxamine 500 BID, you basically see overlap all across the board.

If you look at fluvoxamine 100 milligrams BID, you're going to see overlap studies back and forth across the board. When you put them all together and you let the influence of the TOGETHER trial start to push things, you do see a slight shift to the left. Also, you can also look at mortality, and very similar. A little bit of, we'll say, shift in trend favoring the fluvoxamine 100 milligrams BID on mortality, but not statistically significant. Certainly inferior to what we can achieve with Paxlovid, even molnupiravir. What did the authors have to say in this review?

I think this is important. From the authors, "While we concur that drugs with stronger supporting evidence should be prioritized over fluvoxamine for clinical practice, it is our view that there remains a need for low-cost alternatives to these more established antiviral therapies, especially in resource-constrained areas where the use of drugs like Paxlovid, nirmatrolavir/ritonavir, is costly or logistically prohibitive. As an old generic medicine, fluvoxamine is widely available and costs as low as a dollar per day, substantially cheaper than the $530 per course for Paxlovid and $700 for molnupiravir." I like that you're shaking your head because what is their argument here?

VR: Daniel, it's better to take a cheap medicine that doesn't help you. That's what they're saying. It's crazy.

DG: This is the Paul Farmer line. This is the "Everyone is not worth Paxlovid. Not everyone is - " That is the source of I think so much injustice in the world to say that certain people are not as important as other people. For those folks that can't - no, the problem here is access to these medications. Don't give them something cheap that doesn't work.

VR: It's ridiculous. That's what I said on a live stream last night, someone in Mexico said, "Paxlovid would cost me three months of salary," and I said, "It's ridiculous. Everybody in the world should have access to Paxlovid. We can make enough. We could pay for it. We pay so much money for weapons. We could use a fraction of that for Paxlovid. It's absurd. We don't care about everybody's lives equally. That's the problem."

DG: The article, "Deaths Induced by Compassionate Use of Hydroxychloroquine During the First COVID-19 Wave: An Estimate," was just published in *Biomedicine and Pharmacotherapy*. I think this really brings us back to something, Vince, that you and I were discussing before

we went on the air and I really do hope that this is a lesson in humility. I'll just briefly share the basis of the modeling study and want to spend a little more time discussing what I hope will be the takeaway lesson for the future. Three highlights from the authors. One, hydroxychloroquine was prescribed in hospitalized patients with COVID-19 despite the low-level evidence. Two, subsequently the HCQ use was associated with an 11% increase in mortality rate in a meta-analysis of randomized trials and these findings illustrate the hazard of drug repurposing with low-level evidence for the management of future pandemics.

The authors go ahead and estimate the thousands of people who died because a decision was made to use HCQ rather than keeping one's hands in their pockets and perhaps we did not take those hands out to stop the HCQ. A couple of things here. One is just this concept in medicine. I get calls all the time, why aren't we trying this? Why aren't we doing this? Now, number one, we are not as smart as we think we are, and using unproven therapies can often and usually leads to harm and it also takes the place of stepping in with proven therapies. We could talk a little bit about this but my hope - and I don't think we learned this medicine because I still get the same questions.

Why are we not doing this? Why isn't it worth a try? As if we can just experiment on our patients. We want to do something that might be what draws a lot of people into medicine as opposed to just really stepping back with humility and saying, "If I can't promise you that I can do something helpful, I might actually be hurting you."

VR: I remember when the hydroxychloroquine paper came out early in the pandemic, that's when you were still coming to Columbia to record in my office and you were flipping through the manuscript and saying, "I don't see anything here that's encouraging." You went through it and yet it was pushed through the FDA by political forces that are ignorant of science and medicine and that's the problem. You have to let it proceed at its own pace. This is a good point that you raised. People say, "Why aren't we trying this? It's cheaper. It's already available." That's not how it works, right?

We have to do things safely and here we have an example of something that was not working to begin with, and harmed patients and is probably one of the worst examples of what happened during the pandemic.

DG: I still remember that first paper where there was a wonderful figure and they've got this viral kinetics and look how great this is, but then you actually looked at the patients and the patients in the control group did much better. The people on the HCQ had an increased risk of a bad outcome including death, but yet everyone was so anxious to do something. We saw that article up about fluvoxamine. It doesn't actually work, but it's cheap and the problem is there still are these people out there who are encouraging the use of hydroxychloroquine, still encouraging the use of all these unproven therapies and what's actually happening, and I was sitting down to write a note at one of the nursing stations the other day, and there was this sheet and it was, your doctor may not know, and it was this whole recommended cocktail of therapies that have been shown actually to be harmful. Unfortunately, there are people out there still peddling them. The HCQ, I know you hear it doesn't work but that's because there's a conspiracy. No, there's no conspiracy. We care about our patients. We take an oath. We want our patients to do better.

All right, moving into the second week, I'm going to call this the cytokine storm week. Let's not use that R word in polite company anymore. Remember, you don't want to use those steroids during the first week, but in the second week, only in the right patients. These are folks with an oxygen saturation less than 94%; dexamethasone, six milligrams a day times six days, and this will get me in that conversation I had with that physician today who's on day about 11 of his COVID-19, acute COVID. We had a little bit of a discussion about the fact that unfortunately, someone had given him steroids on day three. Not so great.

We said that why would you shut down this wonderfully vaccinized immune system with a steroid but here we are during week two, and why don't I just give him steroids to calm down the inflammation? Because here's someone who just had a viral illness. They're at risk of a post-viral bacterial process so we really want to be careful. We don't just throw steroids at everyone because it makes you feel better. We want to be really careful. Number two, anticoagulation and again, we have guidance here.

We don't just throw anticoagulation at everybody, pulmonary support, remdesivir if still in the first 10 days, immune modulation perhaps with tocilizumab, and then yes, avoiding those unnecessary unproven therapies. Let's talk a little bit about one of those therapies that's still out there. “Doxycycline for the Prevention of Progression of COVID-19 to Severe Disease Requiring Intensive Care Unit (ICU) Admission: A Randomized, Controlled, Open-label, Parallel group trial (DOXPREVENT.ICU).” Recently, published in *PLOS One*.

Despite this being a viral illness, there continues to be significant interest in using antibacterial agents in its treatment. We've discussed several articles over the last few years, including the article, “Doxycycline for Community Treatment of Suspected COVID-19 in People at High Risk of Adverse Outcomes in the UK (PRINCIPLE): A Randomised, Controlled, Open-label, Adaptive Platform Trial,” published in *Lancet Respiratory Medicine,* where they saw hospitalization related to COVID-19 occurred in 5.3% that got doxy versus 4.5% in the usual care group.

Looking at deaths, you had five deaths in the doxycycline, two in the usual care. Neither of those outcomes really encourage us to recommend doxycycline. Here, perhaps things are a little bit different. What the authors are going to argue is that we're going to give this later on, we're going to give this as an anti-inflammatory agent to help address the cytokine storm. In this pragmatic, non-blinded trial, they're going to look at 387 patients aged 40 to 90 who are randomized to receive treatment with standard-of-care plus doxycycline or standard of care only in six hospitals in India.

We're going to spend a little time, what is standard of care in India? The primary outcome was the need for ICU admission as judged by the attending physician. This isn't whether or not they go to the ICU, it's just does the attending doc think they should? Among the 387 participants, 19.9% developed critical illness where their doc thought they should go to the ICU. They reported that doxycycline was associated with a risk reduction of being judged by their physicians to require admission to the local ICU from the regular medical ward.

I do want to point out about a couple of things. Only about half of the people actually went to the ICU after the doctor felt they needed to go. While we do have well-matched controls to treat it, I will point out the standard of care lots of ivermectin, steroids, antivirals, and antibiotics other than doxycycline being used, over 80% of the folks in each group are getting

doxycycline. Let's look at the actual outcomes, right? There's a little difference in the docs thinking their patient may or may not need to go to the ICU, but how many folks died?

Ten percent who got doxycycline, 10% who got no doxycycline. The authors suggest that they are trying to use doxycycline to target the cytokine storm. To summarize, for doxycycline, no compelling evidence for reduction of need for hospitalization or death, and this one study suggesting an impact on the provider's perception of need for ICU stay.

VR: Dan, is there any evidence that dox is an anti-inflammatory?

DG: There is some, and there are some researchers working on trying to modify it to make it more anti-inflammatory and basically not affect the doxycycline impact on antimicrobial resistance developing. I like the look that you gave there, it's not as compelling as I would like.

VR: We have compounds that work as anti-inflammatories, right?

DG: Yes, but this is cheap and ineffective. [laughs]

VR: It's the same thing that we had before. It's not cheap to do a trial. This is a waste of money. I'm sorry. To have an effect on whether you think your patient's going in is crazy.

DG: It's a poorly designed study. What's more worrisome is most people read the headlines, right? They read the headline in some media about this and the headline says, doxycycline reduces the need for ICU. That's not true. This study didn't show that. This study showed really nothing other than some providers perception in India, where everyone was like on antibiotics and ivermectin. That's the problem with this study. This study actually ends up being harmful. It costs money, it misinforms, it misleads, and it feeds into this misinformation.

VR: Just tell us, what are the anti-inflammatories that you use in the second phase?

DG: Only use prednisone when people meet the criteria. They develop the hypoxia less than 94% and we are clearly in that second week, and tocilizumab. That's it.

VR: Thank you.

DG: Thank you. OK. All right. Now, we have a great paper this week and I know we're going long, but maybe next week, we'll cut it short because I'll be off the coast of Venezuela. Here I am today with an article that I've gotten a lot of questions and we're going to spend a little bit of time. The article, “Muscle Abnormalities Worsen after Post-exertional Malaise in Long COVID,” recently published in *Nature Communications*. I think first off, anyone who's reading these articles out there, it's just like venting to my wife before the show about, like this headline and the headline actually had the wrong information.

It was something about clots. Actually then, you read the article and even in that article, they then authors talk about how there's no evidence for clots. Anyway, so let's go through this. What did this study, what did these authors actually find? We'll start off with the abstract. This is a great abstract. A subgroup of patients infected with SARS-CoV-2 remain symptomatic over three months after infection. That's our three months. That's our PASC. A distinctive symptom of patients with Long COVID is post-exertional malaise, which is associated with a

worsening of fatigue and pain-related symptoms after acute mental or physical exercise, but its underlying pathophysiology being unclear.

With this longitudinal case-control study, we, the authors, provide new insights into the pathophysiology of post-exertional malaise in patients with Long COVID. We show that skeletal muscle structure is associated with a lower exercise capacity in patients, and local and systemic metabolic disturbances, severe exercise-induced myopathy, and tissue infiltration of amyloid-containing deposits in skeletal muscles of patients with Long COVID worsen after induction of post-exertional malaise.

This study highlights novel pathways that help to understand the pathophysiology of post-exertional malaise in patients suffering from Long COVID and other post-infectious diseases. All right. Let's go through the results. We'll go through this nice and slowly. Initially, all participants performed a cardiopulmonary exercise test on a cycle ergometer. They're sitting there on the cycle, they're pedaling away. Maximal oxygen uptake and peak power output were substantially lower in Long COVID patients.

They found that the cardiovascular system was not compromised in Long COVID patients suggesting that the cardiovascular system does not explain the limited exercise capacity in patients with Long COVID. They also found that the lower VO2max in patients was not due to submaximal effort during the exercise test. I think that's really important. It's not that these people are not trying, these people are trying, they're putting in their maximal effort. It's not the cardiovascular system and it's not because they're lazy.

What is it? Next, they go on to assess the skeletal muscle structure and function to see if they can explain the lower exercise capacity in patients. Capillary density and the capillary-to-fiber ratio were not different between groups. We've got the blood supply there. Compared to healthy controls, they observed a higher proportion of highly fatigable glycolytic fibers in the vastus lateralis muscle. This is your lateral thigh in Long COVID patients along with a lower cross-sectional area of fatigue-resistant Type I fibers in females.

The succinate dehydrogenase, the SDH activity, a marker for mitochondrial content correlated with V̇O2max in healthy controls, but not in patients. While patients had a significantly lower oxidative phosphorylation capacity, no differences were observed in SDH activity, suggestive of qualitatively lower mitochondrial respiration rather than a lower mitochondrial enzyme activity. All right. Let's pull this together. They're going to say that collectively, they're suggesting that this lower exercise capacity is associated with more of these highly fatigable glycolytic fibers and lower mitochondrial function.

They then actually go ahead and they're going to do biopsies of the vastus lateralis muscle before and one day after the induction of post-exertional malaise. They're actually going to take these people and they're going to say, "I want you to exercise past that point until you're just going to be completely wiped out the next day. We're going to biopsy your muscle now and then we're going to biopsy it the next day." All right. People signed up for this and all Long COVID patients experienced post-exertional malaise following maximal exercise despite considerable heterogeneity in their exercise capacity.

People went pretty long before they hit that level. Symptoms included muscle pain, greater severity of fatigue, and actually some folks had cognitive symptoms up to seven days after maximal exercise. Really, these people are really doing something here to participate. They measured mitochondrial respiration and metabolic signatures and skeletal muscle before and then the one day after the induction of the post-exertional malaise. What are we going to find here? There's some hypotheses. One is that amyloid-containing deposits in the circulation can block local perfusion.

Maybe they're just not perfusing. They studied whether the amyloid-containing deposits were present in the skeletal muscle and whether this was an indication of post-exertional malaise. They demonstrate that the concentration of amyloid-containing deposits was greater in the skeletal muscle of Long COVID patients at baseline. Visualizing the amyloid-containing deposits together with the capillaries or lymph vessels revealed that these deposits were not in the capillaries or lymphatic vessels, but rather next to them in the extracellular matrix.

I want to point out, this was sort of that issue in that article I just read. They conclude that the post-exertional malaise cannot be explained by the hypothesis that these deposits are blocking vessel perfusion, causing local tissue hypoxia. This part I found really interesting, if you're not already hooked. They found that a larger percentage of Long COVID patients displayed small atrophic fibers and focal necrosis, which increased significantly after exercise, indicating an exacerbated tissue damage response in patients with Long COVID.

When we put patients through this, we say, "Oh, you just got to push through this?" They're actually seeing that you are causing necrosis in the muscles of these folks. This is not just harmless. That whole, “you got to exercise yourself back up,” all those physical therapy and people with this post-exertional malaise, you're actually hurting your patients, by the way. I know David Putrino has been pretty bullish on this finding, but that's the individual at Mount Sinai. They explored the infiltration of immune cells and skeletal muscle upon this exhaustive exercise.

They found more Long COVID patients had the CD868+ macrophage infiltrates in the skeletal muscle. They went ahead and they asked this question, which I know everyone cares about. What about viral remnants? Are those playing a role in this differential immune response? They really found no differences between the controls and the affected people. Let's pull this together. The ventilatory and central cardiovascular system did not limit the exercise capacity. That's important. They demonstrated that the Long COVID was associated with lower skeletal muscle oxidative phosphorylated activity.

They found the differences in these different fibers with a shift towards less oxidative, more glycolytic phenotype. These findings did not support the hypothesis that this was due to chronic tissue hypoxemia. Important to note that this is just more objective evidence to support a biological basis for the reports of those suffering with Long COVID, revealing that local and systemic metabolic disturbances, severe exercise-induced myopathy, infiltration of amyloid-containing deposits and immune cells and skeletal muscle are key characteristics seen in post-exertional malaise.

Really, I recommend everyone take a look at this article. The images are great. You can actually clearly tell the difference when you look at a biopsy of a Long COVID patient who has post-exertional malaise and that of a healthy individual.

VR: Daniel, I always say you have to ask yourself, is there a plausible explanation for what you find? Yes, these findings are interesting. Do they say what they think? Is it all about inflammation causing these issues in the muscle?

DG: I'll leave in a press release from the researchers at the university, Amsterdam University Medical Center, because what they really come down on is that they see a mitochondrial dysfunction being an issue, that these individuals have a problem with the mitochondria, so the energy factories in the muscles producing less energy than in healthy patients. They have a really nice sort of muscle metabolomics pathway where they're sort of looking at where are the interruptions.

Really, when we're having these people exercise, it looks like it's triggering necrosis and damage in the muscles. It also looks like there's some issue with the mitochondria not being able to keep up with the demands.

VR: Presumably, they wouldn't have experienced this if they had not had COVID, right? COVID is somehow -

DG: Yes, well, that's interesting. I was going to say this is all post-COVID. How reproducible is this in the ME/CFS population, that also has the post-exertional way? What if we had those folks also exercise, get pre and post-biopsies? Are we going to maybe get some insight into that process as well? I think the big takeaway is we've talked about exercising people up. We've talked about the different interpretations of the concept of pacing. Really, I think, is we need to be careful. Here's evidence that if you tell your patient with post-exertional malaise to just ramp up that exercise, you can actually be triggering necrosis and more damage.

All right. The article, “Features of Acute COVID-19 Associated with Post-acute Sequelae of SARS-CoV-2 Phenotypes: Results from the IMPACC Study,” was published in *Nature Communications*. Here, we have 1,164 participants enrolled between May 5, 2020, March 19, 2021, followed up to 28 days of the 702 participants who survived hospitalization and were alive on study at three months post-discharge, 84% completed at least one quarterly set of surveys post-discharge. A number of interesting findings, and this is sort of the, is there anything acute that corresponds to how people are doing down the road?

They found a correlation between high, let's say viral burden, I'm going to say RNA copy number, low antibody levels early in disease, and these worse outcomes. They reported that during hospitalization, 76% of the participants received oxygen, 68% steroids, 64% remdesivir. Among the 52% of participants who reported symptoms 12 weeks post-infection and beyond, what were they suffering from? Twenty-nine percent reported shortness of breath, 21% had the muscle aches or pains, 20% with cough. Use of remdesivir and steroids in the inpatient period was not associated with a decrease in the PASC prevalence.

A little disappointing there. Here's one. I think we're getting ready to wrap this up, and this will be the last I mention. The news feature in *Nature,* “Long COVID is a Double Curse in Low-

income Nations — Here's Why." I'm going to say this is worth reading, and I do want to point out that this is a news feature. It's not a research article.

With that said, the article starts with a personal story, and I'm just going to read this. I want people to maybe emotionally connect with this topic, and so we start off by reading: "Letícia Soares stepped off the plane in Brazil feeling traumatized and vulnerable. In 2021, she was returning home from Canada, where the final year of her postdoc in disease ecology had been marred by Long COVID. The condition left her with searing migraines, intense fatigue, body aches, and a variety of other ailments that came and went unpredictably, but never improved. Soares decided to return home where she felt she would have better access to medical support if she were disabled and unemployed.

"Having encountered dismissive physicians in Canada, she hoped she would be better supported at home. But her arrival brought fresh disappointment. More than a year into the COVID-19 pandemic, Soares' physicians, friends and family in Brazil had still not heard of Long COVID. 'People asked me whether Long COVID is an illness of the global north.' " The news piece just discusses how little is known and how little research is being done in low-income countries for folks with post-acute sequelae of COVID.

On that depressing note, I will point out, as we have for quite a while, no one is safe until everyone is safe, and that's not just referring to acute COVID, that's also referring to the post-acute sequelae of COVID, and also all the other vaccine-preventable illnesses out there. I'm hoping everyone will pause right here, go to parasiteswithoutborders.com, click on the Donate button, even a small amount helps. We are right now in January, the last month of our three-month fundraiser for MicrobeTV, where we will double your donations up to a maximum donation of $20,000 for MicrobeTV.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Lori writes, "Happy New Year. I'm a pediatrician in a busy Bay Area practice and wondering what viral fun lies ahead in the next few months. Speaking of looking ahead, it's now time to order our flu vaccine for the '24-'25 flu season. We are being offered a new cell-based influenza vaccine, which "solves the challenge of egg adaptation". Please help. I didn't know I was being challenged by egg adaptation, but perhaps there is something here that explains the poor performance of the flu vaccine for the last several years. Any explanation and advice on what to order is very much appreciated."

DG: Well, for our listeners, just to point, yes, here it is. It's January, February, and we've already got to come up with our orders for next year. I hope the CDC is listening because I remember when they came out with their recommendations for specific types of flu vaccines in 65 and over, then we had to put our orders in. Then we had all scrambling like, "Oh, the CDC wants us to do this." We want to align with the CDC. I'm going to talk a little bit, and then I'm going to go ahead and say, buy the Flucelvax Quadrivalent from Seqirus.

That is approved for persons 6 months of age and older, but let's go through. What is my reasoning? We do have a number of choices, and it can get a little bit confusing. We have our standard-dose egg-based vaccines. We have our high-dose egg-based vaccines, and then we have our standard-dose egg-based vaccines that are adjuvanted. Then we have our recombinant vaccine, our cell-culture-based vaccine, and then we have the egg-based

attenuated spray that goes up your nose, so a little trickier if you take care of those under and over the age of 65.

Because as I mentioned a couple of years back now, the CDC came out with preferential recommendations for folks 65 and over. They said, "Hey, for those folks, we're going to preferably recommend that you do the high-dose quadrivalent vaccine, the flu dose, so that's egg-based, but it's a high-dose, or you can use the recombinant vaccine, or you can use the adjuvanted." Well, they gave us three recommendations, Fluzone, the high-dose quadrivalent; Flublok, the quadrivalent recombinant; or Fluad, the quadrivalent adjuvanted.

What about folks under the age of 65? They said, do whatever you want, so maybe for pediatrics, this is a little bit easier. For the pediatrics, you're basically going to have a choice of the egg-based, the egg-based with adjuvant, the recombinant, or the cell-culture-based vaccine. Now, the cell-culture-based vaccine is Flucelvax by Seqirus. I should share in our internal unpublished data from Optum and UnitedHealth Group, it looked like we were seeing slightly lower hospitalization rates in folks that got that.

Yes, Flucelvax Quadrivalent by Seqirus is a little less expensive and a perfect choice for you for your pediatric practice, and it is fine for persons 6 months of age and older.

VR: Let me just explain to Lori that growth of influenza viruses in eggs can cause changes in the proteins that are important for immunization. If you grow it in cells and culture, you don't have that issue. We've actually talked about this on *TWiV*. In certain years, it's not every year, growth in eggs leads to a less optimal vaccine, basically. Cell-based is going to be better.

DG: Yes. I've always felt that, and I sort of refer to it as the egg-attenuated vaccine, so yes.

VR: Aaron writes, "Thanks for your updates. I received a flu and COVID vaccine in the same arm in mid-November and subsequently felt soreness. When it didn't go away in two weeks, I mentioned it to my local pharmacist who said he never gives COVID and flu shots in the same arm, partly because of the response I've been having. He said it would go away eventually. When after five weeks it got worse, I began to worry, made an appointment with my orthopedist. After my exam, he said there was nothing wrong with my arm, but there have been reports of some people having inflammatory responses to vaccination.

Since COVID, there's a wider pool of people receiving vaccination, so they have more data. He prescribed an anti-inflammatory, said I should take it for three weeks and then we'll see what happens. I've been taking it for a week and my arm feels better when I am taking it, but when it wears off, I have pain when I lift my arm or try to put on clothes. Have you heard about these inflammatory responses? I'm curious if this is something that is common and would like to know your thoughts."

DG: OK, certainly. The first thing is sort of reacting to your pharmacist's comment. This has been studied. We've looked at getting the shots both in the same arm, getting the shots in different arms, getting the shots at the same time versus waiting. There's really no difference as far as the reactogenicity that we see. It is absolutely fine to get both shots at the same time in the same arm. One of the vaccines, whether it's a particular vaccine or the location, is giving you a local inflammatory response.

Sometimes that can be triggered by the vaccine being inadvertently injected into the bursa versus actually being properly injected into the muscle, or it could just be that your body is having a significant reactogenicity to the vaccination. We certainly see this. We see this with different vaccines. We see this with the pneumonia vaccine. We see it with many other vaccines. The approach with the NSAID is reasonable. That will help with symptoms. It's really just going to be a matter of time till this resolves, but it's nothing that is worrisome. It's just uncomfortable.

VR: Nancy writes, "I am a treatment-naive leukemia patient, CLL stage 0, who managed to get a just-in-case prescription for Paxlovid prior to a trip to some remote Indonesian islands in August 2023. I stayed healthy and have not needed to take the Paxlovid. If I get COVID, should I pursue a new prescription so I can get a fresher dose? The box I have was issued under EUA, has an expiration of 9-2023. I'm heading out in late January 2024 for more international travel, and I figured I'd take it with me. Can I rely on it if I get COVID?"

DG: Yes, I like the idea of, your fresh pharmaceutical, like going to the market, right next to the tomatoes, they have the nirmatrelvir just like right off the vine, but no, as we sort of saw, it came to January and there were those boxes and they just put a sticker over the old expiration with a new one. I'm not worried in any way that these drugs are very quickly expiring. It's just a legal thing where they have to put a date on there. We saw this with vaccines, too. They came along and they put stickers on. We're going to change that expiration date.

No, it's a precious medicine. I don't feel like you should toss it and get a fresher dose. I feel like you can rely on it.

VR: All right. Finally, Mark writes, "My daughter has a 2-month-old, 12-pound baby. Essentially, the baby should have gotten a 100-milligram dose of Beyfortus, but they gave a 50-milligram dose by mistake." Mark asks, "Is the 50-milligram dose enough since the baby was only one pound over 11-pound threshold since we may be at the peak of the RSV season? Will the 50-milligram dose provide enough immunity to last the rest of the RSV season?"

DG: OK. This has come up before, so I've actually looked this up. I'm going to give you the recommendations from the American Academy of Pediatrics, but I'm also going to talk a little bit about it. This happens and I'll just explain what's going on here. The pre-filled syringes are either 50 or 100-milligram syringes and boom, you get two doses of the 50s or two doses of the 100s and unfortunately, there's been a shortage of the 100s. Yes, every so often, people are getting two shots of the 50s. They get half the dose that they're supposed to.

The American Academy of Pediatrics has said basically, listen, if a half dose is given inadvertently, go ahead and get that next dose as soon as possible. Go ahead and do the 50-50 one more time so you get back up to the right level. All right. That's what the American Academy of Pediatrics, but you are, as you're saying, you're right on the line. The cutoff is 5 kilograms or 11 pounds and you're at 12 and if you are one less, you'd be like, so is there really this binary in the sand? Do I think you really have to run back out?

No. It's going to be the slightly lower level. Is it going to last this season? Yes. It's not going to affect how long it lasts. It's just going to affect the level of the monoclonal antibody passive

protection that you get. American Academy of Pediatrics wants you to run back out as soon as possible. I'm not sure it's compelling because you're really, as you mentioned, you're just right there on the edge.

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

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

[01:11:42] [END OF AUDIO]