This Week in Virology

TWiV 986 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 25 February 2023

pdf of this transcript available (link)

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 986, recorded on February 23, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today about 50 miles north of Venezuela, Daniel Griffin.

Daniel Griffin: [chuckles] Hello everyone.

VR: What does it mean? It's not in Venezuela, it's in another country?

DG: It is another country. I'm on an island about 50 miles north. It's a Dutch, the Dutch Antilles, so yes. Beautiful spot.

VR: All right, let's get going before the internet dies.

DG: We got a lot to do so let me start off with my quotation. This is from John Steinbeck from *East of Eden*, "An unbelieved truth can hurt a man much more than a lie. It takes great courage to back truth unacceptable to our times." Maybe people will realize later on why I picked that quotation, but we'll talk a little bit about RSV first off, a couple exciting articles this week.

The first one was, "Respiratory Syncytial Virus Perfusion F Protein Vaccine In Older Adults," published in *The New England Journal of Medicine*. I hope everyone's excited already just hearing that title. These are the results of an ongoing international placebo-controlled phase 3 trial with a randomly assigned, in a one-to-one ratio, adults 60 years of age or older to receive a single dose of an adjuvanted RSV prefusion F protein-based candidate vaccine or placebo before the RSV season.

I want you to be thinking about a timing issue here and how that might be translated into the future. The primary objective was to show vaccine efficacy of one dose of this vaccine against what RSV-related lower respiratory tract disease; not infection, not PCR positivity, but RSV-related lower respiratory tract disease. This had to be confirmed by RT-PCR.

Here we have vaccine efficacy for PCR-confirmed lower respiratory tract disease. Efficacy against severe RSV-related lower respiratory tract disease, and RSV-related acute respiratory infection also assessed, and they also did some other analysis, including looking at safety.

They had almost 25,000. 24,966 participants received one dose of the vaccine or placebo, so 12,467 participants got vaccine 12,499 got placebo. They followed them, median follow-up for about 6.7 months and the vaccine efficacy against the RT-PCR confirmed RSV-related lower resp tract infection was 82.6%.

The vaccine efficacy was 94.1% against severe RSV-related lower respiratory tract disease. This was assessed on the basis of clinical signs or by the investigator. Interesting, I will include this, 71.7% against RSV-related acute respiratory infection. They did report that the vaccine was more reactogenic than placebo. People know what reactogenicity is at this point, but most adverse events for which reports were solicited were transient, were mild to moderate in severity.

The incidence of any serious adverse events and potential immune-mediated disease similar in the two groups, weren't seeing any a safety signal there. It's robust, talking about over 12,000 participants getting the vaccine. Just a little background here. This vaccine is an adjuvanted protein-based vaccine that creates an immune response against the RSVF glycoprotein, which mediates viral fusion and host cell entry. The protein is, they say, highly conserved across the two RSV subtypes A and B and the X the vaccine contains an F protein stabilized.

It's pre-fusion confirmation, which exposes epitopes targeted by neutralizing antibodies. Then just little bit more the AS01 is a liposome-based vaccine adjuvant system containing two immunostimulants, MPL and saponin QS-21. They've got a nice Kaplan Mei

er curve showing the cumulative incidents over time. They talk about following them out for a certain period of time, but the RSV season ends so then you just have nothing new in either group, so I don't know. Any comments there Vincent?

VR: In Idaho they're getting ready to pass the bill, making it illegal to use this.

DG: No, this is protein-based. This'll be OK. (laughter)

VR: Oh, OK. I see.

DG: This'll be OK. We'll probably circle back to that but there's a bill in Idaho and I had a couple comments about it. It's a really broad-based bill where they want to take away people's access to anything that's mRNA based. Legislators jumping in and taking away the freedom for individuals to make a decision about the health for themselves, the health of their children, not so ideal, but this is protein-based, so it'll be OK.

We also have the article, “Efficacy and Safety of an Ad26.RSV.preF-RSV pre F Protein Vaccine in Older Adults,” so this is a little bit more complicated, so we'll try to sort this out. These are the results of CYPRESS, which is a randomized double-blind placebo-controlled phase 2b, proof of concept trial to evaluate the efficacy, immunogenicity and safety of an adenovirus serotype, RS serotype 26 RSV vector encoding of perfusion protein perfusion, F protein in combination with an RSV pre fusion F protein.

A little more complicated here, and I'm wondering, why did that other one get the spotlight in the *New England Journal*? This one was off to the side, but this is phase 2b. We only have

5,782 participants enrolled and receiving an injection, vaccine or placebo. Here again, they're looking at vaccine efficacy for RSV-mediated, lower respiratory tract disease. Here they reported vaccine efficacy of 69.8, 80% for different case definitions. Again, seeing no concerning safety signals here.

VR: Daniel, these are for adults. What about the babies?

DG: Interesting. We're not covering it today but there's a lot in the works for potentially vaccine for women who are pregnant, individuals who are pregnant, and then potentially having that protection. Also, there is some ongoing work for pediatric vaccines, so exciting stuff. As we've talked repeatedly, RSV is a problem for the extremes of age. The first few years of life in particular, and then the last several decades of life.

All right, Marburg, so not a lot. As of the morning of February 17, and that's like a week ago now, getting this data from the U.S. Embassy, there have been no new confirmed cases of Marburg virus disease in Equatorial Guinea or the surrounding countries, waiting for any more recent update.

As I mentioned last time, those two suspected cases that cross the border into Cameroon, suspected tested negative for Marburg as well as Ebola so more to come or not. Norovirus, still on the rise. I talked last week when we were in the, 12%, 13%, 14%. We're now up at about 16 or more percent, so norovirus is still rising. Wash those hands.

All right, COVID, so let me start with the issue of COVID vaccine mandates and healthcare settings. This is a nice article by David A. Lieb, and Kavish Harjai, "Healthcare Vaccine Mandate Remains as Some Push for an End," published in the AP, the Associated Press. Now it's interesting, and people should read this article. There were several facilities they talk about where these factors showed up and they said, "We know half your people working here are not vaccinated. What's going on? We'll be back in 15 days to check in and make sure they've all complied with our mandates."

What did the employers do? They just wrote them all exemption letters. Now some employers are suggesting it's hard to staff their facilities unless they are allowed to hire anti-vaxxers. There's a side to this, which is difficult. I'm going to tell a little bit of a story here. It's in the pandemic and as I related, I would do these educational sessions each day. At one o'clock I would appear on One East, in all different providers, nurses et cetera would gather and I would go through the latest updates and also any challenging cases, "Hey, let's discuss them.:"

I would do a similar thing in the ICU. First thing in the morning I'd come in and we'd run through the 20 or more patients that were in the ICU, discussing their care as well, what were some of the latest updates? Periodically, there would be advances in the vaccines. There would be results from trials. I would discuss them. One of the nurses was clearly anti-vax, complained to the medical director in so many words, "Do I have to listen to all this stuff about vaccines when I'm just here to do my job in the ICU as a nurse?" Really challenging.

When people come to the hospital, there's an expectation that they're going to get evidence-based, science-based care, that we're not just going to be waving hands and

dictating care on the basis of anecdotes. It is a challenge when suddenly this influx of anti-vaxxers who feel validated are brought back in. Just trying to add another dimension to all this. OK, [crosstalk]

VR: Why do they feel validated, Daniel?

DG: It's an interesting dialogue. A lot of people have held out, have left the workforce, and have not worked because they were against vaccine. Now if they're hired back without having to be vaccinated, there's a validation. There's, "Oh, OK. Now it's OK." All right. The article, "Past SARS-CoV-2, Infection Protection Against Reinfection: A Systematic Review and Meta-analysis," published in *The Lancet*. This got lots of strong reactions on Twitter. Many are reacting to the media headlines, and I just don't know how many people have read the article. Particularly those that are using it as confirmation bias of their position. Let me go through this article and share what it does say as well as the implications.

This is a systematic review and meta-analysis. This isn't an actual study. This is taking a whole bunch of studies and putting them together. Here they identified, reviewed, and extracted from the scientific literature, retrospective and prospective cohort studies, and test-negative case-control studies published up to September 31, 2022. That estimated the reduction in risk of COVID-19 among individuals with a past SARS-CoV-2 infection who survived, right? You got to do that. You got to survive to be in this study, in comparison to those without a previous infection, symptomatic disease and severe disease.

They included 65 studies from 19 different countries. Their meta-analysis suggested that protection from past infection for symptomatic disease was high for ancestral alpha, beta, and delta variants, but was substantially lower for BA.1. Now, this is the number to look at it and ask, "What judgment would you put on this?" The estimated effectiveness was 44% against Omicron BA.1 symptomatic disease.

Now, protection against severe disease remained high for all variants with 90% for ancestral alpha and delta variants, 88.9% for Omicron BA.1 at 40 weeks. What do I have to say? The data is not surprising. The conclusions and interpretations here seem odd. There's a physician out west who either has issues communicating science or is not getting the big picture here, let me suggest. Let me quote, "I've been considering a COVID infection to the equivalent of a booster in terms of protection against reinfection and severe disease hospitalization/death. These study results indicate that is at least that good, maybe even a bit better."

Are we going ignore the hospitalizations, the missed work, the deaths, the suffering, and Long COVID? Did this person mean to endorse getting COVID as the safe option to prevent you from getting COVID? [laughs] Vincent, I thought you might have run across these conversations.

VR: Yes, this has been discussed as a validation for getting infected, which is crazy. As you say, [laughs], you could die, [laughs] more likely to die than if you're vaccinated. It makes zero sense. If this person is a physician, they need to go back to school.

DG: [laughs] They might be a little too old for that at this point, but yes, it's tough. The interpretation here, it has to be careful. If you look at this and you don't communicate

properly, you're encouraging, “Oh, just go ahead and get infected and then that'll protect you against getting infected.” Wait, why do you not want to get infected? “It's because you could die. You could end up with Long COVID, you could end up in the hospital, you could miss work, you could have ongoing problems.” Yes, so getting COVID is not the safe option, vaccine is.

VR: Let's put it another way, Daniel. Look at it this way. You get a vaccine and then you're ready to go with immunity. If you get infected, you have a memory response that kicks in a few days. If you're not vaccinated, you get infected, it's a crapshoot whether you're going to get sick before your immune response can control the infection. That's a very clear scientific justification for vaccination. I don't know why they would even do this study unless they're just interested in the scientific basis for the comparison. It gives people fuel for saying, "Yes, I'm going to get infected as a way of being protected."

DG: Yes, it's important probably to focus on the numbers, too, as we've been saying. If you get your three shots, you have this 90% durable protection against severe disease, and you get it without risking getting severe disease in the process. If you're going to say, "Oh, those vaccines, I hear they don't work.” Well, then what you're talking about is protection against infection and yes, 44% for a number of months against BA.1, which isn't even here. We have more immune invasive. Yes, if you compare your apples and oranges, yes, you can get better apples and oranges more safely so, all right, I was going to do some tree climbing analogy there. Anyway, all right, [laughs].

Pre-exposure period transmission and testing. The big thing here is have a plan. As I say about those masks, you know what? If you don't wear them, they don't work and I'm not sure we need to do a study to prove that. Just tell them people to wear a mask. If they don't wear it, it ain't doing anything helpful. All right, COVID active vaccination. There's going to be some mRNA technology in here. Those of you in Idaho, if you want to continue to have choices with regard to your healthcare, if you are maybe opposed to having politicians take away some of those, just pay attention.

Another preprint, “A Third Vaccine Dose Equalizes the Levels of Effectiveness and Immunogenicity of Heterologous or Homologous COVID-19 Vaccine Regimens.” This is posted and it's important to make sure you think about this. These are the results of an observational study of SARS-CoV-2 infections among vaccinated healthcare workers at the University Hospital of Lyon, France, with an analysis of immunological parameters before and after the third mRNA vaccine dose.

They reported that following the second vaccine dose, heterologous vaccine regimens were more protective against infection than homologous. Let's just lay out what they're doing here. They're looking at individuals that like stuck with team Moderna or stuck with team Pfizer. They got their two shots, and they compare to people that mixed and matched. If you follow out the cumulative COVID-19 incident, you see a separation. Then when you get to the third dose, no longer the case. Whether you got that, and we've been saying for a while, it's a three-dose vaccine now with the newest variants. When you get to three doses, it really doesn't matter. You can see in a nice curve here, cumulative COVID-19 incidents that heterologous, homologous really very similar.

OK, moving on to COVID, early viral upper respiratory phase. Remember, and it's important, there are multiple phases to COVID. We've labeled these, we've described these for, well about three years now. There is the early viral upper respiratory phase. This is when there's high RNA copy number, low CT values. This is where you have the window of greatest opportunity to jump in with your antivirals. Number one, Paxlovid, number two, remdesivir, number three, monoclonal antibodies. Now with the variants, we have quite a bit of challenge.

This I thought was interesting. This study I'm about to discuss, this preprint where we've always looked at the neutralization and said, "Oh, well, if they can't neutralize, well then that's the only measure of antibodies efficacy." In this preprint, "Sotrovimab Retains Activity Against SARS-CoV-2 Omicron, Variant BQ.1.1 in a Non-human Primate Model," posted on *bioRxiv*. That's all in the title there. These investigators report efficacy of Sotrovimab against this BQ.1.1 viral replication as measured by RT-qPCR in a non-human primate challenge model.

They have some nice graphs, so we can see the decay of the Sotrovimab concentration over the first few days, when it's administered. Then they have a challenge where they're looking at the viral RNA in the trachea, they're looking at viral RNA in the broncho alveoli lavage and maybe people take a look at this but it's nicely color coded. Those that got Sotrovimab are in blue and you see no viral RNA in trachea or BAL. The controls, you see high viral RNA copy numbers in the trachea and the BAL, so interesting.

It's been that warning for us. It's tough. We think things don't work when we lose that neutralization, but we've talked a lot about Fc-mediated activity. I'm not sure how you use this operationally to decide whether or not you can continue using these antibodies unless you're going to go ahead and start sacrificing or using these primate models.

VR: You have to do it in people. If you have a variant that you think is going to be around for a while, you do a small trial and see if it helps, right?

DG: Yes. It's a challenge because you'd probably have those people on Paxlovid or remdesivir.

VR: Sure.

DG: There are people that can't get those, so those people could be at a trial like this.

VR: It would be great if we had some correlates for non-neutralization, Fc and so forth, but they're hard to do. It's a challenge, as you said, yes.

DG: It's a call for setting up those assays. Some Fc-mediated - All right, molnupiravir, we say last and least, at some point we're going to hear an update on the limited role of convalescent plasma. A little bit of time today on avoiding those harmful and useless things. This is where we generate our hate mail today, Vincent, I just wanted to warn you ahead of time. It's one of those things and I like to think of it as common sense.

There aren't things that you just know are true. You have to take a look. Before I came to this island where I am right now, I look at some pictures, I can read about it but it's actually,

take a look, you're not sure. Is the water going to be clear and nice? What are the people like, et cetera. That's all science is. It's just, “let's take a look and let's see what's true.” Early on, as we know, a lot of people were very excited, shall we say, bullish about ivermectin. We honestly did not know and so we went ahead and we did a number of trials, and one of those was this repurposed drug, the ACTIV-6 really asking the question and here we have the article, “Effect of Higher Dose Ivermectin for Six Days versus Placebo on Time to Sustained Recovery in Outpatients with COVID-19: A Randomized Clinical Trial. This was published in *JAMA*.

These are the results from the accelerating COVID-19 therapeutic interventions in vaccines, the ACTIV-6 study group, and investigators. I know if you're following the science, you're perhaps saying, “Enough already,” asking how much the study costs the U.S. taxpayers. If you are pro-ivermectin of the school, that some things you just know are true, then much like that father in Mary Poppins, “I hate to confuse the situation with facts,” but here we go again.

Unlike a Cochrane meta-analysis that is far from a gold standard, this is a double-blind, randomized placebo platform trial, looking at whether ivermectin with a maximum targeted dose of 600 micrograms per kilogram daily for six days, compared with placebo, would shortened symptom duration among adults equal to 30 years of age or older, outpatients with symptomatic mild to moderate COVID-19. They're getting in this early, during that viral replication period, they included 1,206 U.S. adults with COVID-19 during February 2022 to July 2022.

The median time to sustained recovery was, drum roll, 11 days in the ivermectin and 11 days in the placebo group. Those seem exactly the same. In the ivermectin group, one participant died and four were hospitalized. In the placebo group, two participants were hospitalized, no deaths. Adverse events were uncommon in both groups and the statisticians tell us that in this largely vaccinated 84% population, the posterior probability that Ivermectin reduced symptom duration by more than one day was less than 0.1%, so there's still some hope, Vincent. There is a 0.1% chance that ivermectin is helpful.

VR: It's not worth it, Daniel.

DG: We have millions of dollars. Now, we could move more from the budget for education and other things and continue to study ivermectin, this antiparasitic. All right, COVID, early inflammatory, lower respiratory hypoxic phase. Now I'm going to soapbox here for a second. Maybe it's because I've gotten a little downtime but let us return to the original terminology and stop calling this the rebound stage. No rebound here. As Vincent and I have discussed repeatedly, the viral RNA is dropping from the original high.

People do start testing - they have a period of negative positive test results because they're right at the edge of detection. They're not shooting up to these like tens, hundreds of millions of RNA copy numbers. They're fluctuating in the 30s. That's not a rebound. After the improvement in the viral symptoms, a chunk of people start to feel worse with the onset of the cytokine rise and the ramping up of the immune response. If one got treatment in that first week and were vaccinated, there's really nothing foreboding here.

Watch those oxygen levels. There is no evidence that more antiviral medication will be helpful. Remember, this is the early inflammatory. This is not a second viral replication phase. There is no rebound here. All right, what do we do if we miss the ball in that first week? One, steroids at the right time in the right patient. Two, anticoagulation pulmonary support, remdesivir, maybe if we're still in the first 10 days, immunomodulation, consider tocilizumab, avoid those unnecessary antibiotics and unproven therapies.

All right. We actually have quite a bit today on the late phase, the Long COVID, the PASC section. I know they've supposedly debunked Long COVID up at the MGH and even when it happens, it is supposedly one's own fault for being overweight and out of shape, but humor me if I continue to believe my patients that are continuing to suffer. I will remind our listeners that when they first proposed written examinations for the Harvard Medical School, the head of surgery protested, letting dean know that he only estimated 15% of the current class, at that time, was able to read and write.

They have come along way up in Boston from the days when no academic preparations were required. No written exams were mandatory, students not paid tuition. Instead, they bought tickets to each lecture. I'll leave in a link, but let me get to the article, "Serological Response to Vaccination in Post-acute Sequelae of COVID," recently published in *BMC Infectious Diseases*. Here the investigators performed a prospective study where 245 adults clinically diagnosed with PASC and 86 adults successfully recovered from prior COVID were vaccinated and had serology testing performed.

Individuals with PASC mounted consistently higher post-vaccination, IgG Spike antibody levels when compared to the COVID-recovered, with similar results seen for ACE2 binding levels. The post-vaccination IgM response in PASC was attenuated, but persistently unchanged over time compared to the COVID recovery folks. Wherein the IgM Spike response expectedly decreased over time. I thought this IgM drop was rather interesting, it's pasted in the figure here, so curious, Vincent, maybe our immune [crosstalk].

VR: IgM drops anyway, at some point replaced by IgG. I don't know what that means here.

DG: I'm not sure what the mechanism is here. It's interesting that there's - these people, the who are malingering as we now know can somehow have an immunological distinction here. The article, "Sex Differences in Cardiovascular Complications and Mortality in Hospital Patients with COVID-19: Registry-based Observational Study," was published *in BMJ Medicine*. These are results of a registry-based observational study, 74 hospitals across 13 countries participating in this CAPACITY-COVID trial, (Cardiac complicAtions in Patients with SARS Coronavirus 2 regisTrY), so pull some letters out of there. It's interesting from March 20 to May, 2021 of the 11,167 adults reported cardiovascular complications.

We were seeing supraventricular tachycardias, pulmonary embolism, heart failure, so just more evidence that getting COVID is not such a safe way to get that immunity against reinfection.

And the article, "Association 0f COVID-19 Vaccination with Risk for Incident Diabetes after COVID-19 Infection," was published in *JAMA Network Open*. This seemed to get a lot of attention. People do not want to get diabetes. These are results of a large cohort study of

adult patients with one or more COVID-19 infections treated within the Cedars-Sinai Health System in Los Angeles, California, from March 2020 to June 2022. Rates of nuance of diabetes, hypertension, hyperlipidemia, and benchmark diagnosis occurred in the 90 days after COVID-19 infections were higher than those before infections with odds post-infection for diabetes 2.35, hypertension, 1.54, benchmark diagnoses 1.42, hyperlipidemia at 1.2. Also, the diabetes risk after infection was higher among the unvaccinated odds ratio, 1.78. While with vaccinated it was just barely 1.07. Just barely elevated. Another reason why it's a good idea to get vaccinated before you get that infection.

VR: Daniel, have you seen this? Is it treatable with insulin?

DG: It tends to be Type 2. Usually, you're starting with metformin, some of the oral agents. Yes, we're certainly seeing new-onset diabetes after. Here, as you can see, we see diabetes but now we're seeing an odds ratio that there's an association here.

VR: Does it persist? This is a Long COVID symptom, basically, right?

DG: It's interesting. This would fall under- why they call it post-acute sequelae of COVID. This doesn't fall into that classic Long COVID fatigue, brain fog. This is, "I'm doing better but by the way, my glucose is now in the 190s, and I'm having to start medicine for that."

All right. The article, "Postacute Sequelae Of Sars Covid 2 In University Setting," was recently published in *Emerging Infectious Diseases*. I have to say this is usually one of my favorite journals out there, but I am going to be a little critical here. Maybe this prompted that Steinbeck quotation upfront.

In this study, the George Washington University COVID-19 surveillance and testing program identified 4,800 COVID-19 cases during August 2020 through February 2022. COVID-19 positivity at George Washington University was determined on the basis of PCR tests network performed in the George Washington University Clinical Laboratory Improvement Amendments, or Clinical Laboratory Improvement Amendment-certified Public Health Laboratory.

Other cases were identified through results uploaded to the person's medical portal for external positive tests, either PCRs from an external Clinical Laboratory Improvement Amendment-certified laboratory, or self-administered antigen tests. That was about 1,572. Only antigen tests approved for emergency use under the FDA EUA were accepted. So far so good. During July 2021 through March 2022, all 4,800 positive COVID-19 test results reported during this period were followed up with confidential electronic survey sent to each patient at least 28 days after their initial positive result. That included questions about Long COVID.

They defined Long COVID as experiencing greater than one of the following symptoms lasting for greater than 28 days after a respondent's 10-day isolation period ended: Difficulty driving, difficulty having conversations, difficulty making decisions, difficulty thinking, fatigue, feeling anxious, feeling depressed or sad, loss of smell, loss of taste, memory loss, muscle pain, muscle weakness, shortness of breath or difficulty sleeping, trouble sleeping, worsening of symptoms after physical activity, worsening of symptoms after mental activity or other symptoms just in case we missed something.

In addition, [chuckles] respondents were considered to have Long COVID if they reported still experiencing COVID-19-related symptoms at the time of Long COVID survey. Here we are already getting in lots of trouble. They also included anyone who wears shoes just to make sure they had a - now they report only getting a response rate of 31.8%, so about 70% just didn't even respond. Then report that using this very vague inclusive definition of Long COVID, that the prevalence of Long COVID here is here in defined is 36%. What do you think, Vincent? I'm shaking my head just like you are.

VR: First of all, is it useful to use a different definition of Long COVID from say what WHO has established and is much longer? It's not. You have all these things that are lumped in there that many people feel that I don't think are specific because they're probably mostly going to go away. As you say, the response rate is low. This is just a bad study, Daniel.

DG: It's troubling. This is why I started with my Steinbeck quote, is that this is being promoted as, see Long COVID can even be a significant problem. Young healthy college students, and I'm looking at this and saying this is unbelievable. You're going to try to tell people that 36% of young healthy college students that got COVID now have Long COVID. People are going to say, "You know what? That's just not true. Lie to me once I'm the fool, lie to me twice," et cetera. You can't promote something like this. This is a study which undermines confidence and faith. Yes, this is just - yes, sorry to say, this is a terrible study.

There actually is an article in the *Wall Street Journal*, "The CDCs Long-COVID Deception," by Alicia Finley, is properly critical in this article. Physicians and scientists should have the proper training to read this article for themselves. I suggest they do that before pontificating about the results. For the broader audience, Alicia Finley does a great job. She points out that this long - the study suffers from methodological problems, no control group. She also picks up on the poor definition of Long COVID, making it so expansive that I'm surprised so many people did not get labeled as Long COVID sufferers.

Vincent, I go through this list and I'm finding, I'm feeling a little anxious. I [laughs] anyway I won't list all the problems I'm seeing in that list that I could check off. Let me quote the last bit of the article. "By exaggerating the incidents of Long COVID among young healthy adults, the CDC deflects attenuation attention from the mental health problems caused by misconceived pandemic policies. It also fuels public distrust in the scientific enterprise which may prove to be the pandemic's most destructive long-term effect."

VR: That last part is the most important because then you have all this garbage science coming out and people say, "How can we trust any science if so much of it is garbage like this one?" I don't blame them.

DG: Yes, all right. As I like to close, looking out in the entire world not just being so U.S.-centric, no one is safe until everyone is safe. As we've seen access to vaccines, access to therapeutics is still limited throughout the world. Let me close with *The New York Times* article, "Podcast Companies, Once Walking on Air, Feel the Strain of Gravity," is an interesting article. What I took away was that podcasting is still in a growing phase with increasing demand and another 20% increase in downloads from last year. Vincent, should we worry?

VR: I always worry Daniel, but most podcasts are probably not worth continuing and that's why the strain of gravity is affecting them. Now ours on the other hand are important. We're reporting science to you which you can't get anywhere else. I would say that we have a good future.

DG: All right, our future is of course dependent on our listeners. I do want everyone to pause the recording right here. Go to parasiteswithoutborders.com and click "Donate." Even a small amount helps us continue to do our work. We are now in the middle of our American Society of Tropical Medicine and Hygiene fundraiser. During the months of February, March, and April, donations made to Parasites Without Borders will be matched and doubled up to a potential maximum donation of $30,000 from Parasites Without Borders to American Society of Tropical Medicine and Hygiene.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Steven writes: "A friend of about 70 lives with lupus was hospitalized with anaphylactic shock after receiving her first Moderna vaccine dose. She's not received any other COVID vaccine and though she has been sick and a cancer patient, she's not had COVID as far as she aware. What do you recommend? I don't think she's inclined to pursue COVID vaccination in light of her first experience. I wonder were she to consider, say, Novavax, is there a test, an allergist or immunologist could do to know whether she's likely to have an allergic reaction? Would you recommend she have serology done? Too bad Evusheld is no longer effective.

DG: These are some great questions and first, my heart goes out because there's a lot of people in a situation like this. The first is this is great that we have a different platform, as far as an opportunity for vaccinations. This is a great time to be looking at Novavax. It would make sense for her to work with an allergist. They can do PEG testing and confirm that that was the trigger that was the issues. That'd be number one. Get involved with an allergy immunology specialist who has knowledge and expertise in this area. We have some great ones that I've worked with here in the New York area. We've done such testing and then allow people to safely go on and get a Novavax vaccine.

The next is, as we always talk about, have a plan. I'm not a big fan of checking those serology tests. If this person does end up with a positive test, you want to know ahead of time, what are their medications, what is their renal issues, can they end up on Paxlovid? Do we need to be having a plan where they get remdesivir? That's a big thing for this person. Look at potential vaccination, but also have a plan.

VR: Kevin writes: "Does severity of the early viral upper respiratory non-hypoxic phase predict the early inflammatory lower respiratory hypoxic phase? I was seeing a patient with a history of heart failure on amiodarone and ELIQUIS. Got primary vax series plus booster. His family member was COVID positive, so he took a COVID test. It was positive. He has no symptoms other than increased sneezing, no fever, sore throat, et cetera. Vitals normal. Previously got antibodies with his last COVID infection but can't get them now. Ended up with molnupiravir as outpatient. Remdesivir isn't a thing where I am. Got me thinking, though, what's his real chance of him ending up admitted on oxygen a week later?"

"It seems that lack of symptoms in the URI phase would make it unlikely that he progresses to a hypoxic phase, but I'm not sure. Would Paxlovid prevent progression in someone like

him if he didn't have med contraindications? The EUA for Paxlovid is for treatment of mild to moderate disease, but how about asymptomatic disease that is less than mild?”

DG: This is that interesting. It's really two questions here. One is, these different medications, therapeutics are authorized for treatment of COVID-19. Now, not just treatment of a positive PCR, positive antigen test. That's important. The other, and this is a challenge. I worry about this because what a lot of people do is they just see how you do during the first few days. For some reason, they're hesitant to jump in and treat this.

We know the earlier you treat it, the better. There really shouldn't be much of a scenario where you're waiting to see how those symptoms are during the first few days. There might be the rare exception where you're like, "Boy, there's going to be a significant risk benefit here." There's a challenge. I don't think we have great data where we can say, “Oh, just because your symptoms were mild during that first week, that's going to mean you're not going to have that significant early inflammatory surge, that cytokine storm.” Unfortunately, you can't go back.

VR: James writes: “I've been listening to your podcast for a couple of years now. Every week you reiterate that young people are also at risk from COVID. I live in Australia. I have two children, ages 2 and 5. As of right now, my five-year-old is only legally allowed to have two doses of mRNA vaccine, and my 5-year-old is still not legally allowed to be vaccinated at all. The governing body in Australia has deemed that vaccines in the under 5-year-old population is only available for extremely immunocompromised kids,” and he provides a link for the guidance.

“It’s been about six months since this guidance was originally given, which was also months after approval was granted in the U.S. A lack of safety data seems to be the continued line that the committee has taken on not allowing these vaccinations. As a parent of a 2-year-old and an under-vaccinated 5-year-old with no booster yet available, my family has been desperate for any protection that we can get for our child. Would you also agree that giving parents the choice to vaccinate their under 5-year-olds at this stage to be the safest and smartest option for the powers that be in Australia, taking into account, the possibility of severe disease, hospitalization, Long COVID, long-term effects on a child's immune system?”

“I would be more than happy if this question was to make it on the air to raise the profile of this issue within the medical establishment in Australia."

DG: We've covered this countless times, and I do appreciate you raising this. Pediatric deaths are rare, but we have seen here in the U.S., over a thousand pediatric deaths. That is shocking because kids usually don't die once they make it through the first few days of life. I have to say here in the U.S., they really did not to die very much.

The other thing is tens of thousands of hospitalizations. This is a high risk. Your kid ends up in the hospital, that's traumatic for them and the parents, it’s not great. That's a severe outcome. It is so much safer to go forward with vaccination than it is to go forward with getting infected. That's really the choice at this point. Here in the U.S., we see 97% of our children, probably more at this point, have been infected.

The question was, “Do you get a vaccine series in before that happens?” Yes, the three shots make sense. This is tough. What do you want, people traveling from Australia to the U.S. just so they can have access to evidence-based measures?

VR: Come on, Australia. Get with the program. Do the right thing for your kids. That's *TWiV* weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

DG: Thank you. Everyone, be safe.

[music]

[00:45:19] [END OF AUDIO]