This Week in Virology

TWiV 1048 Clinical Update

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Aired 30 September 2023

pdf of this transcript available (link)

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

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VR: From MicrobeTV, this is *TWiV*, *This Week in Virology,* Episode 1048, recorded on September 28, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Daniel, we're moving into October, what's the COVID situation now? Is it still percolating, is it moving up?

DG: I'm going to be discussing a little bit about wastewater and hospital admissions, and giving people an update on where we are. Stay tuned, but let me start with my quotation. This one's from Abraham Lincoln. My son Barnaby is writing his college essay, and so he was recounting a time we visited Abraham Lincoln's cottage on a rainy day. It got me thinking about Lincoln, who has some great words of wisdom, and here we go. “Give me six hours to chop down a tree, and I will spend the first four sharpening the axe.”

VR: Now, what does that mean, Daniel, you should have your tools ready?

DG: I think it's, “be prepared,” and where I'm going to put it is, when you're going to do research, when you're going to try to look into everything, don't just hit the road running, prepare yourself, make sure you're going to do the research properly.

VR: Daniel, that means that if you want to look at infectious virus shedding, you shouldn't just do PCR?

DG: If you're going to do the science, do it right. Take the time, get everything ready, make sure you're asking the question properly, and then ask the question properly. All right. Let's start off with RSV, and for the last email that we read last week, this came in just under the wire. I was actually watching because we record Thursday night and this meeting was Friday, and so I'm hoping it goes otherwise I'm going to quick call to Vincent. Vincent, we've got to change that response, but on September 22, hours before our last *TWiV* dropped, the vaccine

advisory group to the CDC approved a recommendation for pregnant women to receive Pfizer's RSV vaccine as a way to protect newborns, a group at high risk for serious complications.

The ACIP, the Advisory Committee on Immunization Practices, recommended that pregnant women between 32 and 36 weeks gestation receive the vaccine as a single intramuscular dose seasonally to prevent infections in infants. This vote passed by an 11 to 1 margin, and I'll just read what they had to say. “On September 22, 2023, members of the Advisory Committee on Immunization Practices voted 11 to 1 to recommend maternal RSV vaccine for pregnant people during 32 through 36 weeks gestation, using seasonal administration to prevent RSV, lower respiratory tract infection in infants.”

They also voted to approve Pfizer's bivalent RSVpreF vaccine for the Vaccines For Children program, applying to pregnant people under 19 years of age. Just for context here, each year here in the U.S., the U.S. alone, RSV causes 1.5 million outpatient visits, 500,000 ER, emergency department visits, 80,000 hospitalizations, and 100 to 300 deaths in young infants. This is just looking at children there, those deaths, because we know RSV is causing 10,000 to 20,000 deaths in adults.

Let's move into that question, what is going on with COVID? I'll put on my glasses to read the small print here. It looks like we are sitting here about a weekly COVID-19 new hospital admissions about 20,000. I'm seeing we might be getting a plateau, and what gives me a little bit of encouragement is the national wastewater SARS-CoV-2 virus concentration information. I'll leave a link into where we get this data, but you can actually see here in the northeast, we're the highest, but we're starting to go down, and you can actually see it's starting to go down. This has actually been reasonably predictive. We're predicting things will plateau, things will go down a little bit in preparation for our winter.

VR: It's going to go up again, Daniel, I'm quite sure, right?

DG: When do you think it's going to go up? I think the wastewater will start to go up in probably early December, I guess.

VR: I think December, January, into the new year. This was the end of summer surge when people were traveling and people were going back to school and that sort of thing, but we're not yet in the winter part.

DG: Yes. Unfortunately, that's what we are expecting. All right, a little bit of an update on testing. Beginning, well, September 25, already started, every U.S. household can again place an order to receive four more free COVID-19 rapid tests delivered directly to their homes. We'll leave a link to that, but they go ahead and say, this is worth reading. The COVIDtests.gov program has distributed over 755 million tests directly to more than two thirds of American households, 310 million of which went to households in underserved communities. The U.S. government will continue to make COVID-19 tests available to uninsured individuals and underserved communities through existing outreach programs.

Moving on to - I'm going to just tell people right up front, a lot on Long COVID this week, but let's talk about right up front, you have a high risk person, they test positive, they're at risk of progression to severe disease. We're not waiting and seeing, number one, the

recommendation by the NIH treatment guidelines, Paxlovid, now fully licensed. I'm going to share a couple stories here, but I wanted to start off with we continue to have lots of misinformation out there about Paxlovid and the cytokine storm.

I was surprised and disappointed to read a recent *New York Times* article that was again, perpetuating this misinformation. It starts off OK: Experts stress that Paxlovid is an effective life-saving treatment that helps to keep people out of the hospital. It may even lower the risk of developing Long COVID. Unfortunately, this is followed with the comment, while Paxlovid rebound is well documented, it's also possible to experience a resurge of symptoms even if you don't take the drug. Now, they quote a chief science officer for a telehealth company trying to explain why people get Paxlovid rebound even when they never took Paxlovid. He goes on to say, "But it's not totally clear why symptoms can also reappear after a negative test even without taking Paxlovid."

VR: OK. There's the first mistake. They shouldn't have asked this telehealth guy, they should have asked Daniel Griffin, right?

DG: Yes.

VR: I mean, what does he know about this? It's not totally clear. If you read the science, Bub, you would get totally clear. Oh my gosh. Sorry, Daniel.

DG: The science is totally clear. Unfortunately, when people take this opportunity to get their name in the media, this leads to misinformation, this leads to fears, this leads to missed opportunities. Vincent, you and I were talking earlier today. I had a patient today, just died from COVID. The story was, they were not treated during that first week. They ended up in the hospital. We started to treat them. They then developed bacterial pneumonia. We were treating that, they were getting better. This morning they had an acute cardiac event and passed in the ICU.

We are missing opportunities and part of it is that people are misinformed. I know that I talked about the waivers. I had another story this week. It was disturbing, where a patient of mine, I don't know if people know, but seems to be this connection between New York and Florida. A lot of people go down to Florida this time of year. I don't know why, but they do, and a patient of mine, I was checking in, second week, how are you doing? How are those oxygen saturations?

They were actually doing quite well at this point. They completed their Paxlovid course, but they let me know that they reached out to their primary care doctor to check in, and their primary care doctor said, "I'm so glad that your infectious disease doctor gave you the Paxlovid, because if you wanted to get it here in Florida at" - I think it was AdventHealth – "you would have had to come in, we would have had to confirm the positive test. You would have had to sign our Paxlovid waiver." Another waiver down there in Florida.

VR: You think people should stay out of Florida.

DG: [laughs] Number two, remdesivir, remember, that's that early three day access. What about molnupiravir? An interesting article here, and Vincent, hopefully you can help me a bit

with this. We have the article, “A Molnupiravir-associated Mutational Signature in Global SARS-CoV-2 Genomes,> recently published in *Nature*.

Here the authors report that a specific class of long phylogenetic branches, distinguished by a high proportion of G-to-A and C-to-T mutations, appear almost exclusively in sequences from 2022 after the introduction of molnupiravir treatment, and in countries and age groups with widespread usage of the drug. They identify a mutational spectrum with preferred nucleotide contexts from viruses and patients known to have been treated with molnupiravir and show that its signature matches that seen in these long branches, in some cases, with onwards transmission of molnupiravir derived lineages.

Finally, they analyzed treatment records to confirm a direct association between these high G-to-A branches and the use of molnupiravir. I want people to understand this, not just take this on face value. Molnupiravir appears to be incorporated into RNA primarily by acting as the analog of cytosine, so the C pairing opposite the guanine or the G bases, and they have a nice figure. However, once incorporated, the molnupiravir base can transition into an alternative form which resembles uracil instead. This means that in the next round of strand synthesis, you end up with this resulting G-to-A mutation. Simply, we can look for lots of these G-to-A mutations. What do you think, Vincent?

VR: This is an interesting finding. You treat patients with molnupiravir, you don't completely inhibit every virus. Some of them end up getting out there and circulating perhaps in their sample. We can look in the older sequences of SARS-CoV-2 viruses and find this signature, which says this virus was mutated by molnupiravir, and that's all there is to it. It doesn't mean that these viruses are resistant to molnupiravir. It doesn't mean that they're variants of concern.

Someone said the press is saying that molnupiravir causes variants. Well, so does the RNA polymerase. It makes mistakes. These are not variants of concern. They're just changes induced by molnupiravir, and we're seeing them. That's all there is to it, of little concern. The press is over-interpreting this, and that's because they don't understand it, I think.

DG: Wait, so Vincent, the sky is not falling? Suddenly things are mutating, do viruses do that?

VR: Yes, they do that all the time. Molnupiravir mutates them when you use it, so does the RNA polymerase without any drug, it mutates all the time, and this is just a different kind. There's no indication that is of any concern whatsoever. People are saying, "Oh, I knew I shouldn't have taken that molnupiravir." No, it's fine. This is of no [crosstalk]

DG: I agree, and I think it's good that we get this out here. Hopefully this - well, the actual science, level headed, not just how do you sell newspapers, because if you say, "Nothing to see here," a lot, a lot of people are going to read the article. "By the way, nothing to see here," so they can turn off the podcast now. All right. Moving on.

VR: Daniel, to be clear, it's interesting that this is happening, but it's nothing of concern at all. That's it.

DG: All right. Moving on, OK. We've got Paxlovid, number one. Remdesivir, number two. Thor's hammer, molnupiravir is number three. Convalescent plasma in that select group of

immunocompromised patients. As we've been saying for a while, avoid doing those harmful and useless things. One of the things that have been studied, let's look at the article, “Inhaled Fluticasone Furoate for Outpatient Treatment of Covid-19,” recently published in *The New England Journal of Medicine*. More ACTIV-6 results looking at repurposed drugs. More results from this decentralized, double-blind, randomized, placebo-controlled platform trial in the United States to assess the use of repurposed medications in outpatients with confirmed coronavirus disease 2019.

Non-hospitalized adults, 30 years of age or older who had at least two symptoms of acute infection that have been present for no more than seven days before enrollment, were randomly assigned to receive inhaled fluticasone furoate at a dose of 200 micrograms once daily for 14 days or placebo. The primary outcome was the time to sustained recovery, defined as the third of three consecutive days without symptoms. Key secondary outcomes included hospitalization or death by day 28, and a composite outcome of the need for an urgent care or emergency department visit, or hospitalization, or death through day 28.

What are we going to find out? Well, no evidence that the use of this inhaled steroid resulted in a shorter time to recovery than placebo. Of a total of 24 participants, 3.7% in the fluticasone group had urgent care or emergency department visits, or were hospitalized as compared to 2.5% in the placebo group. Trend in the wrong direction, but not statistically significant. We're not seeing a benefit here, but we're also not seeing statistically significant adverse outcomes.

Moving on to the second week, the cytokine storm week. Remember, steroids at the right time in the right patient, not during the first week, only in the second week in the right patient. Remember, six days based on that meta-analysis. Two anticoagulations, we have guidelines from the American Society of Hematology as well as other groups. Pulmonary support, remdesivir still in the first 10 days, immune modulation, and avoid those unnecessary antibiotics and unproven therapies.

Now we move into the meat of today's show. Lots on Long COVID. Let's start off with the article, “Distinguishing Features of Long COVID Identified Through Immune Profiling,” published in *Nature*. A number of familiar names in the author list. We have seven first authors. Then the last author, some of our longtime listeners may know David Putrino or Akiko Iwasaki up at Yale, so David Putrino is at Mount Sinai. Akiko Iwasaki is up there at Yale. Lots here. I really recommend people spend the time reading this paper, but one of the first comments, I'm a little bothered by this. Vincent, this is behind a paywall.

VR: It's too bad, unfortunate, because a lot of people would like to learn about this, don't you think?

DG: Whatever the fee is, somebody needs to step up and basically make this open access. This is a *Nature* paper that people should have access to. They should read the paper. A lot of people really interested in this stuff. Let's not have a barrier between people and the reading of this article, but let's go into it. In standard *Nature Journal* style, after a couple of sentences of background, they start by pointing out that, "Individuals with Long COVID frequently report unremitting fatigue, post-exertional malaise, and a variety of cognitive and autonomic dysfunctions. However, the biological process associated with the development and persistence of these symptoms are unclear."

Let's go through. Here the authors enroll 273 individuals with or without Long COVID in a cross-sectional study that included multi-dimensional immune phenotyping, and unbiased machine learning methods to identify biological features associated with Long COVID. Let's talk about what is unbiased machine learning methods, and I think this is important. Basically, this is data mining. This is, let's go, let's look, let's look at a whole bunch of things, and see if we find anything. This is a tremendous paper, but I just want to point that out. When you find something here, which we're going to find lots of things, you're going to need to go on and you're going to need to ask that question, hypothesis-based, well-planned study in a new cohort.

What did they find? Because they found a lot here, and I think it's exciting, and I think a lot of people are probably excited about what they found. Let's be honest about how much we can hang our hat on so far, but they find marked differences in circulating myeloid and lymphocyte populations relative to the match controls, as well as evidence of exaggerated humoral responses directed against SARS-CoV-2 among participants with Long COVID.

They also find higher antibody responses directed against non-SARS-CoV-2 viral pathogens, particularly Epstein–Barr virus. We'll get into that a little bit more. Levels of soluble immune mediators and hormones varied among groups with cortisol levels being lower among participants with Long COVID. Integration of immune phenotyping data into this unbiased machine learning models identified key features more strongly associated with the Long COVID status, and I think this is nice. Collectively, these findings may help guide future studies into the pathobiology of Long COVID and aid in developing relevant biomarkers. Before we dive too deeply, let me start by going through this study.

We've got five groups that they create that they're going to look at. Group one, healthcare workers infected with SARS-CoV-2 before vaccination; healthy uninfected vaccinated controls; three, previously infected vaccinated controls without persistent symptoms; four, individuals with persistent symptoms after acute infection. Then a second group of individuals with persistent symptoms following acute infection from an independent study, so an external Long COVID group.

Among the groups, enrolled participants had primarily mild non-hospitalized acute COVID, and I think this is really important, samples for the study were acquired on average more than a year after their acute infection. This is a particular subgroup of Long COVID folks. These are folks a year out after their acute infection. Just a little more on the participation, so the participants, because I think this really matters. These participants are from a cohort called the MY-LC. The MY-LC study enrolled 183 participants at one study site, so Mount Sinai, and 90 participants at another, Yale, for a total of this 275 participants.

A few get excluded after review resulting in a final study size of 268. Among the self-reported symptoms from the Long COVID group, fatigue, 87%, brain fog, 78%, memory difficulty, 62%, confusion, 55%. These are the most common things. POTS, so postural orthostatic tachycardia syndrome, also prevalent. Among the Long COVID participants, they were able to cluster them in three groups based upon severity. The different groups underwent systematic multi-dimensional immunophenotyping and unbiased machine learning, as we mentioned. Basically, they looked at a whole bunch of stuff, and what did they find?

Well, they tell us they looked at a number of the immune cell populations. They looked at circulating granulocytes, populations of neutrophils, eosinophils, conventional and intermediate monocytes, dendritic cells, B-cells, T-cells, et cetera. I'm going to actually go down to a couple of the conclusions that they have. In the discussion section, they report a couple things. Participants with Long COVID from two sites had significantly decreased systemic cortisol levels. This remains significant after accounting for variations in demographics and sample collection times.

A couple things I liked about this. One is we are looking at individuals with samples collected on average more than a year. The other, this is one of the first things I asked about, is what about sample collection times? As some of our listeners may or may not know, your cortisol level will vary during the day. We have an early morning surge and then it basically drops off, next day, early morning surge. Getting a specific time on that cortisol is actually particularly relevant.

Now, they also looked at different antibody responses, and as mentioned, levels of different antibodies were found to be higher. They report higher antibodies to SARS-CoV-2, Epstein–Barr virus, and VZV antigens. They say elevated levels to herpes viruses. I want to point out they're not talking about the type of herpes that lasts forever when love doesn't, they're not talking about genital herpes. They're talking about herpesviridae. That's EBV, BZV, maybe CMV, but they didn't find a lot of difference in autoantibodies. Interesting, because that was a big theory. This was like, "Oh, this is just rheumatological. You've got all these autoantibodies." I'm finding maybe something different going on.

VR: Interesting. Now, Daniel, what do you think about the - is this cortisol association biologically or clinically plausible? Does it make sense?

DG: I have to say, that was actually part of this paper that Akiko herself was the most excited about. Look at this big difference. It is. If you go through the data, almost trying to, can we separate the groups? They do, to some degree, separate out. Actually, people have drawn lines like, "Oh, if you put a line right here, there's this 91% discrimination." People who are low in cortisol, people who are adrenally insufficient, they are tired, they are low energy.

There is some biology to say, "Maybe these people have developed this adrenal insufficiency. Maybe their body is not properly correcting. Maybe if these folks are cortisol-repleted, there might be some benefit. Maybe this is also explaining why some of our patients do well when we do these steroid trials and why they continue to want to be and feel better on a lower dose of steroids. Maybe, but it doesn't really get back to the step before, why. Why is the cortisol low? What's going on? Why would this axis have been perturbed?

VR: It is plausible.

DG: It is plausible. Yes.

VR: Very good.

DG: I will just finish off with, I'm going to say, read the paper, and somebody has got to do something about getting people better access. Akiko has a whole tweet series. Are they still called tweet series?

VR: Yes. Why not?

DG: [laughs] She's got her seven key findings. What are these seven key findings? One, patient-reported outcomes alone are sufficient to identify Long COVID patients with 94% accuracy.

VR: Daniel, what do you think about that as a clinician? You want your patients to tell you, and that's all you need to know what they have? [chuckles]

DG: We always say this interesting thing. We say the history is the most important and the least reliable. I would like to be able to recognize something based on a person's history, but then I, like, well, say, every good clinician, I want some way, some verification. I think patients really want that too. I want to say, "This sounds great, this sounds like Long COVID, this smells like Long COVID, you're telling me everything, but did you just read the textbook or do you really have Long COVID? Let's order the Long COVID test." That's what the next things are.

I'm going to jump right down to her number seven: low cortisol levels with the strongest predictor for both defining Long COVID status and predicting disease severity. Makes me want to say, let's look at this in a new cohort. Let's do a prospective. Let's ask this, is this really true? A lot of people are concerned that they're going to be ruled out because their cortisol is fine. Maybe the low cortisol level is something unique to the people who do not get better after one year, so important there.

The immunophenotyping reveals increases in exhausted T cells, IL-4, IL-6, double-positive T cells, activated B cells, double-negative B cells, and non-classical monocytes. We need a nice prospective immunophenotyping study. SARS-CoV-2 specific antibody responses are elevated and evidence of, they say herpes virus reactivation in Long COVID patients. That's based upon these high serology tests for EBV and VZV. That's tough, and they do reference an earlier study where what you would actually, in my mind, want to do is, during that first week or two, measure for EBV DNA. Really confirm that it's reactivation. That it isn't just an artifact of something that's going on with deactivated B cells.

VR: This reminds me of the early days of AIDS, Daniel, where they found a lot of these patients had PCP and candida. That was the case definition and they went back out and looked for validation in additional cohorts like you just said. That's going to be important to do here.

DG: Now, the interesting is her number five. No increases in autoantibodies.

VR: I think there were some people initially saying that autoantibodies were involved as well as others, right?

DG: Yes. This is interesting. They're not seeing it here in this cohort, but again, let's be honest, this is a particular cohort. Maybe some of the folks that have issues early on that that might resolve.

VR: Basically, Daniel, if you take some of these and then go out and look in other cohorts and validate them, then you could develop a test for, say, low cortisol levels.

DG: Maybe it's going to be a panel, like the Long COVID panel, so you do an immunophenotyping, you do an AM cortisol, maybe we want to look at 24-hour cortisols to correct for any variation in when they surge, maybe there are certain points for levels of different EBV serologies or even VZV, or CMV serologies.

VR: I think it's a start. It's good.

DG: Actually, I'm very impressed, by the way. Criticism aside, because that's what we want to do, the highest compliment should be people talking about your paper and making comments.

VR: We will be doing this on *TWiV* tomorrow, so if you want more of a dive, you can listen to both. It never hurts to repeat. [chuckles]

DG: Excellent. Excellent. I even mentioned it on a *Puscast,* so [laughs] this paper is getting a lot of attention.

Excellent. All right. We also have the article, "Early Antibody Treatment, Inflammation and Risk of Post COVID Conditions," recently published in *mBio*. I'm just going to start off, don't read the headlines on this one because I don't know if they read the paper. Here, 882 individuals with confirmed SARS-CoV-2 infection participated in a randomized trial of COVID-19 convalescent plasma versus control plasma.

The primary outcome was PCC, post COVID condition, defined as the presence of any self-reported symptom, they give us a list, at the 90-day visit, and all the trial participants were asked about the presence and severity of symptoms at these different days. You end up with 1,181 transfused trial participants. Five-hundred eighty-nine received control plasma, 592 received the COVID convalescent plasma. 43.4% got the CCP, the COVID convalescent plasma, within five days of symptom onset. They report that there was no statistically significant difference in the effect of the CCP, of the COVID convalescent plasma, compared to control plasma on the incidence of Long COVID.

I want to point that out because that is not the headline that's out there, but they did find that elevated IL-6 was associated with an increased risk of developing Long COVID. Remember, these are people in that first five to 10 days.

All right, the article, "Autonomic Dysregulation in Long-term Patients Suffering from Post COVID-19 Syndrome Assessed by Heart Rate Variability," was published in *Scientific Reports*. This I actually think is a really important article, I want to point out. These are the results of a prospective study that included 103 PCS patients. These are Long COVID patients, post COVID syndrome patients.

Time after infection, 252 days, age 49 plus or minus 11.3 years, 45.7% are women. Patients underwent detailed clinical screening, cardiopulmonary exercise testing, and 24 hour Holter monitoring. They have data from the PCS patients compared with 103 coronary artery disease patients and a healthy control group. Overall, these Long COVID patients showed disturbed diurnal adjustment of heart rate variability with impaired parasympathetic activity at night. Patients hospitalized during acute infection showed an even more pronounced overactivation of sympathetic activity compared to patients who underwent ambulatory care.

The data suggests a sympathetic overstimulation and diminished parasympathetic response in long-term Long COVID patients. This is definitely something we're seeing clinically. We're seeing a lot of these individuals, and it's really a question of looking for it. If we do 24 hour Holter monitoring, we see these tachycardia, this increased heart rate. Usually you go to sleep, there's a parasympathetic activation, the heart rate goes down, but not in a lot of these folks with Long COVID.

VR: I think this is an inflammatory effect, Daniel. Probably not viral replication in all these places, right?

DG: Yes. I don't think it's viral replication. We've talked about this. A lot of people have tried. They do biopsies and they look, these look like viruses. I get a PCR, I get an antigen test, but we don't grow the virus. It'll be very interesting. I think this is why we need to do that Long COVID Paxlovid study for 10, 15, 25, who knows how many days, just to really address, is there ongoing viral replication? I don't think so, but it does look like there is some impact on the autonomic nervous system.

All right, the other article, this has a lot of people upset and let's just talk about it briefly. "Multiorgan MRI Findings after Hospitalization with COVID-19 in the UK (C-MORE): A Prospective, Multicenter, Observational Cohort Study," published in *The Lancet Respiratory Medicine*. These are the results of a prospective, UK-wide, multicenter MRI study looking at adults aged 18 or older, discharged from hospital following COVID-19 who were included in this Tier 2 of the post-hospitalization study, this PHOSP, P-H-O-S-P-COVID, and contemporary controls with no evidence of previous COVID-19.

They actually do the SARS-CoV-2 nucleocapsid antibody test negative. They all undergo multiorgan MRIs. They're doing MRIs of the lungs, the heart, the brain, the liver and kidneys. Now, here's what they report that has a lot of people upset. Multiorgan abnormalities in MRI were more frequent in patients than controls - 61% versus 27% - and independently associated with COVID-19 status. Compared with controls, patients were more likely to have MRI evidence of lung abnormalities, brain abnormalities, and kidney abnormalities, whereas cardiac and MRI abnormalities were not really difference between patients and controls.

I want to put this in context. A lot of my Long COVID patients were devastated by reading this, and also devastated by how this was covered. Remember, these are individuals that were sick enough that they were in the hospital, patients who ended up in the hospital. A lot of these individuals were in the ICU, mechanical ventilation, prolonged hospitalization. It's not surprising that we're able to pick up lung abnormalities in people with severe COVID that survived hospitalization.

It's not surprising that we're able to pick up brain abnormalities and kidney abnormalities. This is not necessarily the case compared to people who did not end up hospitalized. Let's also compare these people to maybe more appropriate contemporary controls that were also in the ICU, also had severe disease. I just want to couch this in the context.

VR: I also want to point out, again, these are probably not virus replication effects, but inflammation maybe, right?

DG: A lot of this may be permanent scarring, right? Someone's been in the ICU, they've been on a ventilator, they had COVID, maybe they had a bacterial pneumonia, maybe they had something else. Yes. All right. I will close it out here with what I've been saying for, well, many years now. No one is safe until everyone is safe. I want everyone to pause the recording right here. We're getting right into October. End of September here, and we are still doing our Floating Doctors fundraiser. August, September and October, we will double your donations up to a potential maximum donation of $20,000. We're only about halfway there, Vincent. People really have to take a pause, go to Parasites Without Borders, help us support the tremendous work they do.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. This is a question that was posed on last night's live stream, and I said, send Daniel an email and let him answer it. Jane writes, "Hello, Dr. Griffin. How long after active infection to get the updated COVID vaccine, right after the end of symptoms or three months later, or?"

DG: [laughs] OK. Well, the recommendation, which I agree with, and we'll talk a little bit about the science, is three months. Some folks now have just recently gotten infected. Three months is the recommendation. That's the recommendation. What is it based upon? It's based upon this idea that the infection is going to trigger some degree of an immune response. You're going to get germinal center maturation of those B cells, mitigating impacts on your T cell, so give it time. Three months would be the recommendation.

VR: All right. Beth writes, "I got the original three COVID-19 vaccines in the beginning of the pandemic. I was planning on getting a booster for travel to a conference the first week of November. To the best of my knowledge, I hadn't gotten infected with SARS-CoV-2 until I got sick in the end of August. I took Paxlovid. I'm feeling better. Thanks for encouraging me to have a plan. Does taking Paxlovid inhibit antibody production, do you think a couple of days before I took Paxlovid is enough to up my titers?"

DG: [laughs] This is a great question. There's two things I want to hit on here. First, I've gotten some questions from my patients. There's this perception out here that the original vaccines have worn off, and that people are now unprotected. That is not true. What we're talking about with the latest vaccines, what we're talking about what happens with an infection, is a rise above that background protection that your immune system is giving you. Number two, and this is important, is people were concerned. I even remember the warnings with the monoclonals about, "Oh, you have to explain to people if they take the monoclonals, they may not get that natural immunity that would develop. We may be blunting that."

We did studies looking at that. We really did not see a huge blunting. You're still going to get this immune experience. It's not like you're wasting your opportunity to get natural immunity. What we're doing with the Paxlovid is we're reducing the severity of the cytokine storm of that second week. No, I would view that as your exposure, your boost. Just like we said to the first person, three months from now is the time to think about getting the updated vaccine.

VR: All right, the next one we don't have to answer because you addressed *The New York Times* article, but Karen and many others said this is not what you have been saying, and so you explained that they got it wrong, so we'll pass that one up.

Ross writes, "Please address the recent study on Paxlovid made available in *JAMA Network Open* on September 21. I have prescribed a lot of Paxlovid, probably more than most of my colleagues, but would like your take on what is being reported as a less-than-impressive effect. I strive to be honest with my patients about the potential risks and benefits of this and other strategies and the consequences of surviving infection." You probably have seen this *JAMA Network Open* paper that Paxlovid is weaker against current variants, 37% effective at preventing death or hospitalization in high-risk patients compared to no treatment.

DG: I think we have to be careful how we interpret this data. I interpret this data, sort of brought up the adjusted hazard ratio of death were 0.16, 84% reduction in death for nirmatrelvir. I'm actually pretty impressed by that. There is no change in the virus with regard to its susceptibility to Paxlovid. I think that's one of the things that people have taken out of this, "Oh, it doesn't work as well against the new milder strains." That's not necessarily true.

Now, in this study, if you look at the adjusted hazard ratio of the combined endpoint of hospitalization or death, not as impressive. We only see 37% in this study. It's a hazard ratio of 0.63. I think that I would not view this as anything negative. I'd view another study demonstrating in a cohort of patients that we are able to step in and reduce the risk of death, the risk of hospitalization in our patients.

VR: Elena writes, "I plan to attend New York Comic Con in mid-October with my husband and 18-year-old son. We have received all three doses of Moderna or Pfizer, considering whether to get boosted before we go. Only one of us has had COVID, and none of us have risk factors. After watching Vincent's recent conversation with Paul Offit, I'm wondering whether the risk of myocarditis or pericarditis outweighs the potentially marginal benefit of boosted immunity to mild illness my son would receive.

He's had no myocarditis or peri with any of the three vaccine doses, but Paul Offit's comment that we don't know yet whether there might be long-term effects and the possibility that he could experience issues with this dose has me concerned. We plan to wear an N95 or KN95 at the convention. What would you suggest for your own adolescent son under the same circumstances? If you'd recommend boosting, will a week before provide enough protection to be worthwhile?"

DG: This is great because I think my kids will probably be at Comic Con as well. I'm sure my daughter Daisy will go. [laughs] I think she got to meet Princess Leia at Comic Con at one point and maybe one of the *Doctor Whos*. Couple things here. You can't have it both ways. You can't say that we know the long-term effects after two months, but then we don't know the long-term effects after two months.

With regard to multiple vaccinations, if an individual has tolerated prior vaccinations without myocarditis or pericarditis, we really have not seen that they then have it with the third or the fourth dose. Really, it was the first or the second dose. Now, the other is, what have we talked about? You want to just be honest with how much you can promise.

The updated vaccines, you're not going into this naked. This is merely a top off, a boost above for three to four months. If you get a shot, it's really two weeks before to give you the peak. One week, you're already on the way up. What will I recommend to my daughter, or what

have I recommended to my daughter and son who may be at Comic Con in mid-October? It's actually to go ahead with the updated vaccines.

We've discussed the science around it. This is not a high-risk population that usually goes to Comic Con, but you do mention you and your husband being in your mid-50s, people above the age of 50, that's really when it goes up 25 times the risk of death from COVID compared to the young kids. Yes, the recommendation across is, in general, as there's a reason not to, we do recommend getting the updated vaccine.

VR: Robert writes, "Hello, my name is Rob. I love your show. I've tried to find data on COVID boosters for quadriplegics but I've not had any luck in finding anything useful. I'm a care provider for a 33-year-old female that is a C1 quadriplegic, and as a result also has autonomic dysreflexia. The little information I did find was from 2021, said that the vaccine breaks down at a faster rate in people with spinal cord injuries than people without those injuries. My question is, based on the data, should this woman get the booster after factoring in the potential risk from the autonomic dysreflexia? I will note that she had the original two-dose vaccine with a booster."

DG: This would be a person who's high-risk, who we would clearly say that the risk of vaccine relative to the risk of getting COVID would favor getting the updated vaccines.

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

DG: Thank you, and everyone, be safe.

[music]

[00:46:13] [END OF AUDIO]