This Week in Virology

TWiV 1086 Clinical Update

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Guest: Daniel Griffin

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

[theme music]

VR: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1086, recorded on February 8, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: The bow tie, I can't see it. What is it, Daniel?

DG: It's blue, and it's got these tiny little red bacilli, red snappers, as we affectionately refer to them. It's tuberculosis.

VR: Wow.

DG: Yes, with the red acid-fast stain. In general, I guess it's any mycobacterium. I saw a gentleman this week with mycobacterium chelonae, so.

VR: Wow.

DG: Yes, enjoy those mycobacterium. All right, let's get right into it. I will start with our quotation this week. "Don't let anyone rob you of your imagination, your creativity, or your curiosity. It's your place in the world. It's your life. Go on and do all you can do with it, and make the life you want to live." Very optimistic quotations from Mae Jemison, the first African American woman to travel in space. I thought that was appropriate for, I think, all of our shared love and fascination with space as well as it's a special month this month, right? Black History Month.

The first thing I wanted to start with was a few comments, sort of in response to some of the responses we had about our discussion of the article, “Job Flows Into and Out of Healthcare Before and After the COVID-19 Pandemic.” We discussed how many people had left healthcare. I just wanted to make it clear that I was not trying to shame anyone who had left healthcare.

I tried to mention sort of gently without being too critical, some of the changes in the healthcare environment for a lot of us, right? That more civil patient-provider interaction has eroded, thanks in large part to the misinformation out there, the suggestion that those of us that are devoting our life to helping people really have some other ends and feel particularly terrible for a lot of the nurses, right? A lot of the non-physicians who have had to leave just because of the amount of abuse, the amount of difficulty.

I was quite, I don't know, taken aback when I saw a recent, I think it was CIDRAP reference to the in 2022, there was a 50% increase in the amount of money going into administrators. I would like to see that going to my colleagues. Because really, some of these people really, it's difficult. I acknowledge that. Yes, just trying to point out that this is a problem and commending the people that have been able to stay in the fray, so to speak, not shaming anyone who's had to leave, but this is a problem.

It used to be, we still see a lot of people apply to medical school, but why is everyone leaving? We still see a tremendous number of people go into nursing. We actually have more nurses right now than ever in history. Why do we have a shortage? Because it's becoming less desirable, less support. I just want to acknowledge that that's the problem that I'm seeing here.

All right. Right up front, let us start by discussing the article, “When and Why People Conceal Infectious Disease,” published in *Psychological Science*. Before we just conclude that people are rotten, let's try to understand this issue. The authors start with the statement, "People sick with infectious illnesses face negative social outcomes like exclusion, and may take steps to conceal their illness from others."

Now, initially, I actually thought this was a review, but no, the investigators actually recruited volunteers, and they conducted different studies and found that about 75% of people reported concealing illness in interpersonal interactions, possibly placing other in harm's way. The concealment motives, interesting enough, they were largely social. I say that surprises me, maybe I'm a workaholic. People wanting to attend events like parties, people wanting to go out on a date, oh, my gosh, I'm glad I'm not dating and people showing up sick, achievement-oriented, such as wanting to get their work done.

A lot of a lot of different and I guess what I want to point out mostly, right, 75%, most people will do this at some point. Participants explain the motivations underlying their concealment decisions in a variety of ways. They might say that I did this because it was going to conflict with other social goals. Less often than I expected, they say infrequently, they cited pressure from institutional policies, lack of paid time off as a motivation for concealment. I'm sort of surprised by that, because I think a lot of people like I'm sick, I got to go to work, I just I've already used all my paid time off, so.

VR: Daniel, being sick is a real inconvenience.

DG: It really is. It's unpleasant, it interferes with what you want to do. There is this challenge, right? In a society, you got a job, you've got certain responsibility, but you don't show up, who picks up the slack? Yes, so, and I was speaking to a mom, actually a mom of an 8-month-old, recently, and, just talking about the fact that, boy, being a mom, you when you feel sick, you

can't take a day off. She's breastfeeding, right? You can't take more than a few hours off, actually, in that case, so a nod to those working in the home as well.

All right, into RSV, we did see that double bump, but it does look like we're moving in the right direction, does look like those RSV cases are on the way down, but we're still seeing them still at a pretty high level. I saw a couple of folks this week as well. One gentleman, unfortunately, he got RSV like seven days after the vaccine. I was like, oh, you just didn't quite get in there quick enough to get that protection. As we've talked about, those vaccines probably have a durability past the year.

The flu, it is on the way back up. We saw a plateau, we were hoping, we saw a little bit of an upslope. Yes, it's back above 16%. As far as those percent positive, still seeing 25,000 positive specimens per week. Yes, flu is having a little bit of a rebound here as some of us were concerned might happen. Again, it's different in different regions. As I like to say, I'm not sure what they're doing over there in Jersey, because it's a little bit better here in New York and Vermont. Just I joke a bit about it. Remember, the influenza can be a very severe illness. Thousands of adults will die every winter, already up to over 56 children have died this year already.

COVID, not a lot of good news when it comes to number of deaths, right? We're up another 120, new deaths, 2,570. We're starting to see a little bit of a drop in the in-hospital, a little bit of a drop in the in-ICU. As I discussed last week, it was looking good with the wastewater on the way down. We're actually starting to see a little bit of an upturn, particularly in the Northeast. We'll keep our eye on that.

All right, I like this one. This was the article. I like the topic, I have to say, I'll be a little critical about the actual paper. All kudos to the authors for this tremendous work. We're here, the science, science is about being critical. The article, "Estimating the Heritability of SARS-CoV-2 Susceptibility and COVID-19 Severity," published in *Nature Communications*. This is the age-old question of how much is due to genetics versus environment, now looking at severity of COVID. Can we tell based on one's genes if they will be that superspreader or that person with minimal symptoms, or the one to get severely ill?

Is COVID severity like severe diarrhea? Does it run in your genes? Reference to *The Last of Us*. Here the investigators estimate the shared environment and heritability of SARS-CoV-2 susceptibility and COVID-19 severity using electronic health record data from New York Presbyterian Columbia University Irving Medical Center. I've heard of that place, Vincent.

VR: Hmm. There's something vague in my mind about it. I can't quite place it.

DG: [chuckles] OK. Linked pedigree data. Not only are they going to estimate how much of the risk of severe COVID disease correlates with one's genotype, but they're also going to suggest that over time, the heritability of SARS-CoV-2 susceptibility increased while the estimates for shared environment decreased. They start by identifying 12,764 patients. Then they're going to have a positive or negative PCR test for SARS-CoV-2. These patients belong to 5,676 families with an average of two and a half SARS-CoV-2 tested members per family.

Vincent, I'm not sure if you spent much time looking at this paper. I was thinking like, where are the Manhattan plots? Where's the genetic analysis? Where are the SNPs. Much of this,

these estimates, as far as heritability and shared environment, they're really looking at shared environment and extrapolating, right? At the end of it, not seeing which particular genetic loci is associated, et cetera. They're going to suggest that genetics explained about 57% of the variation, while shared environment explained about 34%.

Then, and this is what I thought was really interesting, is this change over time, which I think makes sense. Early on, we saw people who are considered essential workers, right? People who are not staying home, staying safe, staying in their in their pod, going out, and I'm going to say, nurses, for instance, right, spending a lot of time in a patient room, not always with proper protection. We had landscapers, we had people delivering food, working in the food industry, we have people working in meatpacking plants, et cetera, et cetera.

Early on, a lot of it was the environment you were in, and then maybe being in a shared environment when someone had come back to, let's say, several people living in a home, they have COVID, now, what's going to happen to you, versus later on, when there was a much broader exposure, and then you were actually starting to see heritability as playing a major role in who would get sick over time, who would actually get infected over time.

VR: Yes, I think this is, you're not going to get Manhattan plots, which are looking at the genetics, actually, of susceptibility, because you need to take samples from people, you need to take blood and do some genome analysis. This is a difficult study because it varies with time, right? From the beginning, throughout the pandemic, you had different susceptibilities, you have different vaccines deployed, you have variants circulating, and you can't take any of that into account. There's a lot of variability. As they admit, they get higher numbers than anybody else has published before. What does that mean? I don't know.

We know that genetics makes a difference. We know that the environment makes a difference. I think it's really hard to quantify unless you get down to individual genes, like others do.

DG: All right. Moving into the article, "Neonatal Outcomes After COVID-19 Vaccination Pregnancy," published in *JAMA*. These are the results of a population-based cohort study from Sweden and Norway. They included 94,303 infants whose moms got COVID-19 vaccination during pregnancy, 102,167 control infants, whose moms did not get vaccinated. They found that the protected infants, so the infants where mom got vaccinated, had no increased adverse neonatal outcomes, there was no downside, but there was an upside.

They exhibited lower odds for neonatal non-traumatic intracranial hemorrhage. That was 1.7 versus 3.2 per 1,000; hypoxic-ischemic encephalopathy, 1.8 versus 2.7 per 1,000; and about a 50% reduction in neonatal mortality. Really dramatic, 0.9 versus 1.8 per 1,000. Really reinforcing this message about vaccination during that last trimester of pregnancy, particularly.

More on vaccines. Was it worth it going out there and getting your jab this fall? The *MMWR,* "Early Estimates of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection Attributable to Co-circulating Omicron Variants Among Immunocompetent Adults - Increasing Community Access to

Testing Program, United States, September 2023-January 2024," was released. Oh my, are these titles getting long for this investigation.

They actually got CVS Pharmacy and Walgreens, these are tests done at those locations during September 21, 2023, through January 14, 2024. Sort of hot off the press, right? Adults who reported greater than one, one or greater symptom, suggestive, consistent with COVID, who went in and got a test, right? You've got a positive test, we've got a test-negative design study. For the full analysis, case patients were patients who received a positive result. The control folks were those who had a negative nucleic acid amplification test result.

Tests among persons fulfilling any of the following conditions were excluded. A lot of people get kicked out. Interesting enough, self-reported immunocompromising conditions. That's not going to be looked at here. Reported receipt of Novavax as the most recent second dose, most recent dose. The reported receipt of less than two total COVID-19 vaccine doses. Reported receipt of a J&J COVID-19 vaccine dose after May 12 Receipt of the most recent dose less than seven days, OK, before the date of testing.

Receipt of a COVID-19 vaccine less than two months before date of testing for those who did not receive an updated COVID-19 vaccine dose, or registration for testing with a version of the questionnaire that only reported month and day of the most recent vaccine dose rather than calendar date. OK, so they're going to remove a bunch of people. In addition, they're also going to kick people out if you had a positive in the last 90 days. They're trying to make this a clean study.

Well, what do we end up finding? They're going to be looking here at vaccine efficacy against symptomatic disease. This is really this question. If I get the vaccine, and this is what people used to think vaccines were all about, am I less likely to get COVID? We're not talking about disease severity. We're just talking about symptomatic COVID-19. They're going to compare the odds of a receipt versus non-receipt of the updated COVID-19 vaccine against case and control patients.

Here we find that among 9,222 NAAT results for persons with COVID-19-like illness symptoms eligible for the full analysis, 36% were positive for SARS-CoV-2. In the full analysis, the vaccine efficacy for symptomatic disease for persons aged 18 to 49 was 57%. For persons 50 and over was 46%, with an overall vaccine efficacy of 58% in the first sort of seven to 59, and 49% for those sort of the 60 to 119 days after receipt of the updated vaccine. It's about a 50% drop.

VR: What does this mean? Because you can't compare it to anything, right?

DG: I guess what you could say is people say, so I got that vaccine, was it worth it? You say, well, you know what, we're looking like if you did, you're about 50% less likely to end up showing up at Walgreens or CVS feeling crummy and getting a positive COVID test. We don't know about severity, but even just being symptomatic and having COVID is something that people would love to reduce their risk of. Here we're seeing data about a 50% reduction in even having symptomatic, molecular-confirmed COVID-19.

VR: There's no group who didn't get that vaccine. That's the point.

DG: Yes. This is interesting. This is like people who are sort of following, and I've been doing everything except I didn't get that last booster and the other person did get the last booster. A person who got their last booster has about a 50% less likelihood of this symptomatic COVID-19. Now if you're going to get that vaccine, Vincent, which arm? Do you get it in the same arm every time? Do you get it in the other arm? There have been some studies.

VR: Doesn't matter, Daniel. It doesn't matter.

[laughter]

DG: Let's look at the data. The article, "Contralateral Second Dose Improves Antibody Response to a Two-dose mRNA Vaccination Regimen," published in *JCI*. Let's see if that's really true. Here the investigators assessed serological responses to initial COVID-19 vaccination in baseline seronegative adults who received second dose boosters in the ipsilateral or contralateral arm relative to initial vaccination. They're going to go ahead and they're going to measure the SARS-CoV-2 spike-specific IgG, RBD-specific, receptor binding domain-specific IgG, SARS-CoV-2 nucleocapsid-specific IgG, neutralizing antibody titers, and they're going to check all this at different time points after the boost.

They reported that in 947 individuals, contralaterally boosting, so getting a boost on the other side, was associated with higher specific spike-specific serum IgG. This effect increased over time from a 1.1 fold to a 1.4 fold increase by 14 months. Knock my socks off. A similar pattern was seen for RBD-specific IgG among 54 pairs matched for age, gender, and relevant time intervals. Contralateral booster resulted in a statistically, I'm going to say, statistically significant higher binding and neutralizing antibody titers with progressive increases over time, ranging from 1.3-fold to 4.0-fold.

We can actually look at the data. Initially, when you're looking at the SARS-CoV-2 specific IgG, it's a lot of overlap here, right? The statistician is going to tell you that the standard error of the mean is going to result in a good p-value difference. When we look at the neutralizing antibodies, it looks a little bit more impressive on this neutralization titer log scale. How do we reconcile this with an article we've talked about before? "Differences in SARS-CoV-2 Specific Humoral and Cellular Immune Responses after Contralateral and Ipsilateral COVID-19 Vaccination," right?

That study by Ziegler et al that we discussed past summer, they had looked at 303 adults. They got their second dose, same thing, either same side or contralateral. They looked and basically saw spike-specific IgG levels did not differ between groups. Actually, in that study, neutralizing activity and spike-specific CD8 were significantly lower in the contralateral group at two weeks after the second dose. They are suggesting that doing it on the same side might be preferred.

The authors here, we'll give them the first word. They suggest that the other investigators looked too soon. They looked at only two weeks past the vaccine. Because of that, they were seeing this sort of head start from those preformed germinal centers. If you wait, Vincent, and you check a little bit later, it's better to get it on the other side.

VR: The real key, Daniel, is that any of this clinically relevant, and there's no answer to that question, right?

DG: That's key. That's key. You're at 1.1, 1.4. These comparative numbers, do they really matter? Do they really make a difference? We say clinically relevant, as in, am I less likely to get sick? Am I less likely to get severely sick? Does it really matter? We don't really know if it actually really matters outside of what a statistician will show you on a figure.

VR: You could design a study to look at that, but it would be a difficult study to look at disease severity, right?

DG: It would take big numbers, and it would cost money, but, yes, you could basically say, hey, we're vaccinating people. You could easily do this next fall and basically say, all right, so half the group, and we'll give you something to participate in this study, maybe like a cool hat, and half the group gets it in the opposite arm from last time, the other group gets it in the same arm from last time, and we're just going to measure who gets symptomatic, who ends up with severe disease, who ends up hospitalized, et cetera. Yes, it's definitely something that we could investigate, and it would be worth doing because I think a lot of us are curious. This is something we do. We get vaccines, and should we be getting them all in the same arm? Should we be sharing it?

OK, moving into COVID early viral phase. You have now tested positive. You are symptomatic. You're a person with risk factors for progression. Still, number one, Paxlovid. As we've talked about, we'll leave links in to the PAXCESS because this is becoming an issue. As Paxlovid has moved from the government paid for it all and you just show up and get your package, now we're actually seeing that a lot of pharmacies are frustrated but are not particularly excited about running it through your insurance, which they should be doing. Some people are sort of getting this roadblock of a financial barrier between them and access. We've really got to keep working on that.

Remdesivir, limited use. Molnupiravir, remember, no renal, no drug-drug interaction. Really an easy lift, a lot better than just sending someone out without any therapy. Convalescent plasma in certain contexts, and then avoiding doing those harmful things. Remember, first week is when the steroids are associated with harm, not benefit. We've talked repeatedly about trying to use antibiotics to treat a viral disease.

Second week, the cytokine storm week. This is when your patient maybe starts to feel better or still feels crummy. When we get that cytokine storm, certain contexts where the oxygen saturation is less than 94%, dexamethasone, 6 mg a day times six days, anticoagulation guidelines from the American Society of Hematology and others, pulmonary support, remdesivir still in the first 10 days, immune modulation with tocilizumab in certain contexts, and avoiding those unnecessary antibiotics and unproven therapies.

Moving on to, and so we're going to wrap it up this week, COVID, late phase, PASC, and :Long COVID. A teaser for next week, I had an enjoyable conversation with David Putrino from Mount Sinai Monday evening. He's back from Kenya. Interesting guy, Vincent. He actually works with elite athletes. People are sort of genetically elite with these just incredibly high VO2s. Then they sort of help train them. I think a lot of us have seen these individuals winning the marathons. He had just gotten back from one of his research projects over there.

He is very involved with the Long COVID Center at Mount Sinai. Next week I'm going to be talking about a lot of the things David and I discussed. How do you approach that first visit? How do you make the diagnosis? What would be initial tests that you might do? Then talking a little bit about what is the state, the current state with regard to evidence-based therapies.

All right, but let us get into the literature. The article, "Sleep Quality among Non-Hospitalized COVID-19 Survivors: A National Cross-Sectional Study," published in the journal *Frontiers in Public Health*. Now, here the investigators conducted a cross-sectional online survey of 1,056 COVID-19 survivors within six months. That's going to be important. Six months, right? It's more than three, less than six of initial COVID-19 infection. I say more than three because that's when we get into Long COVID, but still, we're looking at the full six months here. These are folks that did not require hospitalization.

The Insomnia Severity Index, Depression Anxiety and Stress Scale 14 were used. Now, this was conducted in Vietnam, and participants were 18 years and older. Now, I understand they have great coffee in Vietnam, so I don't know if they were sure to think about that in this study. Anyway, they reported that more than 75% of the participants had insomnia. Really is a lot higher, right, than we've previously seen, and certainly higher than the general population with about 10% to 20%. It's a common problem.

Now, why is this so high? They suggest that one reason for this high number might be that they're looking within six months of initial COVID infection. Maybe there's a little bit of a silver lining here. This may be a significant, a very common issue after COVID-19 infection for that six months. As we've seen from previous studies, it looks like the numbers get down a little bit lower, sort of in the 12% to 47% if you start following these people a little bit longer.

Now, I did see a comment like, don't think it's normal. Well, I think that's appropriate because next week we'll talk a little bit about the melatonin studies on maybe that 3 to 5 mg about being not only particularly symptomatically helpful, but even having an anti-inflammatory role at the right dose in individuals struggling post-COVID.

I also want to discuss the article, "Substantial Health and Economic Burden of COVID-19 During the Year After Acute Illness Among U.S. Adults Not at High Risk of Severe COVID-19," recently published in *BMC Medicine*. This study, a little proud of this one, it included eligible adults who were diagnosed with COVID-19 from April 1 to May 31, 2022, who were 18 to 64 years of age and enrolled in Optum's de-identified Clinformatics Data Mart Database for 12 months before, right? You want to have baseline. Then 13 months after the COVID-19 diagnosis. Trying to see if people can see my little Optum logo on my white shirt, my white coat.

End up including 3,792 patients, 56.5% are men, 44% white, 94% did not require hospitalization, right? This is mostly non-hospitalized. Compared with baseline, patients during the post-acute phase had percentage increases in the diagnosis of blood disorders, 166%. That's percentage increases. Endocrine and metabolic, 123%. A lot of diabetes here. Nervous system, 115%. Digestive system, 76%. Mental and behavioral, 75%, along with increases in related prescriptions. They saw substantial increases in all measures of healthcare utilization. Total medical costs increased by 178% during the post-acute phase.

Those who are hospitalized with or without ICU had the greatest increases in comorbidities and healthcare resource utilization.

I just want to sort of point this out. This is a tremendous challenge, right? Think of how many people have had a COVID-19 diagnosis, and then just seeing this really increased burden, I'm going to say, for the patients, increased challenges for the healthcare system to address all these issues.

VR: Daniel, does this make clinical sense that a virus infection could have all these effects a while afterwards?

DG: It is not, I guess I'm going to say not unprecedented, right? An interesting thing when we looked at people in sort of the Optum database that got influenza vaccine or not, we're not just preventing the flu admissions, we're actually seeing a reduction in cardiovascular issues. A lot of times with viral issues, it's not just that week. It's just not that two weeks. There can be a post-infectious issue that we see down the road. I don't think we've seen such an impact on things like diabetes, as we're now seeing post-COVID. Behavioral and mental, you wonder, actually, part of that might be post-viral, but part of it may actually also be sort of what we've all been through. Just seeing increases across the board.

VR: Yes, I think understanding the mechanism is really important here because if you just say this happens, it doesn't really help, right? Especially not with treating it. You need to know why.

DG: Yes, it's not. Again, this is correlation, right? I think that's really important. It's important for us at Optum to think about resources. We really got to be around and have the capacity if there's going to be a growing demand for care for these individuals, but yes, from a scientific, what exactly is going on? What's driving this? That may actually save us all if we can figure out what the mechanism is and address that.

All right," Predictors of Non-recovery from Fatigue and Cognitive Deficits after COVID-19: A Prospective, Longitudinal, Population-based Study," was published on Groundhog Day in *eClinicalMedicine*. I don't know. That's a big day for me. Here, these investigators analyzed longitudinal data from the population-based COVIDOM/NAPKON-POP cohort in Germany. OK, interesting. Participants with confirmed SARS-CoV-2 infection were assessed at least six months, that's sort of a baseline, and again, at 18 months follow-up after infection using the Functional Assessment of Chronic Illness Therapy-Fatigue, the FACIT Fatigue Scale.

They're going to use a cutoff of less than or equal to 30. They're also going to use maybe something more familiar to our listeners, the Montreal Cognitive Assessment, the MoCA. There, the cutoff is going to be 25 or less. Predictors of recovery from fatigue or cognitive deficits between assessments were identified through univariate and multivariate logistic regression models. They looked at a total of 3,038 participants assessed at baseline, medium nine months after infection. Eighty-three percent responded to invitations for follow-up. That was about 26 months, median of 26 months after infection.

Now, at baseline, 21% had fatigue, 23% had cognitive deficits, according to these cutoffs. Participants with cognitive deficits showed a significant improvement in cognitive scores. I want to point that out. Fifty-seven percent had recovered from cognitive deficits, but they

found significant risk factors for cognitive non-recovery were being male, older age, less than 12 years of school education. Importantly, SARS-CoV-2 reinfection had no significant impact on recovery from fatigue or cognitive deficits.

VR: Daniel, what does education have to do with this?

DG: I was trying to figure that out. Was this, and part of it might be that if you're using the school education and then you've got these cutoffs on these different tests, you sort of move that sort of baseline. I'm not sure, but that was, remember, this is people who had a cognitive deficit. They scored below a certain thing. Now they're actually recovering, or not. I'm not sure. Interesting. Stay in school, Vincent.

VR: I did and so did you.

[laughter]

DG: All right. We will finish off as we have for quite a while. No one is safe until everyone is safe. We have successfully, and thank everyone, we finished the MicrobeTV fundraiser. Vincent, the check is in the mail for MicrobeTV. Thank you, everyone. If you enjoy what we're doing, if you want to continue with our work, we are now entering the ASTMH fundraiser where in February, March, and April, we will double your donations up to a potential maximum donation of $20,000.

VR: Thank you, Daniel, for fundraising for MicrobeTV. Much appreciated. It's time for your questions for Daniel. You can send yours to Daniel@Microbe.TV. Brian writes, "Love the clinical updates. Been listening for years. Something bothers me, though. Why don't we ever hear about interferon treatment? It's been used to treat hep C. Interferon is natural, cheap, and easily increased by raising your body temperature via sauna, steam room, or even getting sunlight. Several studies show increasing your interferon decreases likelihood of severe disease. Why so much emphasis on adaptive immune system and vaccine? Isn't the innate immune system the best place to rid a virus from the body?"

DG: [chuckles] No, Brian, this is a good comment. Again, what we try to do is share the science, right? If there's an exciting paper that comes out suggesting that interferon might have a role, might have a place in the treatment, we'll definitely share that. Now, we did use interferon for a while, right, to treat hepatitis type C, and it was really a hard sell because you'd sit down with a person. I remember these conversations saying, OK, we've got this therapy. There's this percent likelihood of success. Now you're going to feel like you have the flu for two months. They would look at you and say, really? About a weekend, they're like, I feel horrible. I feel like I have the flu. That was in many cases about when they stopped being interested.

Yes, interferon, unfortunately, sometimes at the levels that we were using, like to treat hepatitis type C, not pleasant, and so we've moved away from that for hepatitis type C treatment.

VR: I think he's right in the sense that I think most virus infections are, in fact, taken care of by the innate immune system and we never hear about them. I think those are the ones that never proceed to symptoms. As you say, when you give people a lot of interferon, it's not good.

DG: Yes.

VR: All right. Lorrie writes, "My daughter and granddaughter both have DiGeorge Syndrome, which comes with a host of medical issues in and of itself, but this dang COVID is making life entirely too crazy. Granddaughter went back to school in 2022, managed to get COVID twice that school year, along with all respiratory viruses that were going around. So far, 2023/24 school year, she's contracted the COVID three times and also flu and strep and every other thing available. What in the world can we do? She's had her vaccines. I'm concerned about long-term issues this much sickness may have in her. I feel like I need to hide my granddaughter and her mom under a basket and never let them out, but what kind of life is that? The other frustrating part, people just go on like it's no big deal anymore and we just buried a friend last week who died from COVID. Please wave your magic wand and give me some solutions."

DG: Yes, so this is a challenge, right? A lot of our listeners probably not that familiar with DiGeorge syndrome, but this is it's a genetic deletion. It impacts the immune system, particularly T cells. This is a challenge because, Lorrie, you're, I think, bringing awareness for so many people have said, whoa, the pandemic is over. I remember watching a movie and it was like surviving the plague and it was about HIV. I'm like, is it really over? What did I miss?

For a lot of people who don't really have a robust immune system, we used to have Evusheld, we used to have things like that. We do not have one of those at the moment. I hear what you're saying. It's a challenge. I don't think you have to hide your granddaughter and her mom under a basket. We've tried to talk about what are safer activities, right? Things that are outside. We've talked about increasing ventilation. We've talked about jumping in with antiviral treatment and using the proper testing to make sure you identify an infection in the window for the best treatment. Vaccines, ventilation, and a lot of wise decisions. No, I hear what you're saying. Yes, for Lorrie, for people like you, your loved ones, yes, this pandemic is not over.

VR: Maybe some judicious masking is also called for in this case, right, Daniel?

DG: I would say, definitely. If you're in, and this is the situation where you keep that at N95 or KN95 in your pocket. When you realize, oh, you just pop it on, and that one-way masking with a high-quality mask is effective.

VR: Martin writes, "In week two of COVID, if pulse ox falls to say 92 or 93, is it safe to delay use of steroids until it drops to say 90 in order to avoid any remaining circulating virus from benefiting from increased immune system suppression brought on by the use of steroids? I don't currently have COVID, but should I get it when it comes to the use of steroids, I suspect I would feel tempted to wait until pulse ox was down to 90, providing I didn't feel too ill. Would such a delay be stupid? I know you've repeatedly mentioned a drop below 94, but I'm wondering if there's any leeway based on how ill a patient is feeling."

DG: Yes. The interesting issue here, right, so let's talk about the data. This originally comes from the RECOVERY trial and they use a cutoff, you got to sort of pick something and say, OK, we're going to use this 94% and they're going to see about a 25% reduction in mortality in that study. Then you've got to ask, so what is 87 the same as 93? The answer is probably no.

Sometimes I'll see a patient in the hospital, 95, 96, I see a 93, that is not necessarily going to trigger me to necessarily start the steroid. There is a little bit of judgment here. Ninety-four was what was studied, but you're going to look at the patient and you're going to make a decision, so no, I think thinking things through a little bit of nuance, that is reasonable, you're not being stupid.

VR: Kathryn writes, "I'm very curious about the current measles outbreak in Europe, particularly the tens of thousands of cases in the UK where vaccination levels have been inadequate to prevent outbreaks. Given that many sections of the U.S. have similarly low levels of vaccination, do we anticipate similar outbreaks here? If we do have a similar outbreak in the States, what can be learned from the UK's emergency response and community vaccination outreach? Even though measles is well-studied, is there anything we can learn about the virus itself?"

DG: Yes. You guys have been talking about this on the deep dive recently, Vincent, is, just the fact that with measles, you need a certain percent of the population vaccinated before you really put yourself at exposure here. Yes, in a lot of areas, we're actually falling below that so we're starting to make ourselves vulnerable. Yes, I think there's a lot of concern and we are seeing in some of the recent reports that we're actually having, there's like eight states now that have had issues with measles, not eight individuals, but eight different states, right? Actually, it is, that concern is actually being reinforced with actual consequence here. Yes, I think we can look to people like the UK, how did they respond? Because we're looking at similar problems here.

VR: Eli writes, "The anti-vaxxers say that few people in Africa died of COVID, even though there was little use of the vaccine. Any comments?"

DG: Yes. This has come up. I know, like sometimes we've had discussions where Dickson brought this up and, the really tough thing is, how good was the data? Do we really know? You have a population where there's already a relatively high mortality, now during COVID, it is not, where we do have good data, it's not quite as impressive as the anti-vaxxers would like us to say or think. Part of when you start adjusting for the age of the populations, I'm not sure that the anti-vaxxers really have much solid information here.

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

DG: Thank you, and everyone, be safe.

[00:43:30] [END OF AUDIO]