This Week in Virology

TWiV 1014 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.

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From MicrobeTV, this is *TWiV*, *This Week in Virology,* Episode 1014, recorded on June 8, 2023. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today from New York is Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: How is the air quality out there, Daniel?

DG: That's been the topic of conversation. It was horrendous yesterday. I've been trying to get some kind of a sense. Today it's about half as horrendous as it was yesterday. My eyes had been tearing up. I'm trying to figure out, we need this week and just random things where we can ask someone because they're like, "It's really bad," but it's really bad, is it like if I spent two hours out sailing? Is it like I smoked a cigar or a half a cigarette? I'd love some quantification.

VR: Good question. It's not in my lane, Daniel.

DG: It's not in mine either. [laughs] All right, hey, email us please because I'd love to be able to give some context here. Today I am wearing my HIV bow tie. I will start right with my quotation. “Being honest may not get you a lot of friends, but it will always get you the right ones.” That's by John Lennon. I will jump right into COVID. I will start with the *MMWR,* “Estimates of SARS-CoV-2 Seroprevalence and Incidence of Primary SARS-CoV-2 Infections Among Blood Donors, by COVID-19 Vaccination Status - United States, April 2021 through September 2022,” just came out June 2nd. Now, to estimate the incidence of infection and prevalence of infection or vaccination-induced antibodies or both, data from a nationwide longitudinal cohort of blood donors was analyzed. A lot of people have comments about how representative are those of everyone else.

CDC in collaboration with Vitalant, American Red Cross, Creative Testing Solutions, and Westat, established a nationwide cohort of 142,758 blood donors in July 2021. The cohort included persons who had donated blood two or more times in the preceding year. All blood

donations collected during April through June of 2021 were tested for antibodies against the spike, and nucleocapsid proteins. By the third quarter of 2022, so July through September, 96.4% had SARS-CoV-2 antibodies from previous infection or vaccination. They tried to make some comments about hybrid immunity. They're using anti-nucleocapsid antibody assays, and we've discussed they have sensitivity issues in those previously vaccinated. I think there's a couple of interesting things here. This is consistent with the idea that at this point, almost everyone has some form of immunity.

The other take could be, is that, this is just when you go for the blood donations there. You're all crowded in there together. I don't think that's what's going on. I just want to just shine a light on that. No, I think it's consistent with the concept that at least here in the U.S., there's a lot of immunity out there as our background. All right. By the way, everyone should be a blood donor, so this should be representative of everyone.

OK. All right. Children, COVID, and other vulnerable populations. You're going to like this one, Vincent. I don't know if you read this ahead of time, but the article, "Smart Thermometer-based Participatory Surveillance to Discern the Role of Children in Household Viral Transmission During the COVID-19 Pandemic," was published in *JAMA Network Open*.

I shared this article yesterday with our urgent care doctors, and there were a lot of chuckles about how we allow these walking Petri dishes to go out there in the world, and then we let them back into our homes. Early on, there was this concept that children could not catch or transmit SARS-CoV-2, you didn't have to worry. In this publication, we read that a time when the relative rate of viral illness attributed to COVID-19 was at a high, these investigators were able to take advantage of participatory surveillance methods to gain insight into transmission dynamics among 1.4 million individuals and over 800,000 households using commercially available shared thermometers and a smartphone app. See that was the problem, the shared thermometers.

VR: [laughs]

DG: Now their findings suggest that children play an important role in within households viral transmission. Lots of limitations here regarding the precision of these numbers, so I would not hang any of my hats on any specific numbers, but they report that among 38,787 transmissions in 166,170, households with adults and children, a median 70.4% had a pediatric index case. These proportions fluctuated down 36.9 getting all the way up to about 85%. There actually were some timing issues, a pediatric index case was less frequent during the typical school breaks. Then they saw the winter break decrease was from 68.4%, dropped down to 42%. At the beginning of 2022, it dropped from 80 to 54.5. During summer breaks, the rates dropped from about 81% down to 63. Then they talk about these patterns persisting over two years.

What do you think? Is it possible, Vincent, that children go out in the world and get respiratory infections and spread them to others in the household? Have you ever had such an experience?

VR: Yes. Of course, that happens with many other infections like rotaviruses, and other respiratory viruses, we know this. I have two questions for you, Daniel. First, they're diagnosing it based on temperature, correct? Is that something you would agree with?

DG: There are a lot of limitations here.

VR: [laughs]

DG: [laughs] I'm going to give you that. One of the things they're trying to say here is, "Boy, this was the only game in town. This was a time when almost all these infections, there wasn't much flu, there wasn't much other stuff." That's a bit of a limitation. You're also probably talking about a select part of our society. Folks that have this smart thermometer, smartphone technology. When we had children, I banned all temperature-measuring devices from the home. I felt that that made my wife much more relaxed.

VR: Yes. The other thing is, it would have been nice to do this in households without children to see how the numbers compare.

DG: Yes.

VR: Because they're doing the summer drop as indicators that the kids are not going to school anymore, but it could be something else. It would be nice to know if that happened in households without kids.

DG: I think early on, there was also this concern that when the kids were not in school, kids socialize. You're getting your kids together with other kids in other people's homes and all these discussions.

VR: By the way, Daniel, you have a little note here on masks, you say, "Remember, masks only work if they're worn." I've never seen people jump to masking when the air got bad yesterday. Isn't that amazing?

DG: I called it reverse masking. People were putting on the masks when they went outside, and as soon as they got to the safety of the air-conditioned indoors, off would come the N-95s. I must admit, I went for a run today with an N-95, and yes I'm just not as fit as I wish I was.

VR: You know that it was so hard to get people to wear masks for COVID, but here they could see the air is yellow, "Sure. I'm wearing a mask."

DG: That's actually a challenge that my wife brought up. Yesterday, it was obvious. I felt like I was in a retake of the *Blade Runner*. When it's so visible - but that's the problem with these viruses. They're invisible. If you saw a yellow COVID haze, boom, the mask might pop right on. In the future, if we can make viruses just a little bit bigger, a little more visible in the air, that would be helpful.

VR: Oh, maybe we should saturate the air with a dye that will stain viruses, how's that?

DG: This is like the purple stuff in the swimming pool. When people come over you're like, "Don't pee in a swimming pool because we got that purple dye."

[laughter]

VR: Yes, exactly right.

DG: All right. Moving on to COVID active vaccination. I think we have a few interesting things here this week, and I'm going to be continuing this theme next week. Not this first theme. The first theme is no more J&J shots in the U.S. On May 22, 2023, that was just a couple weeks ago here, Janssen Biotech requested the voluntary withdrawal of the EUA of the Janssen, the J&J COVID-19 vaccine. They informed the FDA that the last lots of the vaccine purchased by the U.S. government had expired, there was no demand for new lots, and they did not intend to update the strain composition of the vaccine. On June 1, 2023, just about a week ago, the FDA revoked the EUA so that's the end of the J&J vaccine here in the States. J&J one and done, I guess. We also have news on COVID-19 vaccine mandates are also going away here. For some background, on November 5, 2021, CMS issued the interim final rule on Medicare and Medicaid programs Omnibus COVID-19 Health Care Staff Vaccination otherwise known as the Staff Vaccination IFC, which revised the requirements that most Medicare and Medicaid-certified providers and suppliers must meet to participate in the programs to include requirements regarding development and implementation of policies and procedures to ensure COVID-19 vaccination of staff.

Now, June 6, the Omnibus COVID-19 Health Care Staff Vaccination Interim Final Rule, lots of finals here, rescinds the requirement for workers and contractors at Medicare and Medicaid-certified facilities to be fully vaccinated against COVID-19. This takes effect 60 days after that June 6 publication date so it's going to expire August 4, 2023. In this publication, we can read that, and I'll just read this, "As conditions and circumstances of the COVID-19 public health emergency have evolved, so too has CMS's response. At this point in time, we believe that the risks targeted by the staff vaccination IFC have been largely addressed so we are now aligning our approach with those for other infectious diseases specifically, influenza. Accordingly, CMS intends to encourage ongoing COVID-19 vaccination through its quality reporting and value-based incentive programs in the near future."

The article, "Changing Severity and Epidemiology of Adults Hospitalized with Coronavirus Disease 2019 (COVID-19) in the United States After Introduction of COVID-19 Vaccines, March 2021 - August 2022." I like that the title here is changing severity associated with the introduction of vaccines because so many people like to say, "Boy, we introduced the vaccines but what really happened is the variants." [laughs] This article published in *CID* of which I love the title. As I said and I'm going to say this again, this is redundancy, apparently that's a good thing to do, so much time has been spent on making claims of how different the virus was at different times during the pandemic but I do want to point out this whole time we were building up immunity mainly through massive robust vaccination campaigns here in the U.S.

If we were not seeing milder infections after vaccination, then this would have been a fail. Why was this story not all about how effective vaccinations were in reducing the risk of severe disease? I'm not sure there's much new here but we do read that compared to adults hospitalized during early COVID-19 variant periods, those hospitalized during Omicron variant

COVID-19 were older, had multiple comorbidities, and less likely to experience severe respiratory disease, systemic inflammation, coagulopathy, and death. As impressive as our immune system might be when we are young and healthy, we still are vulnerable when we are older. Now, what makes Omicron mild? Having an educated immune system ideally from vaccination, early treatment with something. Well, we'll talk about those somethings a little bit later on, and yes, avoiding harmful things like steroids, antibiotics.

The last little bit here on the vaccine news front, we're going to have some exciting stuff in about a week, we also heard news that Novavax is already producing an updated XBB vaccine version of its protein-based vaccine option that will be ready for the fall.

VR: Yes, next Thursday is the ACIP, is that right?

DG: It's, yes, the FDA meeting.

VR: Oh, VRBPAC is the FDA -

DG: It's the VRBPAC, yes. It's going to be the advisor.

VR: They're going to pick the SARS-CoV-2 strain.

DG: Yes, I'm going to have to try to figure out how do I jump on right afterwards with updated information and then still keep my day job.

[laughter]

DG: We're moving into, you have tested positive, your patient has tested positive. Number one, Paxlovid now licensed. I have to say, we really have a lot to overcome with the misinformation about the importance of jumping in here early with effective treatment. A person has a raspy voice, a bit of the sniffles, "the common cold" and next thing they are on some ineffective antibiotic that is disrupting their microbiome pushing us further down the road to the antimicrobial apocalypse. What about COVID? The docs seem a little bit reticent, patients seem a little bit reticent to take something that's actually effective. The article, Effectiveness of COVID-19 Treatment with Nirmatrelvir-Ritonavir or Molnupiravir Among U.S. Veterans: Target Trial Emulation Studies With One-Month and Six-Month Outcomes," was published in *Annals of Internal Medicine* on June 6. The good old VA folks again.

For some context, those of you who haven't been here, the Veterans Health Administration, operated by the U.S. Department of Veterans Affairs, is the largest integrated healthcare system in the United States providing care to more than nine million veterans, the majority of whom are older and have a high burden of underlying medical conditions. Lots of high-risk folks. The VA has provided an opportunity for multiple target trial emulation studies of the comparative effectiveness of COVID-19 pharmacotherapies and vaccines. Here, the investigators used target trial emulation, principals to emulate three trials of Paxlovid versus no treatment, molnupiravir versus no treatment, and Paxlovid versus molnupiravir during the Omicron era.

They evaluated, as they mentioned the title, 30-day and six-month incidents of hospitalization and death among non-hospitalized adult veterans who are infected with SARS-CoV-2 and

were at high risk for progression to severe COVID-19. Eighty-seven percent of participants were male, median age was 66, 18% were unvaccinated. This 82%, this is mainly unvaccinated individuals. Now, compared with matched, untreated, controlled participants, those treated with Paxlovid had a lower 30-day risk for hospitalization. We see a 22 versus 30 per 1,000 participants and death we see 1.25 versus 5.47. Among persons alive at 31 days, reductions were seen in 31- to 180-day incidence of death. The hazard ratio there was 0.66. I like to point that out. We've really focused a lot when we talk about case fatality rates on what happens in those first 28, maybe 31 days.

There's a second chunk of people, and it is a chunk of people that will die after that 31-day as will die in the six months after that acute infections. I'm glad we're seeing data on that. Now, molnupiravir-treated participants also had lower 30-day and 31- to 100-day risks for death. They give some numbers there. Then, the hazard ratio for death in that 31-to-180 days was 0.67. Very similar, about a 33% reduction in that second zone of death. Just to wrap this up for folks, Paxlovid was effective in reducing 30-day hospitalization and death, molnupiravir was associated with a benefit for 30-day mortality but not hospitalization, and further reductions in mortality in that 31-to-180 days was observed for both antivirals. Number two we've got remdesivir, number three we discovered molnupiravir a little bit.

Convalescent plasma for a select group, immunocompromised in the first few days, and yes, let's not do those harmful things. Moving on to that second week, remember we've all learned that the natural history of COVID for some folks is they're sick during the first week, they start to feel better, and then that second week we get that cytokine storm. Steroids we've talked about in those that meet criteria. Anticoagulation, we have guidelines, but are people following those guidelines? What are people doing? We have the article, “National Trends in Anticoagulation Therapy for COVID-19 Hospitalized Adults in the United States: Analyses of the National COVID Cohort Collaborative,” published in *JID*. Here, the investigators used the National COVID Cohort Collaborative and conducted a retrospective cohort study 2020 through 2022, to assess anticoagulation use patterns and identify factors associated with therapeutic anticoagulation.

It's basically looking what have folks been doing. Among 162,842 hospitalized COVID-19 patients, 64% received anticoagulation, 24% received therapeutic anticoagulation. Now, the therapeutic anticoagulation use declined from 32% in 2020 to 12% in 2022 especially after December, 2021. What were the predictors for therapeutic anticoagulation? These included age, being male, non-Hispanic black, obesity, increased length of stay and invasive ventilation. Also vaccination rate was associated with a lower use of therapeutic anticoagulation. Just to remind people of what are the guidelines and why maybe has this changed over time. The guidelines had recommended therapeutic full-dose anticoagulation in those four general medical patients admitted during the second week with moderate to severe COVID. It actually recommended using prophylactic in the critical care settings where the risk of bleeding and other complications seemed to outweigh.

Everything had been qualified with, "Use your clinical judgment, do an individual assessment of your patient when making these decisions." A couple of the things as we're seeing here is over time, we're actually seeing maybe that risk-benefit calculation is shifting, so expect some potentially updated recommendations. Pulmonary support, remdesivir if we're early enough, maybe some immune modulation, tocilizumab, baricitinib, and remember only using those

antibiotics in those appropriate situations. A bunch today on the late-phase PASC, Long COVID. Part of this is also because, boy, did I get a lot of response to our discussion of the article last week, “Development of a Definition of Post-acute Sequelae of SARS-CoV-2 Infection,” published in *JAMA.* A couple of bullet points here. I'm going to leave in a link again.

In this first analysis of data from the RECOVER adult cohort, criteria for identifying PASC based on self-reporting symptoms were delineated and several distinctive PASC subtypes with varying impacts on well-being and physical health were described. The RECOVER adult cohort included SARS-CoV-2 infected and uninfected. Uninfected participants had no known history of SARS-CoV-2 infection. An index was defined as a past negative SARS-CoV-2 result date. There were some questions about whether or not folks were included that developed issues post-vaccine. They say in the statistical analysis section, a rule for identifying PASC was derived in the full cohort. Thirty-seven symptoms had frequency of 2.5% or greater. Just at odds ratio 1.5 or greater for all 37.

Now using the full cohort they identified 12 symptoms with corresponding scores ranging from one to eight. I've got a table too, and the optimum PASC score threshold was 12 or greater. Now, a lot of people had issues with the concept of this cutoff, this binary, you have or did not. It's really interesting, I actually have up for Vincent and me to look at, Figure 2. You really see, OK, there is a little bit of an inflection here when you use different cutoffs. Really what that inflection is related to is the uninfected being classified as having PASC. When you're out at 25, basically you're not pulling anyone accidentally, 18 you're still there. When you get up to about 12 you're starting to see about 3%. Even if you go down to, I don't know, I'll pick eight here, because you got eight and eight. If you pick eight, about 8% of the time you might accidentally pull someone in who doesn't have post-acute sequelae of COVID.

A lot of limitations here, a lot of concerns that people had. I wanted to just discuss those. First, they do say that the proposed paradigm and accompanying decision rule require, and I love this, iterative refinement as additional data becomes available. Now, iterative refinement is not something that I use in common parlance. Basically, [chuckles] they're saying, "Yes, we're going to have to use this for a while and see." They also say PASC score provides an operational definition of PASC and requires further refinement and validation. Recover recruitment is ongoing and not all the participants have reached the analysis stage. Evolution and refinement of phenotypes are anticipated as additional data becomes available. I think Vincent you made this point that they're only looking at this one point in time. What about three months? What about the six months? What about nine months? What about evolution over time?

Second, selection bias was likely among the post-acute cohort participants that may have affected the frequency estimates, including the distribution of the subphenotypes, because past severity may impact study participation. Third, I'm going to say uninfected participants may have had prior asymptomatic SARS-CoV-2 infections, just not detected. That weakens our discrimination characteristics. Fourth, symptoms were self-reported and only some symptoms integrate severity scale. Participants could report other symptoms as pretexts, but these were not necessarily included in this analysis. Fifth, we have a number of confounders, and six, I'm going to say, and I think this is what got a lot of people upset, more than 200 symptoms of PASC have been reported, each with the potential of being life-altering and

debilitating and symptoms highlighted here within may not reflect the severity or the impact of those symptoms.

It's a bit of a challenge. I was trying to figure out who are the current activists for the Long COVID community that can - There was a patient representative on this paper, but I'm not sure at this point who is filling this vacuum and there to help this community.

I think we're getting near the end. Just a couple more here. The article, “Neuroinflammation after COVID-19 with Persistent Depressive and Cognitive Symptoms,” was published in *JAMA Psychiatry*. We may need some twin hosts this week in neurology to weigh in on this one. Here they're looking at persistent, depressive symptoms post-COVID using PET scans. They reported higher activity in certain regions of the brain. I vaguely remember these. The dorsal putamen, the ventral striatum, the prefrontal cortex, the anterior cingulate cortex, and hippocampus.

I'm glad I'm not going to have to answer any quiz about those afterward. They suggest evidence for an inflammatory change, elevated gliosis in the brain of individuals with COVID depressive cognitive symptoms. That's the COVID DC. Gliosis, they say, may be subsequent to inflammation, injury or both, particularly in the ventral striatum and dorsal putamen. Which they say might explain some persistent depressive and cognitive symptoms including slowed motor speed, low motivation or energy, anhedonia after what in some cases is just a mild to moderate COVID-19 illness.

VR: I wonder Daniel, so inflammation is a big part of it I'm sure. I wonder if anoxia at any point was also part of it.

DG: I think that would be important to know, to look at, and have that information, because, boy, not getting oxygen to your brain is not something you would expect to leave you without some chronic changes. I think I've got just two more articles and then we're going to wrap it up. The next article maybe is going to give us a little bit more insight into what we discussed from the RECOVER study. The article, “Long COVID Clinical Phenotypes up to Six Months after Infection Identified by Latent Class Analysis of Self-reported Symptoms, published in *Open Forum Infectious Diseases.* These are the results from a multi-center prospective study of symptomatic adults tested for SARS-CoV-2 with prospectively collected data on general symptoms and fatigue-related symptoms up to six months post-diagnosis. Not just at six months, but up to six months.

These investigators identified symptomatically homogeneous groups among participants with COVID-19 and among others without COVID-19 at each time period for both general and fatigue-related symptoms. Among 5,963 baseline participants 4,504 COVID-positive, 1,459 COVID-negative. 4,056 had three-month and six-month data at the time of analysis. 4,056 at three-month. 2,856 had six-month. They identified four distinct phenotypes of post-COVID conditions at three and six months for both general and fatigue-related symptoms. This I think is a big takeaway. There was substantial class switching over time. Oh my gosh. Those in one symptom class at three months were equally likely to remain or enter a new phenotype at six months. I want to say that's really critical.

Let me just mention the four subtypes. Minimal or no symptoms, fatigue headache and muscle, or joint aches without loss of smell or taste, fatigue, headache, and muscle, or joint aches with loss of smell or taste, multiple miscellaneous symptoms. I think this is really key because what was suggested from the RECOVER analysis is, "Now we've defined our four phenotypes, and now we can try specific things with each phenotype. What if people are bouncing around from phenotype to phenotype? That's going to impact our study design." I think this is important to consider.

The last, and I think this is ongoing issue, the article, “Coronary Microvascular Health in Symptomatic Patients with Prior COVID-19 Infection: An Updated Analysis,” published in the *European Heart Journal Cardiovascular Imaging.* I wish I could phone a friend. I think we need this week in radiology or this week in cardiology. We've got a few cardiology friends out there, right, Vincent?

VR: Yes, we do.

DG: [laughs] Basically they're looking at the microvascular health of the heart post-COVID using PET scans. Now, cases consisted of patients with previous COVID-19 who had clinically indicated positron emission tomography, PET imaging, and were matched one to three on clinical and cardiovascular risk factors to controls having no prior infection. Myocardial flow reserve, MFR, was calculated and comparisons between cases and controls were made for the odds and prevalence of having impaired MFR. They're using a cutoff of less than two. The median inter-quartile range number of days between COVID-19 and infection and PET imaging was 174 with 53 through 338. Patients with prior COVID-19 had a statistically significant higher odds of impaired myocardial flow reserve. Less than two, adjusted odds ratio of that 3.1.

So, three times as likely to have impaired myocardial flow reserve, get a P value of less than 0.001. Now the results were similar in clinically meaningful subgroups, a bunch of subgroups, and the proportion of cases with this MFR are less than two peaked - are you ready for this - six to nine months from imaging ,with a statistically non-significant downward trend afterward, comparable across the variants, but increased with increasing severity of infection.

All right. I will wrap up here with as I've been saying, no one is safe until everyone is safe. Let's continue to spread the knowledge. I do want everyone to pause the recording right here. Go to parasiteswithoutborders.com and click ‘Donate,’ even a small amount. Every bit helps us continue our work. We are now in the middle of our Foundation for International Medical Relief of Children fundraisers. May, June, and July donations made to PWB will be doubled up to a potential donation of $20,000 for FIMRC.

VR: Time for your questions for Daniel. You can send them to Daniel@microbe.tv. Had a question last night on the live stream, Daniel. Someone wanted to know, do Queens and Nassau County hospitals have the three-day outpatient remdesivir infusion?

DG: In our local area, actually, the Catholics have stepped up and done this, and actually some of the Northwell hospitals as well. Yes, actually we do in the local area.

VR: All right. Carol writes, "I've tweeted that there's no adverse effect of mRNA vaccines that isn't also a result of COVID infection and that with COVID infections, it's almost always worse, but I'm not 100% sure that's completely accurate. What do you say?"

DG: That's an interesting comparison. It's probably true. I want to add I guess the nuance here. We just talked about cardiac damage. We talked about how after COVID, a significant number of people have cardiac issues, and then we talked about that rare, but identified risk that particularly peaks in adolescent males might be a slightly different mechanism. Some might take issue and say, "Well, it's a slightly different phenomenon." Guillain-Barré I think we see that much more often with COVID infection than we do with vaccines. This is an interesting way of putting it. I think in general it's true, much, much safer to get vaccinated than to get COVID, fewer, fewer issues with vaccinations but we have identified, unfortunately, some.

VR: "Can you also discuss the claim that mRNA vaccines are causing 'turbo cancer?' Cancer is one of the diseases I don't see being caused by mRNA vaccines but is caused by some viruses. My understanding is that the recent increase in cancer diagnosis following a decline because people were avoiding being screened from fear of getting COVID and hospitals being overrun with COVID patients."

DG: I would suggest that's in line with misinformation. I don't think there's any compelling evidence and boy, we have looked, it's not an absence of looking for a connection with the mRNA vaccines and cancer. I remember a few people who are- I remember one prominent person who's no longer with us, that by now everyone who had been vaccinated would be dead. We're still here, we're doing well, actually better off than folks that did not get vaccinated before they got infected. No, I don't think this cancer scare is based on anything solid

VR: FF writes, "Sometime in June, it'll be six months after my second dose of Novavax. I'm trying to make a decision about whether it's worth getting a Novavax booster then, six months after the previous two, or whether I should wait until the fall for an updated Novavax vaccine. Does it make sense to get a booster in June or will this not be effective towards current variants? I live in New York City, had COVID, once, took Paxlovid. I'm very concerned about getting infected as I've heard people getting Long COVID after their second infection and my first appears to already have caused some issues for me with memory."

DG: This is a very timely question as we just discussed. Novavax has decided to and has already started to produce an updated XBB variant. Be reassured as we've discussed many times, T-cells will save us all. It does look like there is a durable ongoing protection against severe disease that we get from the prior doses. It probably makes sense at this point to look at that XBB vaccination in the fall. Hopefully, getting those neutralizing antibodies, hopefully, getting that three- to four-month reduction in even getting infected and all the benefits that come with that.

VR: Jason writes, "When the show opened for *TWiV* 1012, you made a comment that a lot of COVID deaths are now silent. People are dying in facilities, decisions are being made just to make them comfortable. The question I have is, I would like to see more comment on how do deaths in facilities not get counted as COVID deaths? Does this mean physicians don't put

COVID on the death certificate and write something else? Does it mean COVID is not tested for? What does all this mean in terms of hiding deaths caused by COVID and why would this be done?"

DG: I wouldn't think of it as hiding deaths. I would think of it as not seeing them. A physician goes to the hospital and sees their patients, and they're not seeing these individuals, these individuals are not coming into the outpatient practice. These individuals are staying, they're dying at home or they're dying in the facility. They're not being hidden, they are being counted. They are being identified as COVID deaths. As we talked about with the air pollution, yesterday it looked like you were in some movie, maybe *Blade Runner* came to mind for me, where everyone was like, "This looks so horrible." The masks went on. Today, the air quality was still bad. It was about half as severe, still in the orange and red in many zones, but you didn't see it, it didn't have that reality for people. The masks were right back off until your eyes started burning and you started coughing.

I think that's the challenge here. These are not being hidden. They are being counted, but there's an emotional response to seeing somebody in the ICU on a ventilator. There's an emotional response to seeing the isolation rooms in the hospital, and these people are dying quietly. They're dying in hopefully a better, more respectful, more dignified manner, but it's not on the news. There aren't these refrigerator trucks in front of hospitals or anything anymore.

VR: Ryan writes, "Have you seen any evidence about risk to existing aortic aneurysms from COVID infection? I've read a couple of published studies presenting anecdotes, suggesting dissections have occurred from infections."

DG: Yes, be careful. As I've been saying for a while, the plural of anecdotes is not data. There is some endothelial aspect to an acute COVID infection, some endothelial activation. I am not sure there's any clear significance, but if you get COVID and all the inflammation that goes on and the stress, would I be concerned about someone? Would I make, consider this a high-risk condition? I would say yes.

VR: Christine writes, "As I sit here taking Paxlovid for my first case of COVID, now that I'm retired, I have time to get out and get myself a case of COVID, I'm reading about the nitric oxide nasal spray being sold in Israel, Europe and parts of Southeast Asia called Enovid. You see one study in *J Infection*, August, that reports it lowered viral load in the nose and throat, subjects showed faster symptom resolution. They discuss possible decreased transmission. Do you know any reason why this hasn't been studied more in this country? Do you think it would be harmless enough to try if one were to buy it in Israel?"

DG: [laughs]. This falls into that category of interesting, promising and I've seen those curves and there aren't a copy number, so let's make sure we use the right terminology here. It did stay statistically significant as far as the separation. I don't know clinically and I think that's where we are right now. The goal of the FDA, the goal of a lot of physicians in the U.S. is to do no harm. The whole idea of, "Oh, let's just try it," I think we talked about the SSRI deaths where maybe we actually increased the number of people that died by throwing SSRIs. Hydroxychloroquine probably increased the number of people who died and certainly saw a number of people aspirate on their own vomit because of the GI upset it induced. I am not a

huge fan of just trying stuff until we really understand the safety profile and the benefit that comes with that.

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

DG: Oh, thank you. Everyone be safe.

[00:41:29] [END OF AUDIO]