This Week in Virology

TWiV 1136 Clinical Update

Host: Vincent Racaniello

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 1136, recorded on August 1, 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. I don't like the fact that it's early August. That means the summer's passing much too quickly.

VR: It always goes quickly. It's June, July, August, really. Not technically, but that's really the those are the best months.

DG: You know what, it must be. I was listening to *This Week in Neuroscience*, it's the temperature.

[laughter]

It affects our sense of time, maybe. Probably not.

VR: What's on your tie today, Daniel?

DG: Let's see. What is that? I think it's influenza, which is appropriate. I picked it because it's one of the articles we're going to talk about. Let's jump right in. We've got a lot to talk about today and then I've got to get out sailing. I will start off with a quote by Jonas Salk. I don't know if you're familiar with this researcher, but the quotation, "The reward for work well done is the opportunity to do more."

VR: That's a good quote, but Jonas, after his vaccine, didn't do anything else.

DG: There's actually another quote about something like, "That's the problem with success." When I when I had success, I realized it was all over for me. There's something about, work well done, but there is - I think if we look at Nobel Prize winners, there's a few other examples where when someone sort of has this huge breakthrough, sometimes after that, there's not a lot. That's the interesting thing, the Nobel Prize was the whole idea that, oh, you're going

to identify people who have done exciting work and are going to do more. But a lot of times when that Nobel Prize or some great discovery comes, that's all you've got.

VR: People, if they get it when they're advanced in age, like Peyton Rouse got it shortly before he died.

DG: Yes, and there was a there was a Nobel Prize winner that I had lunch with like a couple of months before they died. There was a rumor that they died and they didn't know, and the award was announced.

VR: Oh, Ralph Steinman? He's the only person who got it posthumously, right?

DG: Yes, because you're not really supposed to. I guess they made the decision before, but they hadn't communicated…

VR: They didn't know.

DG: All right, let's start with what I think is a really important article. I got a lot of important articles this week, interesting enough, but, "Trust in Physicians and Hospitals During the COVID-19 Pandemic in a 50-state Survey of U.S. Adults," published in *JAMA Network Open*. Here, the investigators sought to characterize changes in U.S. adults' trust in physicians and hospitals over the course of the COVID-19 pandemic, and the association between this trust and health-related behaviors. This survey study used data from 24 waves of a nonprobability Internet survey conducted between April 1, 2020 and January 31, 2024. Good dates there if you think about it. Among 443,455 unique respondents aged 18 years and older residing in the U.S. with state-level race, ethnicity, age, gender.

Now, the combined data included 582,634 responses. Overall, the proportion of adults reporting a lot of trust for physicians and hospitals decreased from 71.5% in April 2020, that's our baseline, down to 40.1% in January 2024. Not great. I will actually we'll go back to another study in a moment, but prior to this, when you had this 71.5% or higher level of trust, it was very hard to figure out who are the people that didn't trust docs and why.

In regression models, features associated with lower trust as of spring and summer 2023 included certain age range, so 25 to 64 years of age, female gender, lower educational level, lower income, black race living in a rural setting.

The association persisted even after controlling for partisanship. I think that was a natural go-to. People could thing, oh, you see, but apparently, you don't see. In turn, greater trust was associated with certain behaviors. If you trust doctors, more likely to get vaccinated about five times as more likely to get your COVID shot, about five times more likely to get your flu shot, about four times more likely to get that SARS-CoV-2 booster.

A little bit of discussion here. Vincent, please feel free to jump in. The authors conclude that we have lots of ideas on why this is happening. Then they reference this prior Cochran Review, which goes back to when there used to be a lot of trust for physicians. There they looked at a lot of different variables and they really could not find any meaningful intervention that was associated with this change in trust, because a lot of it is, oh, maybe the physicians are talking for a pharmaceutical company and that erodes. Apparently, that wasn't an issue, as we saw

here, partisanship didn't really matter, your politics. This was across the board, but any thoughts, Vincent?

VR: What is the main driver of this? Do you think it's all about vaccination and side effects?

DG: I don't know, because it's interesting, there's an issue here with trust for physicians. There's also an issue with trust for hospitals. The institutions starting to be this concern or why are you really there, because it used to be this idea that, you went to your physician and a lot of times you get a different result when you ask about, do you trust your doctor as opposed to doctors in general? I'm not sure, and I think that's the reality here, is we need to figure this out, because a lot of our ideas about, you see it's about partisanship, you see it's about physicians, maybe, talking for a pharmaceutical company. A lot of those things just really haven't panned out. I don't think we actually know what's going on.

VR: The idea that it's in people with less education is disturbing, right? Because it's probably stemming from misunderstanding. That's hard to correct in someone who may be hard to teach, right?

DG: I wonder, too, we always put a lot into this edutainment, this science communication, trying to let individuals know that physicians, that scientists, I love your line, what do you do? I work for you. That's really what physicians do. They often ask like, "Oh, who do you work for?" I've started using that at the bedside saying, "I work for you. No matter who signs my paycheck, my oath is to you, and that's my commitment." Hopefully shows like this, maybe we get a little more listenership are the chance for people to hear from scientists, from physicians, reliable, unbiased, honest information.

VR: I think having physicians on programs like this can help. You doing this is great, and what is it, Roger Seheult on *MDCram*, right?

DG: Yes, *MedCram*.

VR: I think that's mainly for med students.

DG: Yes, a lot of med students listen to that. That has a that is a pretty good listenership.

VR: The people in this study who were identified as mistrusting are not going to watch those. It's not easy to reach your audience.

DG: Maybe they'll watch like *Doctor Mike Reacts*. That's another popular - but this is a huge problem. We're going to erode away our ability to help people make choices that are in their best interest. We're about to talk about flu vaccine, and if folks are not getting the flu vaccine, it can't help you. If you're not getting your COVID vaccine, it's not helping you. If you're not getting your booster and that would be appropriate for you, again, you can't get the benefit. This is certainly something we need to better understand and try to intervene.

We're going to move into new technology vaccines and the flu. This is the article, the bow tie-inspired article, "The Potential Benefits of Delaying Seasonal Influenza Vaccine Selections for the Northern Hemisphere: A Retrospective Modeling Study in the United States," published in *JID*. This is not delaying when you get your flu shot, this is delaying when we have to make

the selection of what to cook up for the vaccine, so that we can hopefully shorten the time between making that decision, getting it out there, and hopefully get a better match. Let's talk a little bit about the background.

A couple important background points. Influenza vaccine reduces the risk of medically attended influenza by 40% to 60% in the seasons when the vaccine viruses are well-matched with circulating viruses. About a 50% reduction in folks that end up having to seek medical attention. We've talked about an even bigger difference in reducing deaths if we get a good match. When there is a mismatch, not so good.

Now, how does this work? How do they make the sausage? Each year, the WHO convenes a meeting in February to select the vaccine concoction for the upcoming North. Then they're going to have a meeting in September to select the influenza vaccine for the upcoming Southern Hemisphere flu season. We'll think about the February. You're going to pick in February, what's going to be happening almost a year later, so December, January of the next year?

Now, they get a lot of data here, they review biological surveillance data from the Global Influenza Surveillance and Response System, the GISRS. They look at epidemiological, antigenic, they'll get genetic characteristics of influenza viruses that have been circulating since they last got together. Then they try to choose this candidate vaccine to hopefully get broad coverage across the diverse circulating antigenic groups. Why so much lead time? Why February to predict what's going to happen the next year?

This has a lot to do with the existing technology. The existing timeline for seasonal influenza vaccine decision was established to allow sufficient time for bulk vaccine production, which primarily relies on fertilized chicken eggs. Now the egg-based vaccines account for about 85% of global production capacity for seasonal flu vaccines. This many-month gap between the vaccine selection and the start of distribution gives a chance for the viruses to change, further evolve, and you end up with an increased risk for an antigenic mismatch. Now, is there a solution?

Now the next generation, these next generation influenza vaccines that we've talked occasionally about, the cell-based, the recombinant and the messenger RNA vaccines can eliminate the reliance on egg supply for production. This can really shorten the vaccine production times down to one to three months. Thus, you can end up with a better match between these vaccines and viruses, what viruses might be circulating. This all sounds great. Why don't we just go ahead? What about doing a little bit of science? Here they do this modeling study, where the authors aim to identify a prior influenza season, where this opportunity could have actually made a difference. They're going to look at the Northern Hemisphere, if we approach this with rapid vaccine production, and they're going to try to quantify the impact of this delayed decision.

Their model showed that with rapid vaccine production, revising current timelines for vaccine selection could actually result in substantial epidemiological benefits. As we get an example, for instance, back in 2014, an updated H3N2 vaccine could have averted up to 65,000 influenza hospitalizations in the U.S. that 2014-2015 winter. Sort of a call to action, a little bit of data suggesting that we might want to think about this. I can think about a little bit of a

parallel with the COVID vaccines, where they want extra time to make sure Novavax has enough time. I think Novavax has enough time. I don't think you need to pick in February what's going to happen. We've already sort of pushed that to June. Just think about our experience when you have a change and you get a bit of a mismatch.

VR: I think we have technology to reduce vaccine production times, so this should be possible.

DG: Here's some data showing that really, it really can make a difference. That's tens of thousands of folks.

Now, this should not be controversial, but we have the article, "Personal Protective Effect of Wearing Surgical Face Masks in Public Spaces on Self-Reported Respiratory Symptoms in Adults: Pragmatic Randomized Superior Trial," published in the *BMJ*. Hey, if I wear that surgical mask, am I less likely to get sick? To evaluate the personal protective effects, this is about you, wearing versus not wearing surgical face masks in public spaces on self-reported respiratory symptoms. They looked at 4,647 adults, 18 and over. Basically, got half of them are going to wear a surgical mask in public spaces, like shopping centers, out on the street, public transport. Then the other half are not going to do it. They don't talk about at home, this is this is when you're out in public. We got a little over 2,000 in each arm, we're going to study this over a 14-day period. We end up with 8.9% of the people wearing masks had self-reported symptoms consistent with respiratory infection; 12.2% in the folks that did not wear a mask. About a 30% reduction in getting sick by just wearing a surgical mask for this period of time.

I do want to want to have people think about surgical mask, right? We're all thinking COVID, I wonder if that would really do much for me. We always talk about surgical masks protecting other people from us, but here we have us being protected. This is not necessarily just about COVID. This is a lot about a lot of other things that the mask might protect us, other respiratory pathogens. Let's move on to COVID.

VR: I'm sorry, those are not bad numbers, actually, right?

DG: They're really not bad. Basically, you end up with like 12%, you think about it's the height of like, whatever respiratory thing, flu, all these other respiratory things, 12% of people are getting sick, and you can drop your risk by 30%. Hey, how inconvenient is it to actually wear that mask when you maybe you're on the train, or maybe you're in a public crowded, poorly ventilated situation.

VR: These are surgical face masks, so you can probably do even better.

DG: Yes, if you had a more proper like an N95.

VR: Or even a KN, right?

DG: Yes. Not bad, and pretty compelling, statistically significant data. All right, COVID, still having some problems there in Puerto Rico, still in that 6% to 8% of all deaths in Puerto Rico are due to COVID. We're seeing in that 1% to 2% in a lot of parts of the country, that's like New York and the Northeast here, Texas, California, Alaska. A lot of the country is down to less than 1%. We'll keep an eye on that.

Wastewater, not so good, really did surge up there. It looks like we may have gotten a little bit of a peak in the West, but the peak this summer, actually was up there basically at like last winter levels for some of these places. The South is still on an exponential rise, at least from the data we have. A lot of other places look like they're peaking at a little bit lower level. Fingers crossed, and we're definitely seeing a lot of folks in hospital.

VR: One of the speculations, it's been so hot this summer that people are going indoors, gathering, where it's cool, like theaters and so forth and homes, and they're less outside, right?

DG: Maybe the shopping malls.

VR: Yes, sure.

DG: It is interesting, though. I like that for COVID, but I wonder, why COVID? Why not flu? What's the difference there?

VR: That's it, flu does not do this, and so I think there's biologically something different about the two viruses, obviously, and that's controlling this difference, yes?

DG: Yes. All right. Now we're going to move into a vaccine. We've got a couple vaccine papers here. The first, I think this is a good one, there's this whole idea like, Oh, I don't want to get a vaccine. I want to worry about my heart. Maybe we're going to see that you should get that vaccine because you're worried about your heart. This is the article, "Cohort Study of Cardiovascular Safety of Different COVID-19 Vaccination Doses among 46 million Adults in England," published in *Nature Communications*. I'm thinking this should be cardiovascular protection provided by different COVID-19 vaccination.

For background, we go into this article already with some data that COVID-19 vaccines had led to an overall reduction in cardiovascular events. Now, here using longitudinal health records from 45.7 million adults in England, between December 2020 and January 2022. This study compared the incidence of thrombotic and cardiovascular complications up to 26 weeks after first, second, and booster doses, the different brands combination of COVID-19 vaccinations used during the UK vaccination program.

Over the study period from the 8th of December 2020, to 23rd, January 2022, 45.7 million individuals met the eligibility criteria for first dose analysis. Among these, 37.3 million people received a first ChAdOx1, BNT-162b2, that's your Pfizer BioNTech, or the Moderna mRNA-123 vaccination, and were eligible for second dose analysis. The incidence of common arterial thrombotic events, so that's basically going to be your heart attacks, your myocardial infarctions, your ischemic strokes, were generally lower after each vaccine dose. Similarly, the incidence of common venous thrombotic events, so mainly pulmonary embolism, lower limb deep-vein thrombosis was also lower after vaccination.

Now we have the battle of vaccines. Now that we're all excited, we want to get our vaccine, which is better? "Real-world Comparative Effectiveness of a Third Dose of mRNA-1237," (Moderna), "versus BNT-162b2," (Pfizer-BioNTech), "among Adults Aged Greater or Equal to 65 Years in the United States," published in the journal *Vaccine*. These are the results of an observational comparative vaccine effectiveness study conducted using administrative claims

data from the U.S. HealthVerity database. They're looking September 22, 2021 to August 31, 2022. A third dose of these different vaccines was assessed for preventing COVID-19 hospitalizations and medically attended COVID-19 among adults age 65 and over. The hard data preventing hospitalizations, medically attended issues, not just getting the sniffles.

Overall, we've got over 90,000 individuals in each of these groups. We're going to look at COVID-19 relative hospitalization rates per 1,000 person-years. We get for the Moderna, 5.61, for the Pfizer-BioNTech, 7.06. Medically attended COVID-19 rates, Moderna, 95.05, the Pfizer-BioNTech, 106.55. A little bit of a squeak out for the Moderna in these.

VR: You think that is a relevant difference?

DG: I don't know if it really is. It's, I guess, at a population level. At a population level, when you're negotiating for prices, and if you're looking at a population, you might say, OK, yes, but then when you look at number needed to vaccinate, to really figure out what the price difference, et cetera, should be.

VR: Because with the confidence intervals, the two are really similar.

DG: Yes, they're really close. It might just be a 0.02 difference, as far as confidence intervals.

VR: I would have liked them to throw in Novavax here.

DG: I certainly would have liked them to throw in Novavax. COVID early viral phase, we keep leaving in links to the NIH COVID-19 treatment guidelines. Just everyone should be aware of these, share them. Apparently, they might be going away. The NIH may have felt like they did their deal and people should be on board, but we'll leave in those guidelines. We also have the IDSA guidelines. Really a great way to direct your provider or providers to look at, what is the most up-to-date, evidence-based guidance. It is number one, Paxlovid, number two, remdesivir, three, molnupiravir, four, convalescent plasma in certain groups. Remember the isolation guidance. You are contagious. You can give this to other folks.

Then same, early inflammatory. This is that second week when you might get the cytokine storm. Steroids at the right time in the right patient, right dose. Anticoagulation guidelines, pulmonary support. Remdesivir still in the first 10 days, and in some cases, immune modulation. A chunk of today is going to be devoted to Long COVID. I will start off by saying, nobody wants to get diagnosed with diabetes. We have the article, “Incidence of Diabetes after SARS-CoV-2 Infection in England and the Implications of COVID-19 Vaccination: A Retrospective Cohort Study of 16 million People,” recently published in *The Lancet Diabetes and Endocrinology*.

Now, while some studies have shown that the incidence of diabetes increases after a diagnosis of COVID-19, I've still noticed that not everyone is convinced by the data we have so far. This is one more attempt to investigate this potential issue. These results come from a retrospective cohort study where they investigated the diagnoses of incident diabetes following COVID-19 diagnosis in England in a pre-vaccination, vaccinated and unvaccinated cohort using linked electronic health records. People alive and aged between 18, and you ready for this, 110 years, registered with a general practitioner for at least six months before baseline and with available data for sex, region and area were included. 16,669,943 people

were included in the pre-vax cohort, 12,279,669 in the vaccinated cohort, 3,076,953 in the unvaccinated cohort. Where did they get those people?

In the pre-vaccination cohort, the adjusted hazard ratio for the incidence of Type 2 diabetes after COVID-19, compared to before or in the absence of the diagnosis, 4.3 in weeks one through four and 1.24 in weeks 53 through 102. The adjusted hazard ratios were higher in unvaccinated people than vaccinated people, higher in patients hospitalized and patterns were similar. Interesting enough for diabetes Type 1, although excess incidence did not persist beyond one year after COVID-19 diagnosis.

The authors conclude that elevated incidence of Type 2 diabetes after COVID-19 is greater and persists for longer in people who are hospitalized in COVID-19 than those who are not. Markedly less apparent in people who had been vaccinated against COVID-19.

We have another article here. We have the, "Post-COVID-19 Respiratory Sequelae Two Years after Hospitalization: An Ambidirectional Study*,"* published in *The Lancet Regional Health Americas*. Here's a cohort of COVID-19 patients admitted to the Hospital das Clinicas da Faculdade de Medicina da USP in Sao Paulo, Brazil between March and August of 2020, followed up six to 12 months after hospital discharge. A subset of patients with pulmonary involvement and chest CT scans were eligible to participate in the follow-up at 18 to 24 months. From 348 patients eligible, 237, so 68%, participated in this follow-up. Among participants, 58% of patients presented ground glass opacities and reticulations, 33% presented fibrotic-like lesions. This is traction bronchiectasis, this is architectural distortion.

Now, 2% of the patients improved, 25% presented worsening of lung abnormalities. For those with relevant assessments at both occasions, comparing the CT findings between this follow-up with the previous assessment, there was an increase in patients with that described architectural distortion and this traction bronchiectasis. Traction bronchiectasis, think about sort of a scarring and a changing where the scarring is pulling on parts of the lung into an abnormal morphology. The patients presented a persistent functional impairment with demonstrated restrictive pattern in both follow-ups, 42% and 44%, and reduced diffusion capacity, 42%.

What were the risks? What put people at more risk? Length of hospitalization increased, increased invasive mechanical ventilation. If you ended up on a vent, about three times as likely. Patients' age, it's that 110-year-old pulling things, and consistent predictors for development of fibrotic-like lung lesions. Tough here that, and I think this is one of those things. If you have lung damage during the acute process, you might have sort of an ongoing process that follows you.

VR: Did any of these patients have Long COVID?

DG: In a sense, this is a type of Long COVID, these are folks that have respiratory impairment. It's interesting, this is why they like to use that post-acute sequelae, because they may not have the fatigue, they may not have the brain fog, they may just have damaged lungs as their sequelae.

VR: These patients had some symptoms persisting a long time?

DG: A lot of these did, a lot of these had, because they've got basically lungs that don't work.

All right. Hearing loss. The article, "Incidence of Hearing Loss Following COVID-19 Among Young Adults in South Korea: A Nationwide Cohort Study," published in *eClinical Medicine*. This study was conducted to determine the association of COVID-19 with hearing loss and what they call sudden sensory neural hearing loss, SSNHL in young adults. Huge issue. You get COVID, now you can't hear. The nationwide population-based cohort study used data from the Korea Disease Control and Prevention Agency COVID-19 National Health Insurance Service.

This study population consisted of young adults, age 20 to 39, without a prior history of hearing loss. All participants were followed up from July 1, 2022, until they either developed hearing loss, death, or December 31, 2022. Big study, a total of 6,716,879 young adults were eligible for analyses. During these over 40 million person-months of follow-up, 38,269 cases of hearing loss, and 5,908 cases of this sudden sensory neural hearing loss were identified. The risk of hearing loss, 11.9 versus a background of 3.4, really pretty significant, like basically a three- to four-fold increased risk of hearing loss in the folks that got COVID-19 compared to the no COVID-19 group. They looked at a bunch of different parameters and the results were consistent when they did this secondary analysis.

VR: What do you think is the mechanism there? Do you think it's an inflammatory process?

DG: I do, actually. I do. We definitely see a lot of, say, post-COVID neuropathy. Sometimes it's an autonomic dysfunction. Here, I think we're seeing a neuritis involving hearing. Over 38,000 cases of hearing loss, almost 6,000 cases of this sudden sensory neural hearing loss. Not great.

This is going to wrap it up for us before we get to emails. "The Effect of Long-term COVID-19 Infection on Maternal and Fetal Complications: A Retrospective Cohort Study Conducted at a Single Center in China," published in *Scientific Reports*. In a lot of ways, I'm glad I didn't have all this data when I was first on CNN back in March of 2020, because the more we learn about getting COVID-19 during pregnancy, the more concerned I am. Here, in order to investigate the effect of long-term COVID-19 on maternal and fetal complications, these researchers performed a retrospective cohort study looking at 623 pregnant women who delivered in Kunming First People's Hospital from November 1, 2022 to July 31, 2023.

In the 623 study, there were 209 pregnant women with acute COVID, 72 pregnant women with Long COVID, 342 pregnant women without COVID. Pregnant individuals who developed Long COVID during their pregnancy had an increased risk of experiencing gestational hypertension over 3.3-fold odds ratio, gestational diabetes, odds ratio 2.3, fetal intrauterine growth restriction, odds ratio 2.8.

VR: During pregnancy, it's long enough that you can develop Long COVID?

DG: Yes. It's nine months, and whether you use the eight or the 12-week, it's enough time for you to get COVID and then continue to have ongoing issues. It's interesting to look at the figures because the acute COVID was kind of maybe OK, but it was really the people that developed the Long COVID that weren't better at two to three months that were at highest risk for all these different issues. They're at risk for all the other issues we've talked about with acute COVID.

I want to say no one is safe until everyone is safe. We just switched. We're now in August, so the Floating Doctors fundraiser. Go to parasiteswithoutborders.com, click on the Donate button. Every small amount helps. We are going to be doubling your donations up to potential maximum donation of $20,000. We really need your support. I have to say, we just didn't quite make the $10,000 for the Foundation International Medical Relief of Children. I had to add a little bit to get us to the $20,000 there. Let's not do that. Let's remember, these folks are out there just doing tremendous work. We're trying to do tremendous work, and we need your help, so be part of it.

VR: It's time for your questions for Daniel. You can send yours to danielatmicrobe.tv. Will writes, "Thanks to you, I humbly think of myself as reasonably well-informed. As well as following TWIV, I always listen to the two-weekly *Osterholm Update* and the DataReport.info daily Pandemic Update. While the latter is presented by a complete layperson, he tries to communicate the results of latest reports on COVID activity in the U.S. as faithfully as possible to help his audience stay informed. However, in today's episode, he was asked a question about durability of vaccines and how long they remain protective. His answer revealed that even he really did not understand the way that vaccines protect. He did not differentiate between short-term infection and severe disease.

It's my perception that he represents the vast majority of the public. They always assume that vaccine protection is against infection, not against the risk of severe disease. One knock-on effect of this is to devalue the wearing of N95 respirators, which do give significant protection against inhaling SARS-CoV-2. I'm writing this to request that any time you mention vaccine efficacy, you make it absolutely clear it's fundamentally against severe infection and death. Protection against infection is a variable short-term benefit. There's still a vast amount of education that's needed, and as a trusted source, your constant reminder will help. Will."

DG: Thank you for writing, Will, and also nice shout out to Mike Osterholm. Actually, I support CIDRAP, sent them some money the other day. They're another great source of information, and I think that when they teach vaccines, we really have to reinforce, like what do vaccines do? Vaccines keep you from getting sick. They do not keep you from getting infected, that needs to be on all the tests, and so you get that right, and then you actually understand what vaccines are about. We will keep reinforcing that, I assure you.

VR: Boris writes, "My question regards vaccination strategy for the coming fall. I have dutifully followed your recommendations, and those of my physician, receive mRNA vaccines every year. I'm intrigued, however, by the potentially greater durability of Novavax with its upcoming new formulation. Are there any data for the efficacy of Novavax as a booster on top of mRNAs? I received my sixth shot October 2023, and was infected with my first mild case of COVID two months later. Paxlovid definitely helped minimize disease progression, but I would like to avoid that in the future."

DG: Boris, thanks for the email, and we've talked about that a little bit. We've mused there is a suggestion that maybe there's a different durability with the Novavax vaccine, and for a lot of folks that might be considering Novavax this fall, it would be on top of prior mRNA vaccines. We've shared the data that we have, but as we get more data, we will definitely share it.

VR: Matt writes, "Two items. One, I recently saw an 88-year-old patient who had received only two mRNA vaccines in 2021. She presented on day seven to eight of COVID, feeling very sick with fatigue, cough, congestion. In our parking lot outdoor assessment area, her Sa02 was 92 to 94 percent. I triaged the patient to the ER for further assessment and treatment of hypoxic COVID. In the ER, her Sa02 was mostly 95% with one dip to 93. Chest x-ray clear, and CBC/chem panel looked OK. She was discharged from the ER without treatment.

When I called her the next day, she remained quite ill. She survived, but she has felt unwell for several weeks. How sustained does a low Sa02 need to be before considering steroids and remdesivir?

DG: Let's start off. I guess, there's two questions here. This is an interesting question. We've talked about particularly the recover trial where it was this less than 94%, 93%, 92%, one or two there, is it? These are going to be the people on the edge, because they use that line, but a lot of the people that we're seeing in the benefit probably are people down in the 80s, versus people, above 94%. If you're in sort of 92 to 93, we don't have a specific study where we just looked at them.

The other, which is interesting, is that we've talked about, what are the things that have an impact on Long COVID, right? One is getting the proper antiviral in that first week, getting your mRNA vaccine or your Novavax vaccine, basically getting vaccinated. The other is giving steroids to the appropriate person at the right time. Sort of an interesting question here. If she was in the 80s, clearly we have that evidence that getting steroids to those people can reduce their risk of having a prolonged experience with this. Again, she's right there in that zone where we're not really sure.

VR: The second question, "Is there ample discussion on the pricing and cost of Paxlovid and molnupiravir? Yesterday, I had a patient and pharmacy ask me to switch from molnupiravir to Paxlovid in a renal compromised patient with multiple Paxlovid drug interactions because the share of cost for Molnupiravir was out of reach for the patient, but Paxlovid was apparently covered by insurance at a lower copay. Apparently, the two main oral COVID medications are not even covered at the same level."

DG: This is tough, actually, you go the other way, certain private insurances that don't cover Paxlovid. That's why there's the PAXCESS program where a person, you can even help them, they enroll, they get a special card, they end up not paying at all.

Paxlovid can be a little bit of a challenge, and glad that you were able to, assuming able to navigate this, but we can renally dose the Paxlovid. We can often manage these drug-drug interactions. It's a superior drug than molnupiravir. We have pretty good data on that. It's pretty interesting, this is the landscape of the way things work in the United States.

VR: Karen writes, "I'm writing on behalf of a 97-year-old relative who caught her first case of COVID a week ago. She was given Paxlovid promptly and has a mild case, but COVID seems to have retriggered the sharp muscle pain in her groin that she'd suffered after breaking her hip in a fall at the beginning of May. The doctors deemed her too old for surgery. She's eager to know why would the return of this pain happen? Is it a recognized consequence of COVID? How could it be remedied?" She gives a lot of details on how fit this individual was and had

been doing a lot of exercise, "but now with COVID, even walking a few steps around the house is painful. The isolation is making her stir crazy and she's very eager to get back to her daily walks. She would like to know any suggestions."

DG: We certainly see this and we see it at two levels. One is the first week, it's a viral illness and you feel crummy and things hurt. If you had a bad shoulder, now you feel that bad shoulder. If you had a bad hip, here we had this hip fracture, you're going to start feeling that. We also then see that during the second week when we have that inflammatory surge.

The isolation, I'm sorry about that. That's this issue that you're contagious. It sounds like you're doing all the right things here, the prompt Paxlovid in this high-risk individual. Fingers crossed, most cases in a situation like this, we would expect a good outcome.

VR: Jay writes, "After having COVID, many things seem gross and contaminated. I can wash the laundry, run the dishwasher, and sanitize clean surfaces, what about personal care items? Should the contacts lens wearing COVID patient toss out the lenses they were wearing when they fell ill? If so, when's it safe to start a new pair? They aren't cheap. How about toothbrush and toothpaste? With strep, we're advised to throw out the toothbrush after a few days of antibiotics. Is there any similar advice for viruses? I would not want any of my items reinfecting me, or somehow infecting those in my household."

DG: I remember I had a physician assistant. His name was James when I was out in Colorado. He did the whole strep throat. He had his whole throw out the toothbrush, issues with toothpaste. He had a whole thing. None of that is really evidence-based.

One of the nice things about having an immune system is that if you got this and you go through this, you don't necessarily have to go through this rigmarole. Yes, don't lend your contact lenses to someone else, which you shouldn't do anyway. Don't lend your toothbrush to anyone else, that's just gross. I think my wife and I have separate toothpaste, but that's her issue. But I understand the psychological response here, but, I'm not sure you need to worry about any of this stuff.

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

DG: Oh, thank you. And everyone be safe.

00:42:39] [END OF AUDIO]