This Week in Virology

TWiV 1054 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. [music]

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1054, recorded on October 19, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today here in Chicago, Illinois, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: We're back in another city, Daniel. What are we doing here?

DG: We are here at the American Society of Tropical Medicine and Hygiene annual meeting. I think it's up into the 70s now. This has been going on for a while. As I was saying, this is perhaps my favorite meeting of the year. The bunch of us, the PWB board members, I was talking to Chuck and Dickson this morning, we all got our new COVID vaccines 14 days ago, so we'd have peak humoral immunity for this.

VR: You're not going to repeat last year's episode?

DG: I still have not gotten COVID, so I feel left out.

VR: Not that you know of.

DG: I'm like a gardener who never owned a plant.

VR: You don't know. You might have had an asymptomatic infection.

DG: I may have had an asymptomatic.

VR: Why don't you do some antibodies? You'd have to look for a protein antibody.

DG: I've done. I guess that's the issue. We talked about this with Rich Condit, is people who've been vaccinated don't necessarily get a nucleocapsid antibody response. They cleared so quickly.

VR: On infection, you mean?

DG: Yes, on infection.

VR: Interesting.

DG: You got a positive spike because you got your vaccine, and then you don't get a nucleocapsid because that vaccine is jumping in so quickly, so I may never know. I hope I never know. All right, let's jump into it. Hello, everyone, and welcome to ASTMH. I'm going to start with our quotation. “Most people do not listen with the intent to understand. They listen with the intent to reply.”

VR: That is really good. I like that. Here on *TWiV*, we listen with the intent to understand, right?

DG: I think our listeners are a special group, and I think they know that. I think they do not make this mistake. It's so true when you have a conversation. The person, they're not listening to you. They're just preparing their response.

VR: I do that myself. I'm waiting to jump in so I can say what I want. You're right. You should be listening until they're finished.

DG: Yes. In one of our podcasts, you usually give us the chance to jump in.

VR: For sure. For sure.

DG: All right. That was by Stephen Covey, *7 Habits of Highly Effective People: Powerful Lessons in Personal Change*.

VR: Who's highly effective people? I don't -

DG: I don't know who they are.

VR: How do you get into that club?

DG: We'll have to ask Stephen Covey. I should have asked him. There was a time when I won an award and he came. I failed to take advantage. We're going to start off with polio. Recently in Reuters, we hear the release, “European Union together with the Bill and Melinda Gates Foundation and the European Investment Bank, have announced a new financing package of more than €1 billion to eradicate polio,” the EU and the Foundation said on Wednesday, that's Wednesday, October 11.

I like this number. Cases of polio have declined by 99% since the 1990s, thanks chiefly to mass vaccination campaigns worldwide. However, eradicating the disease completely has proven more challenging. The wild form of polio is now only endemic in Afghanistan and Pakistan, but the vaccine-derived strain is now widespread. I just want to - 99% of what? This virus once paralyzed 7,000 children every week and now only nine people in this last year.

VR: Let's make it clear that what we are eradicating is the disease, not the virus.

DG: Yes.

VR: We cannot eradicate polio virus. Not possible. Perhaps with extensive immunization, the problem, as you point out, is that the vaccine-derived viruses are causing more polio globally than wild polio. We continue to use those polio vaccines. As long as you use them, you're going to have polio. It's a real problem.

DG: Yes. This is amazing. I know, after this, I'm going to go to Peter Hotez's talk, where there's a lot of, we'll say, anti-science out there, a lot of misinformation. You just look at that, 7,000 children every week getting paralyzed.

VR: While you're at Peter's talk, remind him that we do our job to counter bad science information here on Parasites Without Borders and MicrobeTV.

DG: OK. I'll talk to him.

VR: Get up and ask a question, OK?

DG: Yes, right after we work on, I'm going to help him with his bow ties. They're a little frayed there. Moving on to influenza. The *MMWR*, "High Influenza Incidence of Disease Severity among Children and Adolescents Aged Less Than 18 Years - the United States 2022 through 2023 Season," was recently released. Right up front in the summary, we read that the 2022-23 influenza season began early, coinciding with circulation of other respiratory viruses. High hospitalization rates among children and adolescents were observed - among children and adolescents hospitalized with influenza.

I just want to point out, children and adolescents are getting hospitalized during this season. Hospitals participating in the Influenza Hospitalization Surveillance Network, a lower proportion were vaccinated. We were falling down there compared with prior seasons. We almost dropped in half, down to 18% from about 36% to 42%. Yes, about 82% of the children hospitalized were unvaccinated. We also had earlier influenza circulation during the season. Among symptomatic hospitalized patients, receipt of antiviral treatment was only 65%, so lower than during pre-pandemic seasons.

Now, I find the following numbers difficult to put in context, so let's go through what we've got here. During this season, children younger than five years had the second-highest rate of flu-related medical visits. Basically, we saw about one in nine children, when they got the flu, they were sick enough to seek medical attention. Then what about hospitalizations? We saw about one in every 100 kids who went for medical attention ended up being hospitalized. If they were hospitalized, 18% ended up in the ICU. Of those hospitalized, one in 20 ended up on a ventilator, and about one in every 200 of those children hospitalized did not survive the hospitalization.

We read that flu deaths were at 1.2 per 100,000 children, younger than 5, and 0.5 per 100,000 in younger children. Just want to point out, over 100 children died last year from influenza, and almost all of those kids were not vaccinated.

VR: The lesson is very clear, get vaccinated.

DG: I think the lesson is very clear.

VR: Do you think that vaccination rates in that age group are particularly low this year, post-pandemic, or is there some other reason?

DG: They were particularly low last year. I think there's a number of features that are feeding into this. One is, I think we need to do a better job with messaging. We need to really point out just how critical these shots are in younger individuals. There's a new flu campaign for older adults where they talk about, turn the wild into mild. I think that helps with the message. For these kids, they still may get the flu, but are they going to end up in the hospital? Are they going to end up in an ICU? Are they going to end up on a ventilator? Are they going to end up not surviving?

VR: Also, it's important to notice, even though the flu vaccine is widely criticized, it's very effective at preventing you from getting hospitalized.

DG: Hopefully, we've learned from the COVID criticism of vaccines is vaccines may not prevent you from getting infected. They may not prevent mild disease, but when you look at severe disease, you look at people that are dying, that's really where their strength is.

Speaking of COVID, apparently, the BNO is still giving us numbers. The average, we're averaging about 230,000 new cases every week in the U.S. We're actually doing a little better in hospital, 14,500. That's down by about 1,000. The ICU, we've dropped down from 2,000 to 1,600. New deaths, though, still 1,585. We're still over 200 deaths a day, over 1,500 deaths a week. This is worrisome, if we look at wastewater tracking, everybody's doing great except the Northeasterners, of which I am one. You reminded me last week, Vincent.

VR: We are. We both are. This orange curve keeps on rising. This is detection of SARS-CoV-2 in wastewater. It's the concentration of RNA. It continues to rise, which means more people are infected, right?

DG: Yes, and it's higher than it's been for many months and still on the way up.

VR: Yes. Do you have ideas about the Northeast?

DG: Last week, I was blaming it on all the Italians celebrating Columbus Day. No, I'm not exactly sure what's going on in the Northeast, because it's an outlier. The rest of the country seems to be coming down. We all peaked roughly about the same area, so I'm not sure. It doesn't really set us up well for the coming end of November, December holidays.

VR: Maybe it would be the opposite of the rest of the country and go down.

DG: Fingers crossed. All right. Now the next one is very disturbing. I know we actually have someone in the audience here who will care quite about this, the owner of a yellow lab. We have a live studio audience today for our listeners at home. All right. Keep it down, riley crowd out there. All right. This is the article, “Neurological Effects of SARS-CoV-2 Transmitted among Dogs,” published in *Emerging Infectious Diseases*. Much of this is disturbing. Let me go through it. The investigators intranasally infected dogs with the Delta variant, and then the virus subsequently was transmitted to contact dogs. You're going to squirt it up the nose of some dogs, and they got to put them back with other dogs, and then they're going to infect the other dogs. They assess detection of viruses in the brain and damage to the integrity of

the blood-brain barrier, as well as activation of neuroimmune responses in the brain and to test whether SARS-CoV-2 can indeed induce neuropathological changes in the brain. They also assessed patterns of demyelination and axonal damage. Let's go through. How did they actually do this? The first part, it's a little sad. I never really like when they do research on dogs.

The investigators tell us that they purchased 15, 16-month-old female conventional beagle puppies from Orient Bio, South Korea, and then they put them in three groups. You've got three in the control group, six in the infection group, and then six in the contact. They're going to be in the cage getting infected from the dogs that have it sprayed up their noses. The dogs in the infection and contact groups were housed in cages, and they gave us dimensions on those and they seem much too small, to mimic natural infection. They implemented two infection models. That intranasal inoculation, and then you've got the dogs infected via horizontal transmission.

After the dogs regained consciousness, they're going to sedate them to squirt it up their nose and acclimated to the environment. Each of these intranasally-infected dogs were placed in a cage with a dog from the contact groups. They've got veterinarians examining the dogs, checking them out for any clinical signs, any neurological signs. No symptoms in dogs because they can't chat. At each time point in the early and then late periods of infection, 10, 12, and 14 days post-infection, 38, 40, and 42 days post-infection, dogs were sedated and euthanized, and they then performed necropsies. You've got one infected, one contact dog at each of these time points.

They observed substantial brain pathology in SARS-CoV-2 infected dogs, particularly involving blood-brain barrier damage, resembling small vessel disease, including changes in tight junction proteins, reduced laminin levels, decreased pericyte coverage. Furthermore, they detected phosphorylated Tau, remember that from some of our dementia diseases, a marker of neurodegenerative disease, indicating a potential link between SARS-CoV-2-associated small vessel disease and neurodegeneration.

As disturbing as all this is, they reported no significant changes in body weight or temperature. None of the dogs showed neurological or respiratory signs of COVID-19. In many ways, these were asymptomatic infections in dogs that resulted in these horrible brain damage results.

VR: I don't know if it's horrible if they didn't have any symptoms, right?

DG: [crosstalk] yes.

VR: I guess that's science because we can't do symptoms in dogs. They may have euthanized them - 40 days post-infection, the infection would be over by then, really, so this is as bad as it's going to get. It makes me think of mumps virus in humans. When mumps was a thing before vaccines, in almost 50% of kids who were infected, the virus did get into the brain but didn't cause any issues. It could be that many viruses do that without any problem. Now here, we know from human autopsy studies, there's very little virus reproduction in the brain of humans. I just wonder if dogs -

DG: Yes, that's an interesting -

VR: Dogs are not humans, right?

DG: Dogs are not humans. No. That's an interesting point of discussion. We talked earlier about an autopsy in human beings that died of COVID. Not that they're seeing viral replication in the brain, but they were seeing a lot of neuropathology. We commented, yes, it's hard to know as a neuropathology because this is really, really severe. There's a growing bit of literature, not necessarily saying the virus is getting in and replicating in the brain but that the virus can result in neuro changes.

VR: Now, in this study, they didn't look for virus RNA in the brain, correct?

DG: Yes. That's something I'm going to make sure we circle back to because there's always this question, is this due to the immune response or is it due to viral replication? The growing evidence suggests immune response, the timing of all the different changes that we see, the lack of ability to culture replication-competent virus from samples.

VR: Daniel, why did they do this? Is the point to try and get some information about human disease, or do they want to know what happens in dogs? Do you know what the justification is?

DG: I don't think it's to try to find out about the dogs. I don't think this is a bunch of vets wanting to understand. I do worry, I was in the hospital a couple of weeks ago, and there was a patient in the room with COVID, and she had her companion dogs or service dog with her. The nurse is - they're also quite concerned. Their big concern is, is this OK? The dogs are in that room. They're not putting on the gowns and the gloves, and then they're going to come in and out, and they got to use the facilities, so to speak.

I said, "No, I don't really think the dogs are fomites. Dogs have never been a major issue for transmission. Remember the cat issue in the UK, Boris wanted to kill all the cats. No, I think they're trying to use this as a model for some of the neurological issues.

VR: I'm not sure it's a reasonable model, frankly.

DG: Yes, I think -

VR: I think smaller animals would -

DG: Yes, stop giving beagles COVID. I'm going to vote for that too. All right. Let's move on to children, COVID, and other vulnerable populations. If you feel like I'm too high in the soapbox, kick it out. This is, as our listeners probably know, a very sensitive issue for me, the downplaying of COVID in children. For background, we have discussed several times on prior podcasts that the only reason people say COVID is mild in children is by some comparison. While over 1 million adults in the U.S. died from COVID, we had over 1,000 deaths in children in the U.S. In the U.S., by comparison, influenza kills about 100 children each winter, as we discussed.

We also discussed that the majority of these deaths occurred during Omicron, which people like to use a four-letter word in front of. Now we have the article, “Effectiveness of Monovalent mRNA Vaccines against Omicron XBB Infection in Singaporean Children Younger

than 5 Years." These are the results of a population-wide cohort study, including all Singaporean children aged 1 through 4 years. We have 121,628 children. Pretty impressive. The study was conducted from October 1, 2022, to March 31, 2023.

They recorded that during an Omicron XBB surge, mRNA vaccine effectiveness against confirmed infection was 63.3% in fully vaccinated infection-naive children, 74.6% against reinfections in previously infected children with at least one vaccine dose. This is where I really was impressed. There were zero hospitalizations in infected children, zero, and there were no deaths. Zero deaths, zero hospitalizations.

One of the things that I have to say, and I'm going to going to read the CIDRAP quotation first, "Though, vaccinating children under the age of 5 is debatable," the authors say, "rapid increases in pediatric COVID-19 infections coinciding with periods of high community transmission may still place healthcare systems under strain." Now, I didn't like that.

VR: Aren't you more interested in the kids?

DG: Yes. Mom, we need you to vaccinate your child so that your child doesn't strain the healthcare system. Really?

VR: It's a good argument.

DG: What we're seeing here, and I think this is important, is everyone keeps talking about, "Oh, we see the virus has gotten really mild." Every time someone says that is your opportunity to stand up and say, "You mean, boy, vaccines really work?" Look how vaccines, look at how immunity has transformed this pandemic. One of the things we were talking about last week at ID Week was this is our opportunity to help shape the conversation. Whenever anyone says, "Boy, the virus has gotten so mild," you say, "Really?"

Let's look at a population that was naive during Omicron. That's when the majority of the deaths occur. There's no compelling evidence that the virus is mild. There's compelling evidence that vaccines protect, that vaccines work. Here we see, children are going to continue to come into this world. For them, COVID's here. They're naive. They are entering the pandemic, or the post-pandemic, and vaccines are incredibly effective at keeping them out of the hospital, keeping them from dying.

VR: In what world is vaccinating kids under the age of 5 debatable?

DG: Yes. Maybe on the Joe Rogan show.

VR: Oh, OK. Good.

DG: Joe's never going to invite us back. All right.

VR: We were never there, were we?

DG: Yes, we never showed up. COVID active vaccination immunity, the article, "The Effectiveness of COVID-19 Vaccine in the Prevention of Post-COVID Conditions: A Systematic Literature Review and Meta-analysis of the Latest Research." What am I doing talking about

Long COVID right in the vaccine section? This was recently published in *Antimicrobial Stewardship & Healthcare Epidemiology*. Here the authors performed a systematic literature review and meta-analysis on the effectiveness of COVID-19 vaccination against post-COVID conditions, Long COVID, among fully vaccinated individuals.

We read that they found 32 studies, 775,931 individuals, where they evaluated the effect of vaccination on Long COVID. Ultimately, 24 studies were included in the meta-analysis. The pooled DOR for post-COVID conditions among fully vaccinated individuals, basically what's going to be the vaccine effectiveness, was 32%. We have a vaccine effectiveness of 32% for reducing your risk of Long COVID. Vaccine effectiveness was 37% among those that got two doses before COVID infection. You're ready for this? Sixty-nine percent among those who received three doses before getting a COVID infection.

A couple of things there. One is, I think we've all landed on three doses is what it takes for these vaccines to be effective. Not only do they prevent you from getting sick, not only prevent you from getting severe disease ending up in hospital, not only to prevent you from dying, but that's a pretty impressive reduction in Long COVID.

VR: Remember, it's an average because they're putting all these studies together. It could be that in some situations it's even better than that, or worse.

DG: It's always a reduction in what's your baseline risk because we know women are at higher risk, older individuals are at higher risk. Now, this is one that I hope will help people with discussions. It's the paper, "Incidence and Impact of Acute Pericarditis in Hospitalized Patients with COVID-19*,"* published in the *Journal of the American Heart Association*. I have to say, this article was the one when I discussed it at our urgent care meeting this week. This is the one where people said, "Send me the link. I want to have this to have some discussions with people."

One of the reasons that certain people are hesitant to get vaccinated themselves, or vaccinate their children, is they have concerns about the risk of pericarditis, this inflammation of the heart that we've heard about. While very rare, in general, the highest-risk group is young men. This is going to be your late adolescent, early 20s. If you just look at men in that narrow age period, you can get an incidence as high as one in 5,000. As we've discussed, that acute pericarditis tends to be mild, tends to be a discomfort that lasts a day or so, resolves on its own, no evidence other than rarely of long-lasting impacts.

What about acute pericarditis when you get a natural infection, when you let that virus into your body? In this retrospective cohort study, they identified patients with COVID-19, with or without acute pericarditis in the National Inpatient Sample 2020 database. They compared the outcomes between acute pericarditis and non-acute pericarditis groups before and after matching. They had a total of 211,619 patients with a primary diagnosis of COVID-19, and they identified 983 patients who had a secondary diagnosis of acute pericarditis. Just to compare numbers, that is 1 in 200. If you get a vaccine and you're in that highest risk group, 1 in 5,000; if you get infected, 1 in 200.

Now, patients with COVID-19 with acute pericarditis, how severe was this? When they matched it with the non-acute pericarditis, they had twice the risk of mortality. Their

mortality risk was 21%. The risk of cardiac arrest was also doubled up to 5%. Cardiogenic shock went up about eightfold, 4.2%. Having arrhythmias more than doubled at 4.7%. Acute kidney injury was actually as high as 38%. Heart failure tripled up at 14% and significantly longer length of stay. I think there's a big thing here. When people say, "I don't know. I'm not sure about these vaccines. I'm worried about pericarditis," well, the point of the vaccines is to reduce your risk, among other things, of SARS-CoV-2 associated pericarditis.

VR: It doesn't eliminate it because the vaccine itself has a certain risk, but it's much lower than for natural infection.

DG: Yes.

VR: All right. I have a question. My understanding from what you've said is that peri and myocarditis caused by vaccination is eminently treatable.

DG: Eminently treatable. It's mild. Yes.

VR: Yet these complications are in people who are not vaccinated getting infected, so other things can happen that are life-threatening, correct?

DG: Yes. I think that's the issue with the false binary. It's not just, you get your vaccine, your arm hurts, maybe you feel crummy for a few days, maybe you get pericarditis. You get SARS-CoV-2, you get COVID-19, and pericarditis is just one of the many horrible things that can happen to you. All right, now we are moving into the COVID early viral respiratory phase. You've tested positive. Number one recommended treatment by CDC, NIH, by all the major guidelines, is Paxlovid, which is now licensed. A couple of interesting things we heard this week. Pfizer amends U.S. government Paxlovid supply agreement and updates full-year 2023 guidance. What is this all about?

Basically, Paxlovid is now going to be in a new box. It's not going to have that EUA labeling on it. Our pharmacists are no longer getting confused. If you write a script for Paxlovid, they're going to get Paxlovid. There's two separate boxes, one for regular strength, one for renal strength. Now, I also read, unfortunately, something in Reuters. The price is going up. They're going to double the price. As was explained to me earlier today, that's the way things work in the U.S. It'll force the government to pay more for it under Medicare. There'll be programs for people who can't pay. For those of us with private insurance, there may be a significant copay.

VR: It's the capitalistic drug company view, right?

DG: That's the way things work here in the United States.

VR: It was normally $700 for a five-day course. Now it's going to be -

DG: Now they're going to bump it to $1,400. All right, those poor insurance companies are going to have to foot the bill for this-

VR: Poor?

DG: - which they'd rather do than footing the bill for someone who ends up in the hospital.

VR: All right.

DG: All right, number two, we have remdesivir, that's based on PINETREE in the first week, that's just three days. Molnupiravir, convalescent plasma. As we like to repeatedly say, and I'm amazed we need to, let's not do harmful or useless things during that first week. Second week, that period when the early inflammatory phase might kick in, steroids at the right time in the right patient if those saturations are less than 94%. Remember that's dexamethasone, 6 milligrams times six days. Anticoagulation guidelines, really just for hospitalized patients. Pulmonary support, maybe remdesivir still in the first 10 days. Some nice news last week about tocilizumab, immune modulation.

Again, avoiding those unproven therapies. We actually have quite a bit this week on Long COVID, and I'm going to say, exciting. I had the opportunity to be on with - when I tweeted it out, I called him Brain Lehrer instead of Brian Lehrer, who's on NPR. Hopefully, he was complimented because I wonder why he puts up with me. We got to discuss the article, "Serotonin Reduction in Post-acute Sequelae of Viral Infection," recently published in *Cell*. Yes, any paper in *Cell* takes hours to go through, and this is deserving of those hours.

Here the investigators looked at a cohort of 1,540 individuals with PASC at Penn Medicine and performed a symptomatic symptom analysis based on questionnaire surveys, chart review. Like other investigators, they were able to define subtypes of PASC based on similarity. I think that seems to be a consensus. Long COVID is not one homogenous group. There are different subsets. They then went ahead and they performed targeted plasma metabolomics. Metabolomics, that's a new word for me. Metabolomics.

VR: Metabolomics.

DG: Metabolomics?

VR: Yes.

DG: But then it doesn't sound like Bologna.

VR: Say it again. Say it a few times, metabolomics.

DG: Metabolomics. Metabolomics. They did targeted plasma metabolomics on 58 Long COVID patients, who are representative of different clusters, and compared them to 60 individuals with acute COVID-19 and 30 individuals with symptom-free recovery from COVID-19. Now, they report that the metabolite profile of Long COVID patients was distinct from individuals who recovered to a symptom-free state. They go ahead - and I'm just going to jump into the meat of what they find. They identified a set of molecules whose levels were different in those folks that got better versus those that didn't, and the most significant was serotonin. They found that in the post-acute state of infection, the serotonin levels were predictive of whether a patient fully recovered or developed long-term sequelae. Now it gets even more interesting if you're not already hooked, Vincent. They wanted to verify these findings in other cohorts. I love when they do that, like, "Are you data mining? Did you just look at your folks, and you just - what did we find?" They go ahead, and they look at another cohort in one of my favorite

countries, Ireland. They go to Cork, where the Griffins are from, and in this cohort - yes, the Griffins, well, the descendants, the folks in Cork, serotonin was among the metabolites whose abundance was most strongly depleted.

In contrast, they looked at a different cohort, and they didn't find it, the UNCOVR cohort. Not every cohort, just important, and I think this also helps our patients, some patients have this reduction in serotonin. Then they try to explore, what is going on? Why is the serotonin depleted in these individuals? They have a really great graphical abstract, and this is what they're going to suggest is going on. They suggest that there is persistent viral RNA, not necessarily persistent replicating virus, but persistent viral RNA that is triggering TLR3.

The TLR3 is driving interferon signaling. The interferon signaling is interfering with tryptophan to serotonin production, and that low serotonin, along with a reduction in platelets, which is a significant storage place for serotonin, is leading to vagal nerve impacts, neurocognitive impacts, impacts on the guts. Interesting enough, they find that this isn't really just unique to COVID. It looks like this may be a common mechanism in a lot of acute viral illnesses. Maybe this is why you feel crummy when you get occult.

VR: Are there any disease states treated with serotonin?

DG: This did raise the issue of - we have a lot of medicines that target this pathway, our selective serotonin reuptake inhibitors, in certain individuals, might that make a difference? Just to point out, that hasn't always been a slam dunk, but in certain individuals, there are benefits to using those. This is a nice way of introducing those without basically saying, "We're doing this because you're depressed." We're not saying you're depressed, we're targeting a system that's disturbed. People have talked about, there are ongoing trials of basically precursors to serotonin, precursors to tryptophan, to use that to try to help with this change.

VR: The problem is that this wasn't observed in every cohort. Even if you wanted to do a clinical trial, you'd have to make sure your cohort has this reduction in serotonin, right?

DG: Not only in this cohort but maybe a nice thing is that we can actually order this in the clinic. A patient comes in, they've got Long COVID, now we have a list of things we can measure. We can measure the cortisol, we can measure the serotonin, we can measure EBV serologies, putting together a profile, and then maybe that way helping to guide treatment. A lot of exciting stuff for folks with Long COVID.

All right, and we have a paper here in our last section. I think this following article made for great discussion here at ASTMH. “Prevalence and Risk Factors for Long COVID and Post-COVID-19 Condition in Africa: A Systematic Review,” published in *The Lancet Global Health*. Here, the authors conducted a systematic review searching PubMed, the Living Overview of Evidence platform, and grey literature, for publications from December 1, 2019, November 23, 2022. They included articles in English, French, Spanish, Portuguese, basically looking for as much information as they can find. They really get a very broad estimation, really widely ranging from maybe 2% in Ghana to as high as 80% in Egypt.

Long COVID was positively affected with female sex as we discussed. Confirming that older age, non-Black ethnicity, low level of education, and as we've consistently seen, severity of acute infection and underlying comorbidity. I think a lot of the challenges say, what do you

do with those numbers? I think it just shows us how unreliable a lot of these numbers are. People say, "Oh my gosh, Africa, they did great with COVID." I don't know. If we have as many people with post-COVID conditions in other parts of the world as we have in the United States, this is going to be a huge challenge going forward.

VR: I also think that 86% is too high, and it underscores reporting issues when it comes to Long COVID.

DG: Huge reporting issues. Yes, huge reporting issues. All right, before we get to emails, I will close my section as I have for a number of years now. No one is safe until everyone is safe. If you're enjoying our shows, please go to parasiteswithoutborders.com. We are nearing the end of our Floating Doctors fundraiser. I'll be down there in December. Hopefully, you'll click on 'Donate' and support our fundraiser for Floating Doctors.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Maria writes, "I'm a Spanish journalist and a big fan of the show. I'm sure you've already talked about this, but it may be useful as a reminder. My mom, who is over 70 and living in Spain, just got her flu shot, and it's scheduled to have her COVID booster in 10 days. The primary care doctor is suggesting now her to wait a month for the COVID booster because she says having a COVID booster in 10 days will interfere and weaken the immunity my mom would be building against flu.

"Is there any study or other medical basis for saying that? My mom is more inclined to keep the appointment as it is. In Spain, as in many countries in Europe, there's no Paxlovid in wide use. Vaccines are really the only tool against COVID."

DG: Yes, this has been looked at. There is science to help guide this decision. There is, what we think, a clinically insignificant difference in the levels of antibodies you reach, whether or not you get them at the same time or you space them a little bit apart. Recommendation here in the U.S., recommendation based on the sciences, go ahead, get that second shot, keep your appointments.

VR: Could I, Daniel, get at the same time, flu, RSV, and COVID vaccines all in the same arm?

DG: You could. Now, a lot of places where I went, they put my COVID in my left arm, my flu in my right arm. I haven't reached the magical age of 60, but -

VR: You will.

DG: - I will one day, fingers crossed. No, you can, and it would be fine to put them all in the same arm. If you want to put two in one arm and one in the other, that is fine as well.

VR: All right. Ellen writes, "I'm hoping you can weigh in on the differences in outcomes, protection against infection and durability." Well, it's not protection against infection, but we'll substitute disease. "Between new Novavax and the mRNA vaccines. It's been reported that the Novavax vaccination produces fewer IgG antibodies. The question is then how many fewer? What does that mean in terms of protection against either infection or serious illness? On the other hand, how does that compare to the potential benefits of heterologous

vaccines? I've been waiting until the Novavax became available, and now that it is, I'm unsure which way to go."

DG: No, this is, one day we will have, I think, head-to-head trials because what we do now is we try to take one trial and then we compare it to another trial which was done slightly differently, maybe even the definitions of what efficacy meant changed. There's a few endpoints. One is a PCR positive. That's a very high bar because some minimal replication, we clear it, no symptoms. Maybe we'll do studies with certain thresholds where we really have a certain replication level. As far as comparing Novavax for what it's really designed to do, keep you from getting sick, keep you from ending up in the hospital, turn wild into mild, keep you from dying of COVID-19, Novavax looks to be an excellent option.

VR: Michael writes, “My wife is pregnant with a due date, mid-January. We have some questions about the two new RSV treatments, Beyfortus and Abrysvo. One, it seems like the guidance from the CDC is that you don't generally need both. Is this correct?"

DG: Not only is that the guidance from the CDC, but that's what we're implementing in clinical practice. Choose one or the other.

VR: Number two, "If this is correct, how should we decide which to get? We're concerned about the possible increased risk of preterm birth noted in the Abrysvo trials, although it wasn't statistically significant. If both offer the similar protection, we're leaning toward Beyfortus, but we're not sure if there are any reasons to prefer Abrysvo."

DG: What we're talking about here is getting RSV vaccine in the last trimester, last 32 to so many weeks during the pregnancy, or waiting, and then the child is born. The recommendation, if it's during RSV season, getting the monoclonal antibody within seven days of birth. The data's actually a little bit better on the Beyfortus compared to the vaccine. I think they do bring up, it was not as statistically significant. There was a tiny signal. That's actually why they're doing it when they're doing it. You're waiting until you're at a point, it's pretty hard to have a preterm birth once you're already at 33, 34 weeks. Not expecting to see that post-marketing. No, I think it's a reasonable discussion to have with your provider. As long as the child is going to get the Beyfortus in the first seven days, I think that's a reasonable thing to do at this point. We're going to get more and more data going forward.

VR: Finally, Lindsay writes, "While making an appointment for my flu and COVID vaccines through my pharmacy, they offered to add on the shingles vaccine. I was surprised because at 35 years of age and not being immunocompromised, I don't fit into the CDC's eligibility criteria for Shingrix. I've checked with my insurance company and they'll cover for anyone over age 18." Didn't we have someone write in last week that they couldn't get one because they weren't yet 50?

DG: Because they're giving it to the 35-year-old woman here with really good insurance.

VR: "Having seen several friends go through shingles, several of whom were younger than 50, I'd like to avoid it at all costs. Are there any downsides to getting it at a younger age than the CDC recommends, such as a waning immune response that would require an extra dose later in life? Additionally, while there doesn't appear to be any issues with giving the inactivated

flu and COVID vaccine simultaneously, are there any concerns with simultaneously getting FluMist with COVID? How about both of those with Shingrix?"

DG: There's a lot of questions here. The recommendation for doing the shingles vaccine, your two-shot series at age 50, that's when we really start to see an appreciable number of shingles cases. Fifty percent of us who've had chickenpox when we were younger will get shingles during our life if we do nothing. Shingles can be horrible. Shingles can be painful, shingles can occur, I saw a case recently, in the mouth. It can involve the eye. Really when we get to 50 is when we see the risk. As you described, there are certain individuals where maybe there's a family history, something's going on and they get it.

I think signing up for your virology class is a noted risk factor. In that case, maybe we recommend it. No, I wouldn't see any issue, but the recommendation is really starting at age 50 unless there's something else going on.

VR: All right. Then Lindsay wanted to know, "Can you get FluMist with a COVID vaccine and with Shingrix on top?"

DG: Yes.

VR: OK, very good. By the way, I've had a number of students in my class every year come up and tell me they have had shingles in their 20s, right?

DG: Yes, during your class.

VR: Yes, it's my class.

DG: No, I watched your class as well, and I - yes.

VR: Stressful class, yes, I'm sorry. That's *TWiV* weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

DG: Thank you, and everyone be safe.

[music]

[00:43:25] [END OF AUDIO]