This Week in Virology

TWiV 1104 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 13 April 2024

pdf of this transcript available (link)

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 1104, recorded on April 11, 2024. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Is that prions or hepatitis B virus?

DG: Well, there are a number of little RNA segments that can be reassorted to create the virus.

VR: Oh, influenza virus.

DG: [laughs] You've got it.

VR: It could be real virus or rotavirus also, but I figured you'd have a flu tie.

DG: Yes. As we're getting near the end of flu season, it seemed appropriate.

VR: Yes, it's a good idea. I like that.

DG: All right, let me start with my quotation. "Life can only be understood backwards, but it must be lived forwards." That's by Søren Kierkegaard.

VR: I love that one. That's great.

DG: [laughs] I was just in Denmark, so it seemed appropriate to quote a Danish philosopher.

VR: By the way, speaking of Denmark, last night on *Office Hours*, my guest was Alan Dove, who is also a sailor. He grew up in Maryland, right? Someone asked him, who's the better sailor, you or Daniel? No question, Daniel.

[laughter]

DG: Well, we'll have to get Alan up and do some sailing. I look forward to it.

VR: Yes, we should get the *TWiV* team on a sailboat. That would be fun.

DG: Actually, that would be a lot of fun. Yes, we'll plan on that. All right, let's jump right into measles. A couple of things here. I'm going to start off by saying that as of April 4, 2024, a total of 113 measle cases so far this year. We've got that map. I get to test myself. How good am I at knowing where we're seeing lots of those cases?

VR: Daniel, I remember last week, you said 97.

DG: Yes, 97.

VR: It's not logarithmic, but it's still concerning.

DG: Yes, another 16 cases just since our last update. To put this in perspective, I'll leave a link to this map where you can actually see that there are particular areas where we're seeing these outbreaks in Illinois, down there in Florida, and a number of other states. To put this in perspective, we have the *MMWR,* "Measles, United States, January 1, 2020 - March 28, 2024." Just came out April 11, the day we're recording. Hot off the press. That reminded me of my Uncle Jimmy. He was the guy at *The New York Times*. When everything was ready, he would say, "Run the presses" They'd all be hanging out with their newspaper hats. You could get the newspapers. They were warm. They were hot. That's the expression.

[laughter]

DG: It's from some sort of modern internet like, "hot off the released out into the internets."

VR: Some people still buy the paper.

DG: That is true.

VR: I was at a symposium last week for Ian Lipkin. Laurie Garrett was there and she had a copy of *The New York Times*.

DG: Oh my gosh.

[laughter]

DG: That seems appropriate. I got a patient today who was trying to get his *Daily News* put on hold while he was in the hospital. Apparently, there's vacation holds, not as easy to get because they probably expect him to go online and do it that way. You got to figure the people reading the newspapers and, obviously, the ones who find it very easy to go online and pause there.

VR: That's right.

DG: Here we go. We start with some background. Although endemic, U.S. measles was declared eliminated in 2000. Measles importations continue to occur. Prolonged outbreaks during 2019 threatened the U.S. measles elimination status. Then we go on to read, "During January 1, 2020 through March 28, 2024, a total of 338 U.S. measle cases were reported. About a third, 29%, of those cases occurred during the first quarter of 2024. Almost all in persons who were unvaccinated or whose vaccination status was unknown."

Now, this is interesting. We're seeing hundreds of cases of measles. What's going on? How come we're considered to have eliminated this? Well, because of the absence of sustained measles virus transmission for 12 consecutive months in the presence of a well-forming surveillance system, U.S. measles elimination status is still classified as maintained.

All right. Moving on to RSV, the season may be over this year, but this virus will be back. Today, let me share the - this is a Pfizer press release. “Pfizer Announces Positive Top-line Results from Phase 3 Study of ABRYSVO in Adults Aged 18 to 59 at Increased Risk of RSV Disease.” Here, we have immunogenicity and safety data from the ongoing Phase 3 clinical trial MONeT. Interesting. That grabs some letters here and there, but this is RSV immunization study for adults at higher risk of severe illness, where they're looking at a single dose of the ABRYSVO versus placebo in adults 18 to 59 years of age at risk of developing severe respiratory syncytial virus-associated lower respiratory tract disease.

Now, among adults 18 to 49 years of age, 9.5%, so about one in 10, have a chronic condition that puts them at risk of severe RSV disease. This percentage rises to about a quarter of adults in the 50 to 64 years of age. However, no RSV vaccines have been approved for use in adults 18 to 59. The MONeT study was initiated to address this significant unmet need by investigating the immunogenicity and safety in adults aged 18 to 59 at increased risk of RSV disease. These would be folks who have asthma, diabetes, chronic obstructive pulmonary disease.

Now, participants demonstrated RSV-A and RSV-B subgroup neutralizing responses, non-inferior to the response seen in the Phase 3 RENOIR study of ABRYSVO in more than 34,000 adults aged 60 or older, where vaccine efficacy was previously demonstrated. I want to point this out. This is like a bridging study where they say, "OK. Well, we got this RENOIR data. We've got this correlate of immunity, this neutralizing antibody response."

Instead of trying to do just some multimillion-dollar study in this younger group, we're going to see, "Can we get that same neutralizing antibody response?" Participants achieved at least a fourfold increase in serum-neutralizing titers for RSV-A and RSV-B one month following receipt of ABRYSVO compared to pre-vaccination. During the trial, ABRYSVO was well-tolerated. No safety issues. Interesting. I have to say, I use this as a segue into one of the discussions I recently had with one of the pulmonologists. We were talking about a number of human metapneumovirus cases we're seeing. Few, just real tail end of the RSV season at this point, and just the amount of bronchospasm we see.

It was really interesting because he asked me. He said, "This human metapneumovirus, I don't remember growing up with that. I don't remember that being a thing when I trained." It was really interesting. I said, "Actually, this was identified," so human metapneumovirus here, "in 2001. Actually, after you came out of medical school." Just how important it is to continue to

stay up because, yes, we're learning new things. New things can help our patients. We are coming out of the RSV season, so I'll leave a link there. I just shared this because I thought it was important update. Hopefully, not much RSV until next year.

Moving into flu, we are really coming out of this season. I'm going to leave a link where you can actually go down and you can see what does this flu season look like compared to really about the last five previous seasons. You can see different times when it might peak during the season. Sometimes we get these multiple peaks. This year, we had that peak, a December peak, came down just a little bit of a rise before we really dropped down to our baseline background levels of influenza. Really coming out of influenza, but this is not the same everywhere. Still, a few different areas where we have issues.

All right, COVID, moving into COVID. I'm going to leave a link for people to look at. Again, it's not exactly the same story in every single state. In most states, and I think this is reflected in the dropping wastewater, most states, COVID is down, I'll say, less than 2%, less than 1% of deaths, but there still are a few outliers where we're seeing 2% to 4% of all deaths are actually attributed to COVID.

That would be places like Georgia, North Carolina, Maryland, Minnesota. I think good news, right? We'll leave in a link as we always do to that wastewater management really, really coming down. Timing's sort of interesting, right? If you can look at this, it's really coming down like it did last spring. I think before us will be this question of, do we get that late summer, September bump that we got last year?

VR: Yes, I'm curious to see whether that happens or whether we go to the full winter seasonality, right?

DG: Yes, I'm thinking, we might be getting to where we have that flu seasonality where there's not much, and then we get this winter. We will see how long. Well, say how long that takes. I'm predicting the future as if I know that will actually be what occurs.

VR: Well, we'll be here to report it to you, won't we, Daniel?

DG: We will. We will. All right. Well, we've got the article, "Rural-Urban Differences in Long-term Mortality and Readmission Following COVID-19 Hospitalization, 2020 to 2023," recently published in *Open Forum Infectious Diseases*. Here, investigators compared long-term mortality and readmission rates after COVID-19 hospitalization based on rural-urban status and assess the impact of COVID-19 vaccination introduction on clinical outcomes by, I love this word, rurality.

[laughter]

DG: The main analysis involved 9,325 COVID-19 hospitalized patients. Thirty-one percent were from 187 rural counties in 31 states, 69% from 234 urban counties in 44 states. There were 1,738 deaths, 2,729 readmissions during a median follow-up of 602 days. We're getting close to two years there. Rural residence was associated with a 22% higher all-cause mortality and a trend toward a higher readmission rate. The results remain consistent in the sensitivity analysis and in both pre- and post-vaccination time periods.

VR: Daniel, is this because the health care in rural areas is not as good?

DG: I think this is a great discussion, right? Because a lot of people have talked about red COVID with this sort of idea that, "Well, it's because they're Republicans. You're more likely to die." There may be something a little bit more here. A lot of states that are more rural, less urban populations may tend to have more of a tendency to vote Republican, but it may not be actually your political preference. As you brought up, there certainly is a difference in the level of health care in a rural community versus an urban center.

It's not exactly clear. I think that the interesting thing was that this was consistent over time. This wasn't like, as people said, "Oh, now that we have vaccines." No, this was pre-vaccine. This was post-vaccine. There may be a real issue with the different levels. As we know, you really can affect the mortality with COVID, right? Early on when they were giving everyone hydroxychloroquine, that was we now living forward but looking backward, understanding backward.

We know that was associated with probably a 20% increase in your chance of dying, 20% increase in mortality. Then we discovered that, "Oh, you can jump in with steroids at the right time in the right patient." Well, if you do that wrong and do it in the first week, you're increasing your progression fivefold. You do it in the second week, you're decreasing. Then antivirals got introduced. Really great uptake in some of the urban areas, not so great in some of the more rural areas. A lot of this is the access and the delivery of health care.

VR: Also, these rural areas depend on some regional medical center, right? That's not nearby. It can get filled up quickly. Then you have the problem where if you can't treat the people, they're more likely to die because the hospital is full, right?

DG: Timing matters that like, "Oh, I'm just going to wait a few days. If I get really sick, then I'll go to the urban center." Well, the trick with COVID like so many viral diseases is not waiting till it's too late and really jumping in. All right. We will move forward. Just make sure I keep our updates for maybe people a little spotty with their listening, right? COVID active vaccination, we did Wednesday, February 20, 2024.

The CDC recommendation for an additional dose of the current monovalent vaccine this spring endorsed by CDC Director Mandy Cohen. That's for folks age 65 and older. We now have passive vaccination, emergency use authorization for Pemgarda. I say we now have this with a little bit of hesitancy here because still waiting to find out how do we access this, what is the price, et cetera. Not much use sitting on shelves. What is that quotation? Vaccines don't save lives? Vaccinations save lives.

VR: That's right. [chuckles]

DG: Got to start doing those passive vaccinations. All right. Moving into COVID, the early phase. Folks that test positive continue to leave a link for the treatment guidelines. You can get your treatment guidelines from the NIH or the ID Society, not necessarily from the mainstream media. One, Paxlovid. This is an interesting study. We can spend just a little bit of time here. The article*, "*Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with COVID-19," was recently published in *The New England Journal of Medicine*.

This has gotten a lot of, I don't know, retweeting. These are the results of a Phase 2-3 trial with randomly assigned adults who had confirmed COVID-19 with symptom onset within the past five days in a 1:1 ratio to receive nirmatrelvir, ritonavir, so Paxlovid, or placebo every 12 hours for five days. Patients who were fully vaccinated against COVID-19 and who had at least one risk factor for severe disease as well as patients without such risk factors who had never been vaccinated against COVID-19 or had not been vaccinated within the previous year were eligible for participation.

A pretty large group here. Participants logged the presence and severity of pre-specified COVID-19 signs and symptoms daily from day one through day 28. What was the primary endpoint? I think this is really important. The primary endpoint was the time to sustained alleviation of all targeted COVID-19 signs and symptoms. Sort of interesting. This is, "We don't care if you felt better and you just had a little bit of a cough or something that second week." That's just as bad as being sick for 14 days straight.

[laughter]

DG: Yes, you got to be 100% or, I'm sorry, you're still sick.

VR: This is just an absurd study. I'm sorry. [chuckles]

DG: No, but it's important, right? Because I don't think people are reading and looking. They're just like, "Oh, see," and all these vehement tweets out there. Now, the primary endpoint was this, but COVID-19-related hospitalization and death from any cause were also assessed through day 28. We're going to get to look at that. That's sort of a hard outcome. Did you end up in the hospital? Did you die? There were 1,296 participants who underwent randomization and 1,288 received at least one dose of Paxlovid or placebo.

It's a low bar. Just got to get one pill [chuckles] that counts as being treated or not. The median time to sustained alleviation of all targeted signs and symptoms of COVID-19 was 12 days in the Paxlovid group, 13 days in the placebo group. About a day, but we're not hitting statistical significance there. There was a 50% reduction in the composite endpoint of hospitalization and/or all-cause mortality associated with the receipt of Paxlovid.

You end up with 0.8% in the Paxlovid, 1.6% placebo group, but we see overlapping confidence intervals. The 95 confidence interval went from -2 to 0.4. No real difference as far as adverse events. There's a couple of things I wanted to bring up here. One of the first things I wanted to talk about was Type I versus Type II errors. I think it's appropriate that this article was published in *The New England Journal of Medicine* because some of these ideas, particularly the number needed to treat, was introduced in a 1988 *New England Journal of Medicine* article.

This is this idea like, "OK, so if we think that this is helpful, how many people do we need to treat?" This is going to shift. If you've got an 80-year-old gentleman with multiple medical problems, I said "gentlemen" because male sex can be an issue as well, multiple medical problems, a person like that, as we know, with an 80% reduction in - maybe 80% to 90% reduction in the risk of progression, you're not going to have to treat that many people when you're going from a 20% to 40% chance of ending up in the hospital to treating really young, healthy, limited risk-factor folks.

That's one of the things that I think is important to be thinking about. Here are these Type I and Type II errors that I think people want to be thinking about when they read an article like this. Type I error is we conclude that something is a fact erroneously. We call that in our family a rock fact like, "That's a fact. That's a rock fact." You're like, "Oh, so it's a fact, but it's actually not true." That sometimes happens, right?

You have a study and you do a bunch of studies. One of the studies finally gets published because there's this publication bias. Then you think something is true and it was just, "Well, that was one of the 20 studies and it got published." You're starting to think something is true that's not actually true. Now, a Type II error is when you conclude that something is not true when it actually is.

Patients who got the drug did not get better at a higher rate than ones that got placebo. Here, I think a lot of people I worry are falling into this Type II error like, "Oh, it didn't reach statistical significance. Therefore, Paxlovid doesn't work and you should never, ever give it to a vaccinated person." I just want to get that out there. Vincent, I thought you might want to jump in on this.

VR: We got a lot of letters about this, Daniel. I figured you were going to take care of it, so I didn't put any of them in here. They're all focusing on no difference in alleviation of all symptoms, which is not something we've ever talked about as an important part. It's prevention of hospitalization, right? Fifty percent reduction in endpoint of hospitalization or all-cause mortality is darn good, right?

DG: It's interesting because people complain. They're like, "Boy, this drug, it's like $800 for a course. $800 to just feel better a day earlier." Well, I know some people that would pay that. Boy, $800 to reduce your risk of death in half, reduce your risk of ending up in the hospital, and everything that goes with that, OK, yes. We really have focused.

VR: I don't understand why people are so dead set against finding problems with Paxlovid. If you don't want to take it, don't take it. Take a risk. All those people who are dying every week probably wouldn't have if they had been given Paxlovid.

DG: Yes. No, that's the common denominator. I think I understand because there's a couple of things. One is it's a hassle for the doc, right? You got to look at your medicines. You got to look at kidney function. You got to navigate the drug-drug interaction. There is some resistance in the medical profession. They're not seeing those people die each week because they're removed from that.

I remember a study on HIV patients and, "Oh, no one's dying of HIV anymore." I was like, "How come they're all dying on average in their 50s?" They're still dying, but they're not dying in front of you. It ceases to be an issue. The other side, which I think we have to fight against as well, is if they're taking Paxlovid, they're not buying your snake oil. There's billions of dollars at risk if people take an evidence-based therapy instead of buying your snake oil.

VR: That's really, in the end, what it is, right? The same with the anti-vaxxers. They want you to buy their nutritional supplements.

DG: Yes.

VR: There's always money behind the story. Folks, just think about that. When you're considering health decisions, they don't care about your health.

DG: Yes, they didn't take an oath.

VR: That's right.

DG: All right. After Paxlovid, we've got number two, remdesivir. Number three, molnupiravir. Number four, convalescent plasma in certain contexts. If you've got COVID, we have updated respiratory virus guidance. All right. Second week, and remember this, the cytokine storm week. You got through that first week. Then this issue with post-infectious, post-viral replication, cytokine storm, steroids at the right time in the right patient, about a 25% mortality reduction if done correctly, if done during that second, not the first week. Anticoagulation guidelines, pulmonary support. Remdesivir if you're still in the first 10 days. If you're day eight, day nine, hypoxic, this is five days versus three days. In some cases, immune modulation.

Today, we're going to spend actually a lot of our discussion on late-phase, PASC, Long COVID, long-hauler COVID. I saw that used today. We had a nice review back on *TWiV* 1088, clinical update. I'll leave a link in there for a while. Let's go through a couple of articles. The first article was, “Brain and Cognitive Changes in Patients with Long COVID Compared with Infection-recovered Control Subjects,” published in the journal *Brain*.

Now, this study aimed to provide a detailed description of the cognitive profile, the pattern of brain alterations in Long COVID, and the potential association between them. In this study, 83 patients with persistent neurological symptoms after COVID-19 were recruited and 22 now healthy controls chosen because they had suffered COVID-19 but did not experience persistent neurological symptoms.

Patients' controls were matched for age, sex, and education level. All participants were assessed by clinical interview, comprehensive standardized neuropsychological tests, and structural MRI. The mean global cognitive function of patients with Long COVID assessed by using the Addenbrooke's Cognitive Examination III, the ACE-III screening test. I thought that was a nice little coincidence there.

Think of this as an open access alternative to the mini-mental status test or MMSE. Overall cognitive level was significantly below the infection-recovered controls. They observed that 48% of patients with Long COVID had episodic memory deficit; 27% also impaired overall cognitive function, especially attention, working memory, processing speed, and verbal fluency. The MRI included gray matter morphometry and whole-brain structural connectivity analysis.

Now, compared to infection-recovered controls, patients had thinner cortex in a specified cluster centered on the left posterior superior temporal gyrus. In addition, lower fractional and isotropy, that's FA, and higher radial diffusivity. They were seeing widespread areas of the patient's cerebral white matter relative to these controls. What are those crazy things? What is fractional and isotropy, FA? FA is used as a measure in diffusion imaging and it's thought to reflect fiber density, really.

You really don't want to have less fibers in your brain after a bout of COVID. You don't want to have smaller axonal diameters and you don't want to have issues with myelination of the white matter. Correlations between cognitive status and brain abnormalities revealed a relationship between altered connectivity of white matter regions, impairments of episodic memory, overall cognitive function, attention and verbal fluency. I'm going to leave a link into a comment by the authors.

“Our data indicate a specific profile of cognitive dysfunction in neurological Long COVID characterized by impairment in episodic memory, attention, processing speed, and verbal fluency.” That's from Victor M. Serrano del Pueblo, University of Castilla-La Mancha, Albacete, Spain, and colleagues. He goes on to say, "This altered cognitive performance is associated with reduced integrity of specific white matter regions involved in the interconnection of distal regions responsible for these cognitive functions."

VR: This is interesting because in the *TWiV* that we recorded this week, we did a paper where they did cerebral organoids, brain slice cultures from humans, and then tried infecting them with SARS-CoV-2 and they barely get infected. The authors conclude that robust infection is not part of the causation of these CNS issues. Maybe it's neuroinflammation or something else, but it's not that the virus is going in there and replicating like crazy.

DG: It's interesting how emotional people are about that issue, right? At some point early on, it gets in the brain. It's all in the brain cells. You're like, "Oh, my gosh." Actually, the evidence suggests that it's, as you mentioned, being driven by an inflammatory response. We need to know the truth, right?

VR: Yes.

DG: Because the truth is what's going to help us treat folks. It's going to help us know how to make folks better.

VR: The good aspect of this paper that we did is that they actually use infectivity assays, plaque assays. You can know if infectious virus is being produced. In most of the cases, the cells can get infected. The virus gets in. Infectious viruses are not produced. The number of cells that are infected are sparse, right? It's not uniform. I think it's a good study. We have to start looking for other reasons why this is happening, yes.

DG: One of the most disabling things for folks with long COVID is the cognitive impact. It's like, "I can't work. I can't concentrate. I can't do my job. "Yes, really important that we understand this and then we can then move to treatments. All right, in *Nature Communications*, we have the article, “Incident Allergic Diseases in Post-COVID-19 Condition: Multinational Cohort Studies from South Korea, Japan, and the UK.” The investigators used nationwide claims data, claims-based cohorts in South Korea.

I've got 836,164 in a main cohort. Japan, we've got over two million. In the UK Biobank, we've got 325,843. Then they're going to do this 1:5 propensity score matching. They're going to go really pretty robust numbers here, but I'm just going to cut to the chase. They find that the risk of developing allergic diseases beyond the first 30 days of diagnosis of COVID-19 significantly increased really by about 20%, hazard ratio of 1.20, notably for asthma. That's actually more than double. That's a hazard ratio of 2.25. Allergic rhinitis, 1.23. This risk

gradually decreases over time. A little bit of good news there, but it did persist throughout the follow-up period, which was more than six months.

In addition, the risk increased with increasing severity of COVID-19. It's the worst case you had. Notably, COVID-19 vaccination of at least two doses had a protective effect against subsequent allergic diseases, so about a 20% reduction and similar findings reported in the replication cohorts. As we are moving into allergy season, this might be a timely study. The article, “Functional Limitations and Exercise Intolerance in Patients with Post-COVID Condition: A Randomized Crossover Clinical Trial,” was published in *JAMA Network Open*. Now, Vincent, did you get a lot of questions about this on the livestream at all?

VR: No, I didn't.

DG: OK, this has also had a lot of people pretty up in arms. Let me go through, what did they find, what did they do, and why are people upset? These are results of a small, randomized crossover clinical trial of 31 patients with post-COVID conditions, 31 matched-control participants. Non-hospitalized patients without concomitant diseases and with persistent, so greater than three months symptoms, including reported post-exertional malaise after SARS-CoV-2 infection, were recruited in Sweden from September 2022 to July 2023.

Age and sex-matched control participants were also recruited. After comprehensive physiological characterization, participants completed three exercise trials. There was a high-intensity interval training, there was moderate-intensity continuous training, and there was strength training. This was in a randomized order. Symptoms were reported at baseline, immediately after exercise, 48 hours after exercise.

The primary outcome was between group differences in changes in fatigue symptoms from baseline to 48 hours after exercise assessed via the visual analog scale. Questionnaires, cardiopulmonary exercise testing, inflammatory markers, and physiologic characterization provided information on the physiologic function of patients with post-COVID conditions. They reported that patients with post-COVID conditions reported more symptoms than controls at all time points.

However, they report they found no difference between the groups in the worsening of fatigue in response to the different exercises. They noticed that four patients with post-COVID conditions, 13% had postural orthostatic tachycardia and 62% showed signs of myopathy as determined by neurophysiologic testing. I just want to repeat that: 62% had signs of myopathy. The authors conclude by saying, "The findings suggest cautious exercise adoption could be recommended to prevent further skeletal muscle deconditioning and health impairment in patients with post-COVID conditions."

What is going on here? What's the context? Because a lot of people are taking this away, "See? People with COVID, they should be exercising." Well, the context for this study is that the international guidelines from public health organizations, including the WHO, caution against graded exercise for treating patients with post-exertional symptom exacerbation, a commonly reported feature of post-COVID-19 condition.

These recommendations are provided despite the well-documented deleterious effects of physical activity and its close association with secondary health conditions and deterioration

in quality of life. You put that in condition, right? The WHO is saying, "Be careful with exercise. Don't do this graded ramp-up. You got to go keep increasing." They're actually saying, "We realize that there's a lot of negatives to physical activity, but a lot of studies showing that you can actually make things worse if you push these folks too hard."

Now, unfortunately, I think a lot of people are looking at this one study. It's being quoted in the media, tweeted out there, really saying, "We've been wrong all along. People with post-exertional malaise, post-exertional fatigue, you really got to get those folks exercising." I do not think that this study is concluding that. If anything, they say "cautious exercise adoption."

VR: I think this reminds me of ME/CFS. Remember, there was a really flawed clinical study, which concluded that graded exercise therapy and cognitive assistance were important. There was a pushback because the trial wasn't done properly. Maybe now, that's why WHO is being so cautious. I'm not sure, but it rings familiar.

DG: We have a lot of studies now showing that if you push these people too hard, they really can not only have a setback, but we even discussed a study where you can actually trigger necrosis of muscle. Less than ideal. Don't take one study out of context and get yourself into trouble. All right. Well, as we've been concluding for over four years, Vince, and no one is safe until everyone is safe, I do want everyone to pause the recording right here.

Go to parasiteswithoutborders.com and click ‘Donate.’ Even if it's a small amount, every bit helps us to continue to do our work. We are now in April, about halfway through April. We're still doing our American Society of Tropical Medicine and Hygiene fundraiser where we will double your donations up to a potential maximum donation of $20,000. A portion of these funds will go to providing travel awards for two female, qualified, early-career student investigators.

VR: This saying, "No one is safe until everyone is safe," is very important because it recognizes that every human life is important. Some people think only their life is important and that's not right.

DG: Everything in nature is connected. I think to poorly quote Paul Farmer, let's see how well this goes, is, "The source of all problems in the world is the idea that some individuals are less important than others."

VR: That's right. That's absolutely right. It's time for your questions for Daniel. You can send them to Daniel@microbe.tv. Amy writes, "You had a question on the April 6 podcast concerning nasal washes. You said to use distilled water, wasn't sure about normal salt because of the iodine. I don't use nasal washes often, but when I do, I use tap water that I bring to a full boil for at least a minute, then cooled to slightly warm. I add a teaspoon of a mixture 3:1 fine sea salt and baking soda. Is this a bad idea? Could there still be amoeba present?"

DG: All right, so let's see. You're going to boil it, a full boil at least a minute. What altitude are you living at? No, that should be fine. It is interesting because I had learned in wilderness medicine and I remember studies that getting it to a boil, we don't really have too many places in America that are going to get you into trouble, with a one-minute boil, that should be enough. No, this actually sounds pretty reasonable. Good luck, Amy.

VR: Lewis writes, "I never miss your shows. I'm currently in Argentina where there's a dengue epidemic. I've never had dengue. I'm 60 years old. Can you talk about the vaccine options? I'm usually in Argentina three months out of the year. I'm really confused about whether I should get a vaccine that isn't available."

DG: Yes, no, count yourself among the many when it comes to the dengue vaccination. Here's a couple of things we talked about with dengue. The one which is maybe taught more than it should be just because it's so fun to talk about is that often people get one episode of dengue, and then they might get a second episode where they get this antibody-dependent enhancement, we think. The whole idea is you have antibodies for one. You've got your dengue Type I, II, III, IV, so maybe you get a dengue III. Now, it's a dengue II and you get sicker.

Just to put some context, actually, a lot of people can get quite sick with their first dengue episode. Dengavax was a vaccine that came out. They actually realized that because it was priming, at least that was the understanding in adolescents, you were having a problem with adolescents who would then get dengue after and have worse outcomes. A lot of issues here about that. Now, there is a brand new dengue vaccine. It might be appropriate for you like I'm doing an advertisement here. Talk to your travel health doctor. This is a different approach and commercially available. It's sort of a new and improved dengue vaccine.

VR: Merle writes, "I'd like to revisit an answer you gave on *Office Hours* about the second monovalent booster. I agree. We all need to wait for more data about this newest XBB vaccine, but does it make a big difference that the predominant variant now, JN.1, doesn't derive from the same variant that XBB does? Is this akin to when flu viruses are chosen for the annual flu shot? I'm pretty sure it's just a good idea to have gotten the flu shot anyway even if you end up with a virus that's not in the shot."

DG: This is a good email, Merle. A couple of issues here. We talked about the paucity of data, the fact that we would not have the data we wanted until after the fact. COVID is on the way down. Just the idea that when the monovalent was given, we're seeing a pretty consistent 50% reduction. It's holding pretty strong. We don't know if there's a cliff and we won't know whether there was a cliff until the future. The review was actually of the bivalent and then there was a cliff. We don't know whether that cliff was any waning of the immunity or it was because there was a new variant.

Now, the nice thing is the current vaccine is providing protection against JN.1. We're not seeing that variant shift to something where we're not generating neutralizing antibodies, where we still feel like we're getting some kind of protection there, and then you go into flu. Flu really varies. Sometimes if the flu shot is just a total miss, we really don't see much of any protection at all. It's not always that we can guarantee getting the flu shot was the thing to do. We can't always guarantee that it offers protection because sometimes we just miss.

VR: Cheryl writes, "Aloha, Doctor. As I listened to you and Vincent on the podcast, it occurred to me that maybe you could identify what I experienced. I was pregnant about four to five months long when I caught a bad cold, very sore throat. I began recovering. Suddenly, experienced severe pain when I touched anything with my fingers. Same terrible pain in the center of each and every toe like at the center of the whorl of each finger and print and toe print. Couldn't bear to wear shoes, lasted a day or two."

"There was one dark red spot in the center of each fingerprint. No broken skin, no other rash, no blisters. The red spots were super sensitive. Crazy painful if touched. It affected each finger, thumb, and toe. My doctor's ears perked up when I told her of my finger-toe symptom. Assuming that I had experienced strep throat and worrying about scarlet fever and the baby's heart, my doc prescribed penicillin for 10 days. Since that time, I tried to look at the fingertip symptom, but I've never found it. What the heck was that? I would love to know your thoughts."

DG: Yes, so this actually sounds a lot like a post-infectious vasculitis. I'm just looking at the timing here. Probably the most recognized phenomenon, you can google this, would be Osler's nodes that we see in endocarditis. Endocarditis, we have Janeway and Osler's nodes. They were biopsied. There isn't actually bacteria in there, but there is this vasculitis that is seen. They appear much like what you described.

We see it after CMV and a few other viral infections where you get your infection. The viral replication goes away. Probably antibody-mediated, but I'm not sure. You then develop this vasculitis. You have these red spots, central like very red area, incredibly sensitive. You touch those and they really hurt. That's why they call them Osler's nodes within the context of endocarditis. I don't think you had endocarditis. Yes, that's what I'm guessing in retrospect having not seen these.

VR: Alina writes, "I'm a 69-year-old woman. Good health, slender, exercise, family history of diabetes and heart disease. I've been on 5 mgs of rosuvastatin and ramipril for about a year."

DG: Crestor. [chuckles]

VR: Say that again?

DG: Rosuvastatin or Crestor.

VR: Crestor, OK, and ramipril. "I had a full cardiac workup. My cardiologist says everything looks good. I had COVID in July '22. My symptoms were weird. Achy lower legs, but I never had fever, dyspnea, or other worrisome things, recovered. I've been vaccinated seven times, caught COVID again in February. My symptoms were mild, but in the last few days, I had two episodes of sudden-onset tachycardia. My heart rate was 100-133 for over 30 minutes and dropped to the 90s and took nearly two hours to come down to normal."

"Then I took very small doses of clonazepam to help with the anxiety. I hope that was the end. On March 15, I had another episode. I took clonazepam immediately. Heart stayed above 100 BPM, just lying down for 15 or 20 minutes, and then came down to the 90s. The whole episode lasted an hour and then had another episode on March 15, long-lasting enough that I ended up in the ER."

"Troponin and 12-lead ECG were normal as with other blood work. I saw reputable studies, reports online that COVID can mess up electrical signaling in the heart causing tachycardia. Is there anything more known yet? Is it likely to eventually stop happening? Is there permanent damage? Is there anything I can do? I contacted my doctor and all she said was to monitor. I don't find that very reassuring."

DG: OK, so we certainly see this after COVID. We've shared some studies, probably about a doubling of the incidence of arrhythmias in the first six months after COVID. A nice thing I will say is a lot of this will get better over time. It does not look like there's evidence of permanent damage to your heart. The doctors say just monitoring it, maybe with the reassurance of this is something that tends to get better over time. I classify this into post-acute sequelae of COVID or a type of Long COVID, maybe some degree of arrhythmia, some degree of autonomic impact. You will tend to get better over time, so do not worry quite as much as perhaps it sounds like you have been worrying.

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

DG9: Oh, thank you. Everyone, be safe.

[music]