This Week in Virology

TWiV 994 Clinical Update

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Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick. From MicrobeTV, this is *TWiV*. *This Week in Virology,* Episode 994, recorded on March 23, 2023. 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: Daniel, just casual inquiry, seems to me that more people are being infected with SARS-CoV-2. Is that a trend right now? Do you know?

DG: It is really hard to get the data anymore. It's hard to find out what exactly is going on. Certain place, I know Canada's having a bit of an issue. The UK is having a bit of an issue. Locally, at least when I go to the hospitals, there are very few people that are actually SARS-CoV-2 positive. The biggest challenge, is going to be a challenge going forward, is really knowing because we're not testing. It's a lot less testing going on.

VR: Your ICU is not full of COVID patients anymore, right?

DG: No. It's a very different experience in the hospital.

VR: This is my last question for now. Do you have any sense of what fractions of tests actually get reported so that we know how many people are positive in the U.S.?

DG: My impression is the minority because most folks are doing home testing. A lot of times, that's how we do it. If someone has consistent symptoms, they have a good story, I saw someone was actually an add-on, maybe I'll even mention them later on, but an add-on at the end of the day, Tuesday. It was a young lady, early 30s, pregnant. She started feeling just crummy, fever, cough, trouble breathing. She did a rapid, it was positive. Actually, between the time she did the rapid and the time that I saw her, she found out that her grandmother who had just gone to the emergency room was also positive, as was her mother.

In a situation like that, that person is never going to go get a test that's going to be reported.

VR: Does your hospital require testing for admission?

DG: It's really interesting. A lot of the required testing is going away. We're not testing everyone who shows up anymore.

VR: Do they have to be vaccinated though?

DG: No.

VR: Wow.

DG: Actually, the Catholic hospitals a little while back actually even just did away with mask mandates. The Northwell system, no longer mask mandates. The Optum organization, we're still - whenever you're in a patient-facing encounter or patient-facing situation, you're wearing masks all the time. I think my patients might be a little bit surprised if I showed up without a mask on. I was at New York-Presbyterian this morning, mask at all times when you're in patient care areas interacting with patients. I'm still wearing a mask. I wore my mask on the subway this morning. Head on into Columbia and I'm wearing masks when I'm around patients, but it's moving away from the mandates, more of a make a choice.

VR: You're protecting your patients essentially, right?

DG: That's what I think the big thing is when a physician wears a mask. Actually, if you ask patients, most patients would like their physicians to protect them by wearing a mask. They themselves might not want to wear masks. They might not want to protect their physicians from them, but OK.

VR: I understand that patients also would like their physicians to be vaccinated.

DG: It's interesting. They would and they definitely want their surgeons wearing masks when - [chuckles]

VR: Sure.

DG: Apparently, they're big sticklers on hand washing, particularly when it's us who are supposed to be washing our hands. All right. Well, we'll give you many more times to ask questions as we go, but I will start off with a quotation. This is by John M. Barry, I'm working my way through the book, *The Great Influenza: The Story of the Deadliest Pandemic in History*. It's a great book. I have to say I was a little bit surprised at how good a book it is and how broad the scope is, and how much they talk about the history of medicine and really science coming into it and evidence-based medicine starting to come in, but here's the quotation. “You don't manage the truth, you tell the truth.”

I think there's a great lesson there. When you start managing the truth and not just telling people the truth, I think it's going to come back and bite you.

We'll jump right into the first topic. Vincent, I'm sure you'll like the fact that we're starting off with polio. The Global Polio Eradication Initiative has received notification of the detection of circulating vaccine-derived poliovirus type 2 in Burundi and the Democratic Republic of the Congo linked with the novel oral polio vaccine type 2.

The viruses were isolated from the stool samples of seven children with acute flaccid paralysis. Six in the DRC, (Eastern Tanganyika, and South Kivu provinces), several in Burundi, and from five environmental samples collected in Burundi, all reported isolates stem from two separate and new emergencies of this vaccine-derived polio vaccine. I think this is actually important and interesting. Actually, I'll let you comment, Vincent, about why this is so important.

VR: All right. OPV type 2 has been a problem because when you give it to people, it reproduces in the gut. It gives you immunity, but it also reverts, so it can cause polio. There are hundreds of cases throughout Africa caused by circulating type 2 OPV. A couple of years ago, an effort was made to modify it so that it wouldn't do that, wouldn't cause polio in the recipient, and hopefully wouldn't circulate. However, it does cause polio in some recipients. The frequency is much lower than OPV. It's probably 50 times over, which is great, but it's not zero. I don't think we want to keep paralyzing kids with vaccines.

More importantly, and what every story is missing on this issue, this virus is now in the environment, which means it's going to circulate and cause polio in under-vaccinated populations. That's just what OPV2 did. This is no different than that property and that's the real issue here, that the idea that you can have an OPV that's not going to circulate just didn't work and it's too bad.

DG: I think it's a good wake-up call because there was a lot of optimism. I'm going to leave a link into actually, *The Lancet Infectious Diseases* article, "A Novel Tool to Eradicate an Ancient Scourge: The Novel Oral Polio Vaccine Type 2 Story," which gives a nice background about this optimism about hope. Well, the hope was that this would not revert to neurovirulence. It's less likely, but once it reverts to neurovirulent, you've now introduced this into the environment. This is why, as far as here in the U.S., I hope, I don't think that anyone's going to start using the oral, even this updated novel type 2 polio vaccine.

I think we're going to be sticking with the inactivated, which is inactivated. It's not replication-competent, it's not going to revert. We don't have this risk.

VR: You know that, Daniel, you cannot bet on a virus not to revert, that's the moral here of this story.

DG: Yes. I feel like this is a *Jurassic Park* lesson [laughter]. All right. Let's get right into COVID. I think it's funny, I got some communications this last week about people. They came for the COVID, now we force them to learn about other stuff. I was entertained by that, but right into COVID and I want to start our COVID section with, I won't call this a disturbing article, "Prior COVID-19 Infection Associated with Increased Risk of Newly Diagnosed Erectile Dysfunction*,"* published in the *International Journal of Impotence Research*. Not an article that I spend a lot of - not a journal I spend a lot of time reading, but this caught my eye.

Using IBM MarketScan, which is a commercial claims database. I'm actually going to leave a link to a whole paper, like, what is this IBM MarketScan database? Using this commercial claims database, men with prior COVID-19 infection were identified. They created a cohort using this cohort along with age-matched men without prior COVID-19 infection. The researchers assess the incidence of newly diagnosed erectile dysfunction. Covariance were

assessed using a multivariable model to determine association of prior COVID-19 with newly diagnosed erectile dysfunction.

They ultimately had 42,406 men that experienced a COVID-19 infection between January 2020 and January 2021. Think about the timing there, because that's going to come up. When was that relative to vaccines? In this group, 1.42% developed new onset erectile dysfunction within 6.5 months follow up. On multivariable analysis, they control for diabetes, cardiovascular disease, smoking, obesity, hypogonadism, thromboembolism, malignancy.

With all this, they found that prior COVID-19 infection was associated with about a 27% increased likelihood of developing new onset erectile dysfunction when compared to those without prior infection. Now think about those dates. This was prior to the widespread implementation of the COVID-19 vaccine. This is, you're not vaccinated, you get COVID-19. We're basically seeing about one in 60 men are developing erectile dysfunction after that infection. If there's more than 60 men listening in the audience who now have erectile dysfunction. Just all those people that want to go out there and get "natural immunity".

VR: Yes. Daniel, there's no evidence here from this paper that vaccination blunts this at all. Right?

DG: That's what we've got to see now, is now we have to - The great thing about the IBM MarketScan, somebody do this study, you can go ahead and you can now create a cohort of individuals who are vaccinated and then got infected after vaccination. Because I'm fingers crossed and everything else crossed that vaccination is going to prevent this from happening.

VR: Would you consider this another symptom of Long COVID?

DG: It is a post-acute sequelae.

VR: It's not great, but compared with the other aspects of PASC, there is a treatment for this. It's not as bad as it seems, right?

DG: Yes, we'll get into quite a bit of a discussion later on about post-acute sequelae of COVID. My gosh, if you're going to pick a sequelae, I know for some men who are listening, this would be the world ending for them. This is not quite as world-ending as some of the other post-acute sequelae.

VR: Yes, it's treatable, right? It's treatable.

DG: Yes. There's the little triangular pill. There's the Viagra. You don't know what I'm even talking about.

VR: I didn't know it was triangular. No.

[laughter]

DG: All right. Let's move into children COVID and vulnerable populations. People may have caught the news this last week. Again, sharing disturbing things, but the National Center for Health Statistics reported 1,205 pregnant women died in 2021, representing a 40% increase in maternal deaths compared with 2020 and a 60% increase compared with 2019. Remember 2019, that was before COVID. The count includes deaths of women who are pregnant or had been pregnant within the last 42 days from any cause related to or aggravated by the pregnancy.

Now a separate report by the Government Accountability Office has cited COVID as a contributing factor and at least 400 of those maternal deaths in 2021 accounting for much of the increase. Couple things, one, you could do the math there in your head or just repeat it, because I just said 400 mothers died in 2021. When the mother dies, you're also usually losing the baby. That's a real serious number when we talk about try to protect these pregnant individuals. Couple things, August 2021, the CDC came out with unambiguous guidance supporting vaccination for pregnant women. Most of the pregnant women who died of COVID had not been vaccinated.

We've discussed quite a number of articles about the benefits of vaccination for a pregnant individual and also for the newborn. I'll also put right in here an article that I believe we discussed previously, “Adverse Maternal, Fetal, and Newborn Outcomes among Pregnant Women with SARS-CoV-2 Infection: An Individual Participant Data mMta-analysis,” published in *BMJ Global Health*. Where in this analysis they estimated that unvaccinated pregnant women with SARS-CoV-2, as compared with uninfected pregnant women, were at significantly increased risk of maternal mortality. Relative risk of 7.68, relative risk of ending up in the ICU 3.8, and your relative risk of ending up on a mechanical ventilator 15.23.

VR: Daniel, I presume in 2022, this number should go down, right?

DG: Yes. I think it's interesting - challenging, I guess, is probably the right word. Some of our colleagues out there who are advising women considering pregnancy or who are pregnant, "Oh, why don't you just wait and let's see." I just think the way we get this number down is by not giving that bad advice. We get this number down with vaccination. I am actually going to move into a couple of vaccination articles we have this week. Some good ones, actually. I think some interesting ones. This article, you get the headline, you get what the news media interprets and then you actually read the article and maybe you got a different sense.

Here's the article, “Correlates of Protection against COVID-19 Infection and Intensity of Symptomatic Disease in Vaccinated Individuals Exposed to SARS-CoV-2 in Households in Israel: A Prospective Cohort Study,” published in *The Lancet Microbe*. This was interpreted as, large study identifies antibody concentration thresholds that correlate with protection from symptomatic COVID-19.

What does the actual science say? These are the results of a prospective cohort study looking at household context in homes in which a new SARS-CoV-2 infection, that's the index case, was detected within the previous 24 hours. They included adults aged greater than 18 years of age, who had received one or two vaccine doses, had an initial negative SARS-CoV-2 PCR, so the baseline not infected, no previous infection reported and then had a

valid IgG and neutralizing antibody result. The exposure of interest was the baseline immune status, including this IgG antibody concentration, the neutralizing antibody titer, and they also threw in T cell activation.

The outcome was a PCR positive SARS-CoV-2 infection between day two and day 21 of follow up. They're also looking at intensity of disease symptoms. You got someone in the house, they got the COVID, and now you're looking and seeing about these other individuals. They're going to do this via a telephone questionnaire. With this really nice Figure 2, I want anyone who's going to be reading the headlines to look at Figure 2. Because Figure 2 is really worth looking at, to really see. If you look at Figure 2, and Vincent, you can look at it too, and you can tell me if I'm being honest or not, there is a statistically significant difference in the mean, but there really isn't a clear threshold.

Some people with super high antibodies got infected, some people with low antibodies did not get infected. There's a correlation, but I'm not seeing this clear cutoff, this threshold at which you are safe and don't have to worry.

VR: No. You're absolutely right and the means are very similar between infected and uninfected.

DG: They're statistically different [laughter], statistician.

VR: I'm thinking maybe non-neutralizing antibodies are important. If you look at the total IgG, it's the same. It looks the same in both infected and uninfected. Not even that gives you a correlation.

DG: Yes. I think this is big. Because I read this headline and I'm like, "Oh, my gosh, this is great," and I'm like, "Oh, but the science."

VR: Where do they get the headlines from? Did the journal call them and say, "Use this headline?" I don't get it.

DG: They called Dickson actually, no.

VR: Oh, OK [laughter].

DG: All right. No. Actually, to be honest, or I think to be friendly to our - a lot of times the person writing the article doesn't actually get to pick the headline.

VR: No, that's correct.

DG: A lot of times that's an editor.

VR: That's correct.

DG: You're like, "What? What headline?" All right. We also have the article, *"C*orrelates of Protection and Viral Load Trajectories in Omicron Breakthrough Infections in Triple Vaccinated Healthcare Workers," published in *Nature Communications*. These are results of a prospective cohort study looking at infections in triple vaccinated healthcare workers with and without prior non-Omicron SARS-CoV-2 infection during four weeks in January through

February, 2022. This is the first period of Omicron transmission in Sweden. Hello to our Swedish listeners out there.

During this study period, BA.1, BA.1.1 and BA.2 circulated in Stockholm, Sweden, allowing for comparison of these infections with the three sublineages post-vaccine. The association between serum antibody levels, protection against infection, and viral RNA trajectories were analyzed. Here, I like this, they reported high serum antibody titers are shown to be protective against infection linked to reduce viral load. Actually, they say that, but then again in their discussion, they comment that they're looking at RNA and this is not necessarily viral load - Thank you for doing that - and time to clearance.

Now, an interesting section is their discussion of mucosal IgA. They point out that they had recently demonstrated an association between mucosal spike-specific IgA and protection against Omicron post-vaccination infection. In this cohort, they report that the addition of mucosal IgG or mucosal IgA did not change the risk estimates associated just with looking at serum IgG. In some analysis, they suggest that IgA might be a mediator of the effect of prior infection against another infection.

The authors go on to say, I'm going to just quote them, "Taken together, these findings may suggest that while high serum IgG titers protects against infection regardless of mucosal immune responses, the additive protective effect associated to prior infection is largely mediated through mucosal IgA and not by serum IgG."

VR: They have a different conclusion from the previous paper. They think high antibodies do prevent infection. The other paper did not.

DG: Yes. I put in the figure. This is actually an interesting way they did it. If you look at Figure 1, you go down to Section C, if you actually take people and break them apart - and I think this is why it's good to have had that other paper in here. First, you say, "Let's take the people in the greater than 75th percentile of the IgG, let's compare them to people who are not in that," then you can see a separation. It almost makes you think that at an individual level, you can say, "Oh, I'm in the top 75, I'm doing great." but as you see, if you look at the figure, even the people in the top 75, they're still getting infected and most of the people in the lower 75, they weren't getting infected.

Let's move on to a question I am getting a lot this past week. This is the question, "You know Dr. Griffin, it's been a while so what about another booster now?" [chuckles] I'll start by saying that health officials in the UK and Canada have recommended additional boosters for high-risk individuals such as the elderly and nursing home residents so people are asking. I will just get people up to speed. There are ongoing discussions about whether more than one booster per year might be recommended for high-risk individuals.

We will certainly discuss when anything happens on this front here in the U.S., but I thought, Vincent, you and I might have a little bit of a discussion about what do we know and what is the thought here? What could people realistically expect from another booster?

VR: I will quote Paul Offit, who put it very clearly. A booster will boost your antibody levels for a couple of months so that it will reduce the likelihood of infection. Three months, let's say, and then you're back to low levels and you're going to get infected. He says, "Well, in

most people, that doesn't matter. If you're over 75, it could." He said, and you may comment on this, "Some people, any infection, any little infection puts them in the hospital," and so you don't want them - For them, maybe you do frequent boosting, but for the rest of the population, his view is that frequent boosting is not a good public health strategy, as you know.

I think that makes perfect sense. I think if you're in a risk group, just have a plan, as you say, to be treated with an antiviral.

DG: I think we're all on the same page. I think that's a realistic thing, is boosters boost, but only about three months of that extra. You're boosting above this 90% durable reduction. I think that's with the literature, that's with the science, that's what Paul Offit and we've been saying repeatedly, but there are certain individuals who you say, "It's been six months out. We can, four, three months, let's say, reduce your risk of infection." There may be certain high-risk individuals where it makes sense.

The science is here, the understanding of the immunology is here. That's not going to change whether or not an organization makes a recommendation or not. This is a reasonable thing to have a discussion with your provider. What's your risk benefit? What's your particular benefit for going down this route? Yes, I would agree. A public health benefit of boosting people, what? Four times a year, so you keep at that every three months, that makes no sense from a public health. Telling everyone to get a booster, again, I don't think that makes any sense.

VR: Daniel, are there some populations where we do two influenza vaccines every year?

DG: Interesting. Prior to COVID, and I think we brought this up, there were certain individuals that would get a second flu shot. We've talked a little bit about this. Some primary care docs will give folks a flu shot in August, and it's part of this whole like, "Oh, I give people their flu shot. It's how I bring them in for their physical." I'm like, "Yes, schedule the physicals in October, November, please." [laughter] If someone got their flu shot in August and now suddenly we're starting to see influenza spiking in March, that person, particularly if they're high risk, they're probably better off getting another flu shot.

VR: All right. There's some precedent in certain populations, but certainly not for a year. We talked about this before. It's not even clear what the seasonality of COVID is yet. We know flu is a winter disease here so you can do your two shots during the winter. If COVID continues during the summer, it makes it difficult to know when to give those two shots, right?

DG: Yes. I think that's huge. All right. Let's move on to the early viral upper respiratory non-hypoxic phase. You're acute, that first seven days, you're feeling crummy, you're in the viral phase. Couple updates here. Start with the article, “Effectiveness of Nirmatrelvir–ritonavir,” - let's just call it Paxlovid – “in Preventing Hospital Admissions and Deaths in People with COVID-19: A Cohort Study in a Large U.S. Healthcare System,” published in *The Lancet Infectious Diseases*. These are the results of a matched observational outpatient cohort study in the Kaiser Permanente Southern California healthcare system.

Data was extracted from electronic health records of non-hospitalized patients, that's great, age 12 years and older who received a positive SARS-CoV-2 PCR test between April 8 and October 7, 2022. They had not received another positive test within the proceeding 90 days. This is acute, you just got diagnosed with COVID. Not just to keep testing positive. They compared outcomes between people who received Paxlovid and those who did not by matching cases by date, age, sex, clinical status, including care received, presence or absence of acute COVID-19 symptoms at testing. Lots of other stuff, I will just say.

The primary endpoint was the estimated effectiveness of Paxlovid in preventing hospital admissions or death within 30 days of a positive test. The study included over 7,000 individuals who received Paxlovid and 126,152 folks that did not. They give us an overall estimated effectiveness of 79.6% for this combined endpoint of hospital admission or death. Here's the number I really want to hammer home. If these folks were within the first five days and they get started on Paxlovid within 24 hours, 89.6%. Remember, this is during Omicron, mostly vaccinated.

Vaccinated individuals we got, let's say, that 90% reduction. With our vaccination, we're throwing another 90% reduction. Real-world data here. I will make a couple comments just to be honest here. There's a big difference between an individual's relative risk versus actual risk. We've already gotten that number pretty low for some individuals. If you're 30 years old, you're vaccinated, boy, your risk of ending up in the hospital is already quite small. Let's say you're 92 years old, you've got hypertension, you've got some other medical problems, that's where that 90% reduction is a significant actual risk reduction or absolute risk reduction as we'd like to say.

VR: That's the plan, right? If you can take this drug, instead of being boosted so frequently, you take it and it gives you 90% prevention of hospitalization.

DG: Yes, 90% plus another 90%; 99% with a combination of vaccination and getting your Paxlovid right up front. Don't wait. Don't wait to see how you're going to do. Don't wait till the window closes.

VR: When I tested positive last November, I said to you, "What should I do? Can I wait and see?" You said, "No."

[laughter] Not that I knew I shouldn't, but I was just curious as to what would happen to me, because I'm a scientist. Right?

DG: Yes, but you know what, that's a problem. You would only been an N of one.

VR: Yes. That would be the only experiment if it failed.

DG: Exactly. That'd be your last experiment. All right. Number two, in some areas we still have access to remdesivir, molnupiravir, convalescent plasma, remember for those immuno-suppressed folks who have no other options. Let us move on to week two, the early [crosstalk]

VR: Can I ask you a question? I'm sorry.

DG: Yes, go for it.

VR: We had talked about oral remdesivir a while ago, is there anything happening on that?

DG: At the moment, we don't have access to it, ongoing studies, but yes, we're still waiting.

VR: OK, got it.

DG: I will certainly include that when we have more information.

VR: I'm sure.

DG: All right. Now week two, remember the cytokine storm. I probably should have just stuck with that. This is when we think about steroids, after the first week when those SATs are dropping, anticoagulation, pulmonary support, immunomodulation, and I'm going to actually spend a little bit of time today, a little bit more than we often do on late Long COVID PASC. I want to discuss just a couple folks because sometimes these stories, I think at least for me, really bring things home. I recently saw a patient, this week who got COVID this summer and actually has now developed really debilitating Long COVID.

I also saw a physician again, a repeat visit who actually just recently got COVID and now has Long COVID, unable to work. It was really interesting, the physician was making a comment to me that early on, a lot of people had Long COVID and so they felt like they missed all that camaraderie of being it in together. Now getting Long COVID it's just people are annoyed by you because COVID is supposed to be over and they certainly are not supposed to be getting Long COVID. I just want to point out this is still happening and still could be debilitating. I will mention an article, SARS-CoV-2 mRNA Vaccines Decouple Anti-viral Immunity from Humeral Autoimmunity," published in *nature communications*.

Basically, I'm going to plug *TWiV* 993. I'm going to leave in a link, COVID-19 drives autoimmunity. Really, I thought it's a difficult article, particularly because the title - I don't know if someone made them change the title. Maybe it was some editor. Really the point here was that if you look at folks that got COVID-19, you see a lot of autoreactive antibodies being generated quite different from what you see with vaccines. This whole idea that, oh, you saw a spike and that's why you're getting all these auto-reactive antibodies. The auto-reactive antibodies are actually quite common, something we certainly see in COVID-19, but rare, probably with vaccines, at least based upon this research.

I did want to make the comment that vaccines are not just about preventing severe disease and death, they also have this effect upon preventing post-acute sequelae of COVID. As we've actually talked before, some of the preventative and therapeutic impacts for PASC. I also want to give people a heads up on another one of these studies looking at, can I treat my folks with Long COVID with Paxlovid? Will it make a difference? Is it an effective treatment? Our friends up at Yale, so Harlan Krumholz and Akiko Iwasaki, they actually have started this trial and it's a decentralized trial. It's a randomized double-blind superiority, placebo-controlled study where folks do not require site visits.

If you're in Connecticut, Florida, New York, you can enroll, an interesting tri-state, not the tri-state, but a tri-state. They'll actually deliver the study drugs to the participants' address.

We can leave in links here to the study teams' phone number 203-497-1246 and Yale Paxstudy@yale.edu. I know there's another study going on at Stanford, so it's always great to have more access. We have more evidence-based guidance.

One of the challenges I want to talk about, and I want to say this in a positive way, is that we do actually have ways of approaching and helping folks with Long COVID. I actually was communicating today with the folks that run our post-COVID recovery center here. I don't know what we are right now. I guess we're Optum, we used to be ProHEALTH. How do we approach this? This is just a straightforward approach. We usually start by spending a lot of time on the history and trying to understand when did the symptoms start, and then trying to identify what symptoms are affecting the patient, looking at cardiac, looking at pulmonary, gastrointestinal, neurological, I'll say, immune.

Then as we talked about new diagnoses, people now they have diabetes, now they have thyroid, now they have adrenal, now they might have erectile dysfunction, if we ask. Important to know what the timing of the first COVID infection, timing of reinfections, timing of COVID vaccinations because that may actually have an effect upon what we recommend. Have they been hospitalized? How often are they accessing the medical system? What have they tried so far? What are they trying now? How have they done with those different things?

I want to point out, there are a lot of system-specific things that we can focus on. If it's a cardiac issue, we will often involve cardiology. If we're concerned about PoTS, and that's postural orthostatic tachycardia syndrome, we might go ahead and do tilt table testing. We might do a NASA 10-minute lean test, we might talk about sodium supplementation, increased fluid intake. Be careful with those sugary drinks because sometimes sugar can be a trigger for these individuals. There's a number of medications, fludrocortisone, certain, but not all beta-blockers, avoiding alcohol, certain types of physical therapy, even aquatic therapy with arrhythmias.

We have medications to address that, chest pain, determining whether or not it's an ongoing inflammatory process, looking a lot at post-exertional issues, pacing as we've discussed. When it comes to pulmonary, we might see cough, we might see dyspnea, we might see pulmonary function abnormalities, and interesting we were discussing today, we're seeing a lot of new-onset sleep apnea, something important to recognize and address. Some folks, it's a GI involvement predominant. Sometimes we're using our famotidine rather than our PPIs, sometimes antihistamines.

Interesting enough, sometimes we're using montelukast, or Singulair, which is actually a leukotriene receptor antagonist. Interesting, a lot of times people have a headache when we start it and then we restart it, neurological, right? A lot of new-onset migraines. We can handle migraines. We have a lot of medications, we can work with neurologists. Just want to really let people know that if you're suffering out there, reach out, find a provider who's familiar with this. Actually, we can, in most cases, make a difference. I will wrap it up there. Low and middle-income countries, remember, there's a whole big world out there. 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 a small amount helps. We're now in the middle of our American Society of Tropical Medicine and Hygiene fundraiser, February, March, and April. Donations will be doubled up to a maximum donation of $30,000 for American Society of Tropical Medicine and Hygiene.

VR: It's time for your questions for Daniel. You can send them to Daniel@microbe.tv. Hannah writes, first off, "Thank you for your consistent, honest COVID, other infectious disease info. Your updates on *TWiV* have been very helpful as I seek to guide my family medicine patients through the COVID maze, MD at a small clinic hospital. My question, what is the long-term efficacy data for the bivalent COVID booster in non-pregnant and adults of average risk under age 65?

"From articles I've read and your discussions on the podcast, I'm not picking up strong data behind the booster, at least for severe disease protection beyond two to three months, especially in this lower-risk group. Seems that the original two-dose mRNA series continues to be the mainstay of protection. I strive to give my patients all the data we have, not popular opinion, want to make sure that I'm representing the science correctly."

DG: Thank you for writing in. Thank you for your kind words. Hopefully, our discussion today helped with this. Boosters do boost that three-month reduction in infection if you don't get infected, can't have severe disease. Then you get into what we talked about, relative risk reduction versus absolute risk reduction. If you have a significant risk of severe disease, then your actual absolute risk reduction is going to be significant.

If you've already reduced that quite a bit, so we're talking about young, healthy individuals, then the absolute risk is not going to be that significant. Remember, if that young, healthy individual gets pregnant or there's any other issue that significantly increases their risk, we talked about a 15-fold increase of ending up on a mechanical ventilator if you're pregnant and gets SARS-CoV-2. Hopefully, our ongoing discussions will help inform you.

VR: Wouldn't you say that the three-dose mRNA series is what we should be doing for everyone?

DG: I think it's a three-dose series. I think we're almost - well, I don't want to operate by consensus, but I would say the science, the preponderance of data would support this as a three-dose vaccination series.

VR: Ann writes, "Wondering if you could explain the difference between a cytokine storm and septic shock. To the best of my understanding, both terms described an acute, overwhelming immune response triggered by an infection that leads to organ failure and potentially death. I also know there's a certain amount of disagreement or controversy when it comes to defining both of these terms. What is the difference between the two or is there a difference?"

DG: Yes, there is a difference, actually. Thanks for asking. I'm going to try to answer this broadly and then I'm going to ratchet it down and focus on in the context of COVID. The concept of cytokine storm, for a lot of us, our approach and understanding of it came from

CAR-T therapy. People have listened to other *TWiV*s or maybe even *Immune*. This is where we actually re-engineer a person's T-cells and give them these chimeric antigen receptors.

One of the problems is, as those T-cells expand, usually using it to fight a cancer, this can trigger this tremendous cytokine storm. You end up with different levels of different cytokines, so interferon-gamma, IL-1β, and actually because what you're deciding or trying to decide in these often young kids is, are they having a cytokine storm from the CAR-T, and you're going to treat this with immunosuppressants? Maybe steroids, might be IL-6 inhibition, or did they get an opportunistic infection you want to jump in with antibiotics? You can actually use a combination in CAR-T therapy, checking interferon-gamma, checking IL-1β, trying to make a distinction there.

Now, in COVID, let's go to COVID. COVID it's week two or three. You're trying to decide the drop in blood pressure, the fever, all this inflammation. Is it coming from the cytokine storm of COVID? Is it coming from a secondary infection-made bacterial or fungal? We're doing blood cultures, we're looking for bacterial fungal infections, maybe we're doing a history of physical, and here different parameters, sometimes we'll actually use a ferritin procalcitonin ratio.

The inflammation of COVID is going to cause your procal to rise, but it's going to cause your ferritin to shoot way up. We're in a bacterial infection, you'll end up with something of a rise in ferritin, but a much more significant rise in procal. A ferritin procal ratio of less than 800 is going to help steer us more towards a bacterial sepsis relative to a COVID cytokine storm. All right [chuckles].

VR: OK. Emma has a silly question, "If an infection were spread to me from petting my dog, would she be considered a vector or would her fur be a fomite?"

[laughter]

DG: I like that. If the dog is healthy and let's say someone's got the flu or norovirus, I'm going to use norovirus here, and they're not cleaning their hands and they're petting your dog for comfort. Then the dog comes over and you pet the dog and the dog stays fine, then I'm going to call the dog a fomite, a moving fomite.

VR: I would agree. All right. Sam wants to know, “If the New York rats have COVID. Can humans catch it from rat breath?”

DG: We got to do the studies [laughs].

VR: I don't know, but how are you going to get close enough to a rat to breathe in? I don't think that's possible. All right. Finally, Michael writes, "Recently a pediatric patient presented for needle phobia in treatment for acquired aplastic anemia, which her parents attributed to complications from the COVID-19 vaccine. Do you have a clinical comment on the parent's perception? Is it just as likely that the patient had asymptomatic COVID and unfortunately developed this sequelae?"

DG: I don't know. This is going to be hard. It's going to be a hard to know what happened there. You're on your own [laughs].

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

DG: All right, thank you. Everyone, be safe.

[music]

[00:45:08] [END OF AUDIO]