This Week in Virology

TWiV 1006 Clinical Update

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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 1,006, recorded on May 11, 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: I made a point of saying 1,006 because last time, I said 1,000 and 6 and 1,000 and 5. I made a point of saying I said it correctly. When I heard it later, I realized I didn't.

DG: [laughs] OK, all right. Well, let's get right into it. I think maybe we'll add a slogan, "Be nice to Vincent."

[laughter]

DG: "It's so hard to forget pain, but it's even harder to remember sweetness. We have no scar to show for happiness." That's Margaret Atwood's *The Handmaid's Tale*. I think we've gotten to a point where it's just a lot of - Well, even that, "Be nice to Vincent," let's be a little more gentler [laughs] across the board. We are getting well to the end of norovirus winter-vomiting disease, maybe in a big way. A vaccine to prevent another experience trying to obtain natural immunity, no?

The article, "Immunogenicity and Tolerability of a Bivalent Virus-like Particle Norovirus Vaccine Candidate in Children from 6 Months Up to 4 Years of Age: A Phase 2 Randomized, Double-Blind Trial," recently published in *Human Vaccines & Immunotherapeutics*. Early work, looking at antibody response and safety, but some encouraging stuff. It would be great not to have to, what's the opposite of "look forward," dread [laughs] winter-vomiting disease season each year.

VR: Do we know what the correlates of protection are or antibodies, the whole story there?

DG: That's going to be interesting stuff that will come out of this. This is early work looking at antibody response and safety. What I really want to know is efficacy. Does it work? That's going to help us come up with some good correlates here.

VR: OK.

DG: All right, influenza, the season has ended here in the United States. Looking toward the future, we have the very exciting article, and I do think it's really exciting. “An Influenza Hemagglutinin Stem Nanoparticle Vaccine Induces Cross-Group 1 Neutralizing Antibodies in Healthy Adults,” published in *Science Translational Medicine*. A tiny bit of background here for our listeners. Influenza has its own spike-type protein, the HA or hemagglutinin. Not technically a spike, but a glycoprotein. Is it technically a spike? I think it's a spike.

VR: Yes, it's a spike.

DG: We'll say it's a spike. It's a protein decorated with some sugars that binds the virus to its target cells. It's a trimer. It's a little familiar here. Three of these proteins all put together to form this spike structure on the surface of the flu virions. It has a receptor-binding domain. It's a good thing about COVID where all people are starting to be familiar with this stuff.

In this case, instead of ACE2, it binds to sialic acid on our or other animal cells. The challenge for us from an immune standpoint and for vaccines is that the head of this flu spike that binds the sialic acid can change enough while still binding that our antibodies do not effectively bind to it. I think of this molecule like a big maple tree and that stalk or trunk rising out of the virion surface. That's the part that is invariant.

VR: We think, "Where do we put pressure on it?"

[laughter]

DG: That's interesting. That is the big concern, right?

VR: Well, you have to try it.

DG: We got to try it. We got to see - Well, that's the issue. If you apply selection pressure, will it start to change? This is science. [laughs] A little bit more about our flus. We've got our Flu A or Flu B or Flu C or Flu D. Really, the Type A is that classic seasonal one that bounces around. Then people are probably familiar with, "What are all these different numbers? What's H1 and N1? What's that about?"

The H's have a bunch of numbers, 1 through 18. The N's have a bunch of numbers. We start off with H1N1. That's our ancestral 1918. Then as things went, then we got H2 and H3. Same on the other side. N1, N2, up to N11. What I will say is, what's exciting here is, could we actually do this instead of guessing which of those - not only which of the H's and which of the N's, but even more, which subtypes can we just go ahead and target what we think to date has been relatively invariant?

Here is the chance to read about this first-in-human dose-escalation open-label phase 1 clinical trial that tested an HA-stabilized stem ferritin nanoparticle vaccine. These aren't

huge numbers: 52 healthy adults, aged 18 to 70 years old, enrolled to receive either 20 micrograms or 60 micrograms with a prime-boost interval of 16 weeks. I like the timing there. Thirty-five, so 74%, of the 60-microgram dose participants received the boost, whereas 23% boost vaccinations were missed because of, well, public health restrictions in the early stages of the COVID-19 pandemic.

The primary objective at this point was to evaluate the safety and tolerability. The secondary objective was to evaluate antibody responses after vaccination. They found this was safe and well-tolerated with expected mild, solicited local and systemic reactogenicity. Most common symptoms included pain or tenderness at the injection site. That was about 20% of folks. Headache, that was about 20%. Malaise, that was about 12%.

They found that this elicited cross-reactive neutralizing antibodies against the conserved HA stem of group 1 influenza viruses despite previous H1 subtype head-specific immunity. It's interesting. I've pasted in a figure to distract Vincent. These responses were durable with neutralizing antibodies observed more than one year after vaccination. Now, do we know what that threshold is for it to still be above what threshold at one year? It was nice to see the data. Also, what about what we think about a mucosal site? Still a bit here, but very exciting to see this trial.

VR: Look at that, 40 weeks after the - Well, there's the prime and then the boost at 16 weeks as you said, but 40 weeks, we still have pretty good neutralizing. They do go down a bit, right? They're still there.

DG: That's 24 weeks after that boost, right?

VR: Yes, six months.

DG: We're not seeing any of that. What do we call it? Waning, contraction? Who knows what we call it? Dropping of those levels.

VR: Well, slight dropping, Daniel, OK? They're dropping, all right? Not a lot. They're going to eventually go down lower. There's no question about that. It's interesting that it's durable. I wonder why. What about this that made it like that, right?

DG: Yes, it is interesting. I'm curious to see more on this. I'll leave in a link. There's a cool link to CDC's subtypes of influenza A. You can see which different animals get infected with which different H's and which different N's. I think we have an audience that will enjoy that.

VR: I did look at this paper. I was thinking about it for *TWiV* but didn't make the cut only because I found an interesting one about Epstein-Barr virus causing chromosomal breaks, which I thought was very interesting. They're not looking at T-cells. We do think that T-cells are really important for influenza protection. Hopefully, they will do that at some point, right?

DG: Yes, I think that would be great. There's always been a focus with influenza on antibodies and correlates of immunity, but it would be great to have a better understanding of T-cells. I think if anything we've learned from the last few years, T-cells are really important to be looking at. I know it's harder to look at them, but don't just, you know -

VR: Yes.

DG: Moving into COVID, just a few minutes there. Now, here we are back to COVID. I guess I should say, we'll start right with the *MMWR*. We're recording this on May 11. The *MMWR*, "COVID-19 Surveillance After Expiration of the Public Health Emergency Declaration - United States, May 11, 2023," came out on May 5 as an early release. Very timely that we're talking about it today.

We'll talk a bit about the CDC later on today in this recording. Let me read here that authorizations to collect certain public health data expire at the end of the U.S. public health emergency declaration on May 11, 2023. People who are listening, it will have already expired. Weekly COVID-19 hospital admission levels and the percentage of all COVID-19-associated deaths will be primary surveillance indicators.

Emergency department visits and percentage of positive SARS-CoV-2 laboratory test results will help identify early changes in trends. The genomic surveillance will continue to help identify and monitor the SARS-CoV-2 variants. Just a little context here. Everyone's been beating up on the CDC lately. On January 31, 2020, the U.S. Department of Health and Human Services, the HHS, declared, under Section 319 of the Public Health Service Act, a U.S. public health emergency because of the emergence of SARS-CoV-2.

After 13 renewals, the public health emergency expired, past tense when people hear this, on May 11, 2023. Authorizations to collect certain public health data expired on that date as well. We will get less data. It will be less timely, like getting the weather three weeks after the fact and just the average temperature with a wide margin of error. [laughs] OK, all right.

Also, another *MMWR,* "Provisional Mortality Data - United States, 2022," came out. Remember, this is CDC stuff. The graphical abstract really captures the data well, so maybe our surgeons can enjoy this as well when they look at the pictures. The National Center for Health Statistics' (NCHS) National Vital Statistics System collects and reports annual mortality statistics using U.S. death certificate data. I think we've talked before about the fact that you don't put COVID on the death certificate. It's not going to end up here. We know that there might be some underreporting in certain parts of our country.

Because of the time needed to investigate certain causes of death and to process and review death data, final annual mortality data for a given year are typically released 11 months after the end of the calendar year. That's the final step. Provisional data, which are based on the current flow of death certificate data, provide an early estimate of deaths before the release of final data. This is still provisional.

In 2022, approximately 3,273,705 deaths occurred in the United States. This is actually down 5% from the year before. It's very important to have a sense, right? We're a big country. During 2022, COVID-19 was listed as the underlying or contributing cause of 244,986 deaths, so about a quarter-million deaths, 47% decrease from the 462,193 deaths in 2021. I just want to compare these numbers to the estimated 19,000 flu deaths for this recent season.

In what way is COVID now the flu? I just have to echo that every time people use the word "mild" in the same sentence as COVID, this contributes to people not getting treatment and people dying. I'm going to vent a little here. Nineteen thousand deaths from the flu. Last

year, 244,000, almost a quarter-million, deaths from COVID. Remember, that was the time of Omicron when everyone was starting to say things were so much better.

VR: Daniel, it clearly went down, 47%. Come on, it's clearly mild.

DG: Yes, it's only 5,000 deaths a week. That's nothing. [laughs] Now, I was out for a walk the other day. The person who said this asked not to be identified as the person who said it, but their comment was, "Where are all these people coming from? Didn't all the old people and vulnerable people with medical conditions, didn't they already die? What are we doing? Making new ones every day?" Yes, Virginia, we are making new ones every day.

Every day, each of us gets older. Each day, new people are developing new medical problems that put them at risk. Just to give people context, it's estimated that every day, about 10,000 people age into Medicare. Plenty of us apply for people to continue to have issues with COVID.

All right, the article, "Targeted Vaccine Messaging to Promote COVID-19 Vaccines for Children and Youth," published in *Pediatrics*.

I was recently down in Atlanta. While down there, I was talking to my friend, Yuan-Po Tu. We were talking about, what did we need to do a better job? Lots of articles coming out. Lessons learned, what do we need to do better? One of the things that we settled on was we needed better communication, particularly around the vaccines. The objective of this study was to assess the effectiveness of distinct messaging types in promoting COVID-19 vaccination intentions for parents of children and adolescents.

The investigators collected data from Voices of Child Health in Chicago Parent Panel Survey from October to November 2021. Parents were randomly assigned to read one of four message types and then report their intentions to vaccinate after this. It's really interesting. There's an introductory format and there's really, I'll say, four things that they can talk about. They can talk about it being well-tolerated. They can talk about it being safe and tested.

They can talk about trusted parents vaccinating their children and then they talked a last one where COVID-19 vaccine will be available and recommended. The sample included 898 parents compared with a control group, which didn't get targeted with these messages. The proportion of parents who are very likely to vaccinate their children was higher when messages highlighted that other trusted parents have vaccinated their children.

That's that story when I say, "You know what? My children all were vaccinated," or "The vaccine is safe and thoroughly tested," but not when we use words like "well-tolerated." After adjusting for parent and child characteristics, the odds of being very likely to be vaccinated remained high in the trusted parents group, but not in that thoroughly-tested group. That seems to be the biggest message, is talking about the fact that parents they trust are doing this.

I think it's important for us to study and understand, "Well, what's the best messaging to get across when we're talking about vaccines?" I'm also going to leave in a link to a paper I published a few years ago about how much people trust their physicians and those

conversations that they can have with physicians. I also want to make a comment about nurses here, Vincent. I'll leave in a link to a Gallup poll where, for the 21st year in a row, nurses are the most trusted profession in the U.S. Yes, I listened to the other episodes, but I wanted to say something here.

A lot of times, I see interactions between physicians and nurses that are, I'll say, a bit hierarchical. I'm going to encourage physicians to move away from that paradigm. Nurses are our colleagues. If you take that time to educate and explain vaccines to a nurse and they understand that, they are going to spend a lot of time having discussions with patients. They are actually even more trusted than we are, so just my nod to nurses. I'll even throw in the fact that my oldest child just got into nursing school, so we're quite proud.

All right, [chuckles] so I wanted to talk a little bit as we get into testing. I'm going to share a story. It's this question. Have we forgotten how to make the diagnosis? We had an individual show up at one of our hospitals on Saturday. The story from the daughter was, "My dad is just not right. He's normally a sharp, bright guy, but he's confused. We brought him in. We're not sure what's going on. His neighbor has COVID and his neighbor just keeps coming over visiting. I'm quite worried that maybe this is COVID. Could you test him?"

Unfortunately, the response was, "We have just done away with routine COVID testing. Since your dad doesn't have a fever, doesn't seem to be acting like COVID, we're not going to test him." Well, two days went by. By Monday, he was febrile. He was starting to require oxygen. The daughter apparently was driving people crazy. To placate her, they tested him for COVID, and, oh, my gosh, Vincent.

VR: He was positive.

DG: He was positive. Ouch. Well, I mentioned I was down in Atlanta with my good friend, Yuan-Po Tu. We discussed a little bit about the presentation for COVID. One is that it may have changed. The presentation for the last two years is someone had a positive test. We are no longer seeing loss of smell as often and sore throat. The first one to three days seems to be a very common symptom.

I know the media doesn't agree with this. We're just not seeing conjunctivitis as a symptom. I have to say, Po and I see a lot of COVID. My colleagues see a lot. Historically, this has been about 2%. If you put that in someone's ear, maybe they start to get some confirmation bias, giving them the benefit of the doubt there. Maybe they're not just trying to get quoted. Some folks, especially young, healthy, they might really only just have a few mild days of symptoms.

They may not even know they had COVID unless they go and test. Some older folks, I think this is the example of, "Grandpa is not quite right." That first patient that pose a little bit famous, you saw that patient at The Everett Clinic. That first patient in Washington in February 2020. That presentation was at a temperature of 104, a rash, conjunctivitis. They were thinking enterovirus, maybe measles.

This was a 17-year-old. Actually, that was one of the first hospitalized patients. One of the first ones I saw here in New York came in with horrible, profuse diarrhea and no fever. A lot of places start thinking about this. If you have an older individual and they've altered mental

status and your old paradigm of maybe it's a urinary tract infection, throw COVID in the mix as well.

VR: When they do test positive, what do they do?

DG: For instance, this individual, because people want to know, "How did it work out?" Monday, I was called. [chuckles] Grandpa has a positive COVID test. He's requiring five liters of oxygen. We got the sense of timing that we probably were about eight at this point. Went ahead, started him on remdesivir. He was in the hospital, started him on dexamethasone. I was chatting with him today. He is completely lucid. He was in the Air Force. We were talking about Barstow, where he spent a couple of years. Apparently, not Arizona. There's one down in Louisiana. He's doing much better.

VR: What's the limit for remdesivir? How many days out from -

DG: It's really within the first 10 and it's interesting. There was some recent data, I don't know if I'm covering it today, where if you're still within that 10-day window, maybe you miss your first five days, which is really the time to do it. Still, if you're within the first 10 before someone progresses to be on a ventilator, you still have a pretty significant impact.

VR: OK.

DG: OK, all right. People mark their calendar here. A heads-up. The Vaccines and Related Biological Products Advisory Committee meeting, June 15, 2023. We're expecting some comments about vaccination strategies going forward. Let's move into the early viral upper respiratory, non-hypoxic phase. I just want to comment. Isolation for the infected. I think sometimes we forget about that, but that comes up.

People are like, "How long do I have to stay isolated? What's going on here?" This was updated, March 21, 2023. We'll leave a link in. I just want to keep everyone on the same page here. These recommendations, interesting enough, no longer change based on COVID-19 community levels. That makes sense. Bunch of discussions, but then they talk about ending isolation after Day 5.

One of the things I will comment is when you go through this, you actually get linked back to some isolation recommendations for healthcare workers that have not been updated since August or September of 2022. I might circle back to the comment there in a moment. Here's, I think, also a perfect place to put a link to the article, “How to Overhaul the CDC,” publishes an opinion in *The New York Times* by Tom - How do you pronounce that? Ingsby?

VR: Inglesby.

DG: Inglesby and J. Stephen Morrison. Just some context here. Inglesby?

VR: Inglesby, yes.

DG: Inglesby is the director of the Johns Hopkins Center for Health Security. Dr. Morrison is a senior vice president at the Center for Strategic and International Studies. They conducted an investigation of the CDC's pandemic preparedness and response during the COVID-19

pandemic. The first two sentences outlined the issue. "Long recognized as the nation's leading public health institution and widely respected around the world, the Centers for Disease Control and Prevention has recently seen its reputation shaken, its performance compromised. As a result, public trust in the institution has eroded."

The study has some very critical comments. These are their comments. "The CDC stumbled terribly at the beginning of the pandemic when it could not meet the urgent imperative to distribute COVID tests widely across the country. It then struggled to clearly and quickly communicate its changing guidance on vaccines, masks, and precautions for workplaces and schools. The state and local public health agencies, as well as the private sector, became exceedingly frustrated in their attempts to engage with the agency. Governors and congressional leaders lost patience, stopped listening, and made their own choices. This fed a chaotic national response that put people at risk and further eroded public confidence."

They then go on to say, "'The CDC's communications are terrible' is a common refrain we've heard from senior elected officials. The agency is responsible for communicating new information and analysis to the public and private sector, its assessment of the latest infectious disease threats to congressional leaders, its recommendations to the Department of Health and Human Services and the White House and more."

"It also remains imperative for the agency to speak directly and meaningfully to skeptic Americans, in part by combating pervasive conspiracy thinking and dis- and misinformation. Right now, these major communication demands exceed the CDC's capacity." After the criticism follows, there are lots of constructive comments. Some comments about the great people at the CDC. I will say, I agree that this is an historic opportunity for change that cannot be squandered. It is imperative that we improve things at the CDC.

VR: Daniel, you should be the director.

DG: You know what? I'm going to muse here a little. What I think they need, I think they need a communication center in Washington, right there. It's a little bit of a problem that the CDC is in Atlanta and our government is in Washington, DC. In a sense, maybe the director of the CDC is too big a job. You want someone with that title doing the communication in Washington.

We need that. It needs to be one-on-one. They need to be accessible. They need someone trained in science communication. Don't sign me up for all the bureaucratic responsibilities that go with the other part of the job.

All right, I think there's an opening. All right, the article, “Impact of Severe Acute Respiratory Syndrome Coronavirus 2 Variants on Inpatient Clinical Outcome,” was published in *CID*.

This one, I'm going to say, it's a little bit tricky. I want to be careful for people not to just use this for supporting their agenda, but they are investigating outcomes of patients hospitalized with different variants. We do not have the first comparison between the number of infected getting hospitalized. You end up in the hospital. They're going to look at the variants and they're going to tell us about the different outcomes.

In this study, inpatients with COVID-19 at five hospitals in the eastern United States were included if they had hypoxia, tachycardia, tachypnea, or fever. They also had that SARS-CoV-2 variant data. The data is now in. They found that although risk of severe disease or death for unvaccinated patients with Omicron was lower with Delta, it was similar to ancestral lineages. Severe outcomes were less common in vaccinated inpatients with no difference between Delta and Omicron infections.

VR: Daniel, again, you said that a lot of people are dying. What is this, risk of severe death is lower? How can they compare that to a previous season?

DG: That's an interesting issue too, right? They're trying to sort this out. I think what they're trying to do is ask that question that people were saying. There's this idea out there, right? Four-hundred-sixty-six-thousand in 2021. Quarter-million just died in 2022. Was that difference variant-specific, or if you break it out, is it really a difference that's driven largely by unvaccinated versus vaccinated? Here, you're looking at folks that end up in the hospital. You look at the variant data. It's not a big driver. The big difference is being vaccinated versus unvaccinated.

VR: Of course, the patients are different as well. That's sometimes hard to control for because they are maybe different in ways you don't know about, right?

DG: You'd almost expect the Omicron to be a little bit better because the most vulnerable died, right? Over a million people have died of COVID. The most vulnerable people have already died. I think something interesting here that was in that early *MMWR* data is there's a trend towards a higher percent of the deaths occurring in the nursing homes, in the homes. Early on, people were being rushed to the hospital. They were ending up in ICUs. They were sitting on beds for weeks filling the place.

It was very, very visible, people dying. Now, when people ask about their experiences, they say, "Hey, there aren't that many people here in the hospital with COVID." Yes, because we are just basically letting them die at home. We're letting them die in the nursing homes. We're saying, "We know enough now to say, that's not going to be helpful to bring them in and put them on a ventilator for weeks and let them die there."

VR: Interesting. Oh, so that's a factor if you're using hospitalization as a metric, right?

DG: It's huge. If you're looking at ER visits and hospitalizations and, now, more and more people were just making that decision to leave them home, yes, that's going to-- and also, it's a big impact on perception. You're not seeing them. The deaths are becoming more invisible. I think it's important not to let them be invisible.

I think it's important for people to continue to make decisions about who is high risk and who can I help and when you are looking at someone who's high risk, who actually has a chance of progression to severe disease, to death, ending up in the hospital, any of the other disease issues. Number one, Paxlovid, remdesivir, molnupiravir, convalescent plasma in that particular setting. Let's avoid doing harmful and useless things.

VR: Daniel, yesterday, I was at an Infectious Diseases Society of New York meeting at Columbia. I was talking with an ID person there. She said some of her colleagues keep telling her about Paxlovid rebound. She can't believe it. [chuckles]

DG: You know what's really tough, Vincent, is early on, this is just like, "Do the variants cause conjunctivitis?" A lot of media folks called around and they found people that tend to always say what they want them to say. They talked about, "Oh, my family members. I had eight of them and four of them had rebound." I'm wondering, is this person actually even seeing patients or how come they're prescribing Paxlovid to their family members?

You would think that they'd be prescribing to other people who have more experience. This rebound terminology has really gotten stuck in there. I think we have to be careful. My warning to my colleagues, "Don't just say what the media person wants you to say. Say the truth." You could say, "You know what? I've been doing mostly administrative work. I haven't treated hundreds of patients." Let's stop with this misinformation.

Let's call this what we called it early on. It's the second week. It's the period of the cytokine storm, the hypoxic phase. No rebound here. When you get into there, this is when people might end up in the hospital. When we talk about steroids at the right time in the right patient, oxygen saturation less than 94%, and that's at rest. You don't have to walk the COVID patients up and down the stairs to find an excuse. Let's update those electronic health record order sets**,** anticoagulation guidelines.

We just had American Society of Hematology meeting this morning for a couple of hours, so we have guidance there. Pulmonary support, we talked about remdesivir a little bit earlier. If you're still in the first 10 days, some immune modulation beyond steroids with tocilizumab or baricitinib. Avoid those unnecessary antibiotics and unproven therapies, unless you get into that later Week 3 or if this person has a concomitant bacterial infection.

Remember, that's present in some cases, particularly people that are staying in the ICU for a long period of time. It's Week 3. They start to decompensate. That's when we were seeing a lot of the secondary infections. Coming in the door, a low percent. All right, we will move into what I thought was going to become the majority of this talk, which hopefully will as we learn more. Lots of good articles in *CID* this last episode, so the late phase PASC, Long COVID.

The article, “Prevalence of Post-Coronavirus Disease Condition 12 Weeks After Omicron Infection Compared with Negative Controls and Association with Vaccination Status.” The data here supports two main things. One is that vaccination is a tremendous tool for reducing the risk of Long COVID. Here, symptoms were much less common in vaccinated versus non-vaccinated individuals with Omicron infections. You have a background of 9.7 versus 18.1, right? The unvaccinated, twice as many reporting issues.

Then if you go ahead and you say, "Well, what about our background? What about people who got Omicron were vaccinated?" Encouraging is that an Omicron infection after vaccinated has only a low but non-zero risk, so only about 1%. The differential prevalence of post-COVID conditions and functional impairment attributed to Omicron BA.1 and BA.2 is

low when compared with negative controls. Vaccination is associated with a lower prevalence of post-COVID symptoms.

I do like the fact that they still talk about the Omicron subtypes because Omicron is now - I think someone who maybe it was the same person who was talking about all their family members with rebound was saying, "What's really good is we don't have to memorize all those Greek letters anymore." The virus is still changing. I will say, maybe it's been a while since I've said this. The plural of the anecdote is still not data. [chuckles]

Although I have lots of anecdotes from patients about improvement with probiotics, I was very interested to hear about a late-breaking abstract presented at the annual Digestive Disease Week conference. I didn't see you there, Vincent. “Gut Bacteria Cocktail Helps Long COVID.” These are results of a randomized, placebo-controlled trial in which patients receive the active microbiome treatment called SIM01, which comprises three Bifidobacteria species with a total of 20 million colony-forming units per daily dose for six months versus placebo.

70.2% of patients with digestive complaints at enrollment said they felt better after six months with SIM01 compared with 54% of those on placebo. Placebo rate is pretty darn good. Findings were similar for the other four symptom categories with improvement rates of 42% to 77.3% with the microbiome product. Response rates with placebo were roughly 15 to 24 points lower in all categories with p-values well below 0.05. Interesting, big placebo effect, but you're actually seeing about a 20% above placebo impact here. This study is actually like, "What's the science here?"

The study builds on gut microbiota-derived symbiotic formula, SIM01, as a novel adjuvant therapy for COVID-19. An open-label pilot study actually reported that the plasma levels of interleukin, IL-6, monocyte chemoattractant protein-1, so MCP-1, macrophage colony-stimulating factor, M-CSF, tumor necrosis factor alpha, and IL-1 were reduced significantly in the SIM01, but not in the control group. Is this applicable to all probiotics? Should we start recommending Bifidobacterial species over lactobacillus-containing probiotics? Should we do more studies? It's always the last answer.

All right, so let me close out by saying no one is safe until everyone is safe. I do want everyone to pause the recording right here and go to parasiteswithoutborders.com and click ‘Donate.’ The little bits help. The big amounts help. We are now having our Foundation for International Medical Relief of Children fundraiser. May, June, and July donations made to Parasites Without Borders will be matched and doubled by PWB up to a potential maximum donation of $20,000 from PWB to FIMRC.

VR: Time for your questions for Daniel. You can send them to daniel@microbe.tv. Bob writes, "Dr. Griffin, is it known whether the new RSV vaccine can be received concurrently with COVID-19 and/or influenza vaccines?"

DG: Looking at the study, I don't remember that there was any concurrent, and it would be ideal to know that, right? Because when people come in in the fall, it would be great to be able to get your, "Here's your flu shot. Here's your RXV." That's that catchy name for the RSV vaccine. It'd be important to know. I don't know that at the moment.

VR: Jamie writes, "As a dermatologist, I have prescribed dozens of courses of Paxlovid when my patients could not reach their doctors or were told to wait and see even when they were high-risk. All right, I wonder what you would advise me and people like me to do now that the public health emergency has ended. I have a genetic immunodeficiency and secondary lymphoproliferative disorder."

"I've been on maintenance rituximab for 13 years. Despite holding it for nine months from the start of the pandemic, got no antibodies from any COVID vaccine. For three years, I've worn a pamper at work as a dermatologist. I have to be right in people's faces. Even oropharynx since I treat mucous membrane pemphigoid. I always wear an N95, never eat indoors, generally isolated, but my daughter will be home from college and work at a summer camp this summer."

"I am left out of CME dinners. Not sure how safe I will be as the only masked person at conferences. My husband had COVID a month ago. Amazingly, I did not get it. There are no data on how people like me are faring with COVID. I have a plan, of course, and will get Paxlovid and likely convalescent plasma if I test positive. I don't fight viral infections well, but IVIG has helped a lot."

"I've survived influenza with a fairly normal course and Tamiflu. Do I have to isolate forever? Do I have to make my daughter live in the basement? There's so little guidance for people like me. I'm not aware of any transparency on who is still dying of COVID, the thousand a week. The elderly, yes, but also transplant patients, B cell-depleted patients? I can't help feeling like my life is considered an acceptable loss at this stage of the pandemic. Thank you, as always, for your compassion, guidance, and care."

DG: Yes, Jamie. This is tough, right? We talked about communication. This is when people say things like, "Well, fortunately, only people who are older or have multiple medical problems are dying." What's that? You actually are doing a tremendous amount. We want to keep you around, right? I really appreciate that. As a dermatologist. you're stepping up and prescribing Paxlovid when, my gosh, people who really should be doing it should be doing that when their doctors are telling them to wait and see or just being inaccessible.

You're in a tough situation here. It's not easy to get a good access to a T-cell test to be able to give you individualized assessment of your risk. I think I've talked about-- well, I think it was the last time I talked about, there is a replacement for Evusheld on the horizon. AstraZeneca is doing its SUPERNOVA trial, I think it's called. Hopefully, that's going to be something that you can add on here. Jumping in with that Paxlovid early. Once Paxlovid is licensed, I think people like you will probably have it there in the house so they could start as soon as possible because that really seems to be with the antivirals. The sooner you get going, the better.

I do not think you're going to have to isolate forever. This is one of these challenging things. We're not going to get any data going forward that is better, but who are those quarter-million people that died last year? The majority of them are people over the age of 75, people that have multiple medical problems, people who are immunocompromised. You, unfortunately, are a high-risk individual.

VR: Isabella writes, "Tested positive for COVID first time, December 22. I have been dealing with Long COVID symptoms ever since. Fatigue, new onset of migraines, brain fog, upper chest tightness, et cetera. Twenty-three-year-old woman with asthma, vaccinated and boosted, been diligent, been out wearing a mask, started to mask less when I got COVID. I've gone back to wearing a mask everywhere in public, but I see very few other people wearing masks now. I wonder if having Long COVID puts me at a greater risk for complications if I get a second COVID infection. If you would recommend someone with Long COVID, continue wearing a mask in public?"

DG: Yes, this is one of those situations that we've been talking about for a little while about moving to a one-way masking situation because there was a point in time when everyone was wearing masks and this idea that each person was doing something with regard to source-control themselves. Should they have a pre-symptomatic or asymptomatic infection or, gosh, particularly as we read in the VA study, right? Fifty percent of healthcare workers symptomatic going back to work.

Again, like the individual above, you're someone that I would be worried about. Right now, you've demonstrated that with that COVID infection, you developed Long COVID. The story you're describing here is actually very similar to some of the patients I take care of. The fatigue. I'd love to have a conversation about post-exertional malaise or not. New onset migraines. Yes, we see quite a bit of that. The brain fog, upper chest tightness, worsening of asthma because of this inflammatory trigger. Yes, I would be concerned. If you got another COVID infection, would that exacerbate your Long-COVID symptoms?

VR: Ellen writes, "Dear Daniel, the CDC guideline says four to eight weeks for the initial two shots. WHO say eight to 12," and she gives a link for that. "What, in your opinion, is the best interval to shoot for? Sorry for the pun. I thought I learned from *TWiV* that a longer interval gives better protection, but is that in terms of efficacy or durability?"

DG: I'll start there. Yes, [laughs] both. I hate to be critical to CDC, but I know that the initial studies were done three to four weeks and then saying four to eight weeks. We've talked a lot about our understanding of the immune system. It probably was too quick. It was done because we're in a pandemic. We probably should not be recommending still that four weeks. I would say, based upon what we know, based upon the science, the WHO guidelines make more sense. It really probably would be a minimum of three months. Six months may actually be ideal. Vincent, I'm going to let you jump in on that too to make sure we're on the same page.

VR: I think eight to 12 is good, the WHO guidelines, but physicians in the U.S. are going to probably follow CDC guidelines, right?

DG: I think it's tough. I think the CDC has to move a little bit quicker. I vented a little bit up above about we're still following health care, staying-home-from-work guidelines from August and September, have things not changed when they came out with that guidance in March. You need to clearly say right at the top. This is for everyone, except healthcare workers. The science, I think, is pretty good at this point that if you give someone a second shot at four weeks, that may have been what we studied, but we did that because we're in

the middle of a pandemic. It's better to wait three months minimum between the first and the second shot. Let that full germinal center process evolve.

VR: Yes, I agree. I think four weeks is way too soon. Eight weeks is better, but eight to 12 weeks is even better.

DG: Go to 12. Go to 12 weeks. [chuckles]

VR: See if you can convince your doctor to do - Tell him to call Daniel.

DG: [laughs] Thank you.

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

DG: Hello, everyone. I will say, be safe out there. I know with the one-way masking, a lot of people are not wearing masks. A lot of people are making decisions. Don't be critical. Remember that quotation I started with. A little kindness, a little bit of conversation. Everyone, be well.

[music]