TWiV 1372 Clinical Update

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Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick.

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VR: From *MicrobeTV*, this is *TWiV*: *This Week in Virology*, Episode 1372, recorded on November 5 2026. 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: What's on your tie, Daniel? Blue?

DG: Actually, for those that can see closely, it's these little yellow Gram-negative rods. It's plague, *Yersinia pestis*.

VR: I see, which has been in the news lately.

DG: Not only has it been in the news lately, but yes, I was thinking that with what happened this week, maybe the end of the plague or something. OK. [laughs] I got political there a little bit.

VR: I see.

DG: All right. Let's start with a quotation because we have a lot to talk about. Actually, I don't know if you know this, Vincent. I spend a lot of time on these quotations, trying to pick something.

VR: I heard, yes.

DG: When I got this one, and the more I went into Wilma Rudolph's story, I was like, "Oh, this one's perfect," so, "Never underestimate the power of dreams and the influence of the human spirit. We are all the same in this notion: The potential for greatness lives within each of us." I don't know if you knew this story, and maybe your listeners, but this is by Wilma Rudolph. She was an American sprinter who overcame polio as a child.

VR: That's right.

DG: Went on to become a world record-holding Olympic champion, international sports icon in track and field. She won a bronze medal in the 4x100-meter relay at the 1956

Summer Olympics in Melbourne. Melbourne, how do we pronounce that?

VR: Melbourne, yes.

DG: Melbourne, Australia. She also won three gold medals in the 100- and 200-meter individual events and the 4x100-meter relay at the 1960 Summer Olympics in Rome. She was acclaimed as the fastest woman in the world in the 1960s.

VR: Cool.

DG: She had polio as a kid. I was out running today, and I don't run very fast. I was thinking, "How fast could she have been if she had not had polio?" Wow.

VR: Yes, but she was born before the polio vaccine. That's it, 1940. Yes, maybe she would have been faster. It has to take something away, right?

DG: It's pretty amazing, right? I was thinking we should make a list of polio survivors that have gone on to accomplish things in this world. It's quite a number.

VR: We've got a lot of people. Itzhak Perlman, Neil Young, many others.

DG: All right. Well, let's start off with some good news. Feel free to jump in with some other good news. Among the winners who helped flip the House and Senate during the midterm elections were six doctors and public health professionals who were supported by, I don't know if people know about this, 3.14 Action Fund. It's a political action committee dedicated to bolstering Democratic candidates with STEM, science, technology, engineering, and math, backgrounds.

VR: I didn't know about it, but I guess that's pi, that number, right?

DG: Yes, that's 3.14, at least they stop at the 4. They could just keep going.

VR: Bernie Sanders wants to get rid of PACs, so this may have to go.

DG: You have to get rid of this, right?

VR: Yes, I don't think they're a good idea because it lets anybody give as much as they want, right?

DG: It's a problem. It's that whole Citizens United stuff where it's not Citizens United, or it's corporate -

VR: It lets very wealthy people like Elon Musk try and change things, although he failed this time.

DG: Yes, spent hundreds of millions of dollars to try to push an election in their -

VR: People had an idea that they did not want this anymore. It was quite clear.

DG: Yes. We would like to say that they saw the tragedy of public health, but we know it has a lot more to do with the war in Iran, with affordability, with a lot of people being upset with this police state that ICE has created for many of us, but let's go through, because it is exciting that we're going to have health professionals in Washington.

VR: That's great. Of course, the guy in Louisiana is departing, right?

DG: Cassidy.

VR: Cassidy's going, which is good because he's the one responsible for RFK Jr. Goodbye.

DG: Dude, you weren't re-elected. You're done anyway. You could have at least prevented - Well, we're going to talk about what you could have prevented. In the Senate, we had Dr. Annie Andrews, a pediatrician, South Carolina. Flipped the open seat, previously held by the late Lindsey Graham. Now, she is the first Democratic doctor elected to the Senate in nearly 60 years alongside El-Sayed. First-ever pediatrician senator.

VR: That's cool.

DG: Yes. Now, Dr. Abdul El-Sayed, also physician-trained. He's an MD, PhD. He was a former Detroit-Wayne County health director. He spent some time at Columbia at Mailman, and he won the open seat. He completed medical school but pursued public health rather than residency or practice, and then in the House. Actually, there's a quote. I should read this quote: "The last time a Democratic doctor sat in the Senate, Congress passed Medicare and Medicaid."

[laughter]

DG: We're expecting big things. In the House, we've got Dr. Richard Pan. Another pediatrician. Look at that. I'm a little worried we're losing our pediatricians when we need them most, but maybe they can do California's 6th District, and highlighted for prior work on vaccine policy in California. Mitchell Berman, registered nurse, emergency room nurse, Wisconsin's 1st District. Kristina Knickerbocker, an oncology nurse practitioner and Air Force veteran, Ohio's 10th District. Dr. Adam Hamawy, surgeon, former U.S. Army combat surgeon, New Jersey's 12th District. All right.

VR: Great. That's all great. It's good to have physicians in Congress, for sure.

DG: I'm excited that we're going to have some health care.

VR: I think you need to run some time, Daniel.

DG: I did think about it. It's a backstory. We'll talk about that some other time.

VR: You have the savvy to do it. You speak well. You could do it. People would like you, yes.

DG: Yes. I mispronounce things, though.

[laughter]

DG: If I had you there, I'd be like, "Vincent, how do we say that?" All right, anyway. [laughs] OK. All right. Right up front, I'm going to talk about this twice because we hemmed and hawed a little about what Cassidy could have prevented. There's two quotations that I think are - I don't know. I'm sure we didn't coin these. The first is, "When you mix politics and science, what do you get? Politics." The other is, "If you mix politics and medicine, you get dead children." Yes, it hasn't even been two years, and we have children dying in the U.S. of a vaccine-preventable illness that we haven't seen these deaths in quite a while.

Let's take the first one, "Child Dies From Measles in New York State's First Fatal Case in 30 Years." Vincent, I talk with my kids and my wife about, "Well, we see what's going on, but at least here in New York, it'll be OK." We live in 50 somewhat united, somewhat not United States, but at least here in New York, we have these good vaccine laws that protect them. Daisy, maybe at some point she's going to be with child. She's my oldest.

Here, a child in New York's North County died after contracting measles, the first death in the state from the viral disease in 30 years. This was announced Monday by Governor Kathy Hochul, said the death was a signal that public health protections were eroding as a growing number of families forgo vaccinations. A child died in Lewis County, northeast of Syracuse. Pennsylvania, another measles-related death, an unvaccinated resident of Jefferson County. There's some confusion whether it's the sixth or seventh death. A baby; this is hot off the press. Unfortunately, today, a baby in Wisconsin has died from measles. Third death just this week. An infant in Wisconsin. This is the first death in the state from measles in 36 years.

VR: This is really unacceptable, right? There should be no measles deaths in the U.S.

DG: There really shouldn't, and we didn't have them.

VR: No, and this is all attributable to RFK Jr.

DG: It really is. Proof of the pudding. We had eliminated measles. We did not have children in the U.S. dying of measles. RFK Jr. comes in, destroys our public health infrastructure, and we have children dying. I just don't understand why this isn't at the top of everyone's list. Everyone's talking about, "Oh, we've got to impeach Hegseth." I'm like, "I think the first person we have to get rid of is the one responsible for little children dying of vaccine-preventable illnesses, for lying to people, for misinforming them," because these parents are making decisions that they think is in the best interest of their child because someone in a position of power is lying to them for personal gain.

VR: He will probably resign before January, so they can't go after him.

DG: All right. We're going to talk about these again. Mpox in California. Four cases of Clade 1 mpox, recently reported out in Stanislaus County. Chagas in Texas. A couple of things here. The article, "Autochthonous Acute Chagas Disease with Fulminant Myocarditis in a Texas Infant Exposed to a Peridomestic Environment with *Trypanosoma cruzi*-infected Vectors and Animals." This is published in *CID*.

Here, they describe the case of an autochthonous. This is a little child, didn't leave the country, living in Texas, doing what little kids do, put things in their mouth. This peridomestic investigation revealed *Trypanosoma cruzi*-infected vectors and animals. 10-month-old Corpus Christi presents to the hospital. Fever up to 38.9 C, rash, fatigue, diarrhea, bilateral periorbital edema, vomiting, and the blood smear shows these trypomastigotes, these motile, infective forms. It's lost the flagellum, so the trypomastigotes become the amastigotes, develops fulminant myocarditis, toxic megacolon, just horrible hospital course that they describe here.

VR: Is there anything you could do to prevent this? Obviously, the trypanosomes are there, right?

DG: That's interesting. What do you do? Is this really a failure of public health?

VR: Was he probably bitten by a vector?

DG: He may have actually put a bug in the mouth or something, right, because they found it in the local environment?

VR: Yes. This is a problem because this is what happens in other countries, right? I just don't know what you would do to prevent it other than keep the child indoors, but it could be the bugs indoors as well.

DG: It'll be interesting. We might get a guest to join us, a couple of guests to join us at ASTMH who are doing a documentary on Chagas. We can ask a lot of these questions, like, "How do we control Chagas?" A teaser for our listeners that we'll have an upcoming deeper dive into Chagas.

VR: Is it controlled in other countries at all?

DG: Not really, actually, yes.

VR: Aside from Texas, where else are trypanosomes in the U.S.? Do you know?

DG: Actually, they're all the way up. There was the issue, I think, in Tennessee. It's a different type of reduviid bug. One of the differences that we thought would protect us, which is not going to protect you if the kid puts it in the mouth and eats it, is some of the South and Central American reduviid bugs. When they're feeding, they'll defecate right away. They'll bite, and there'll be an open wound, but then they'll leave infected feces, infectious feces, and that gets rubbed in the wound. The ones in the U.S. eat and then defecate later. It was the idea that reduces it, but we see Chagas in dogs because they'll eat the bugs. Here, the concern was that maybe this child actually ingested a bug.

All right, "Mysterious Anthrax Outbreak Kills Hippos in Africa - Raising Concerns for Human Spread." This is in *Nature*. An anthrax outbreak has killed at least 30 hippos in the DRC. They've got enough problems going on there. No cases in people so far. They're monitoring it. The dead animals were first found in September in the Virunga National Park in eastern DRC. Lab tests confirmed they died from anthrax. This is an infection caused by the bacterium *Bacillus anthracis*. The outbreak comes at the same time as they're dealing with the Ebola and cholera and ongoing humanitarian challenges. Hopefully, we'll have some updates on what exactly has happened there.

VR: It's pronounced anthracis.

DG: Anthracis?

VR: Yes. I want to go back to the Chagas. Could you treat this kid?

DG: Oh, yes, and they did. Actually, if you read the article, there's benzimidazole and nifurtimox. They're not exactly that easy to get immediately. There were some challenges they described at accessing the medicines as quickly as they would have liked.

VR: Would you even know to diagnose this? That's the thing, right?

DG: The interesting thing is you look at a blood smear. You can see the trypomastigotes on the smear.

VR: If you had a child with fulminant myocarditis, would you do a blood smear?

DG: I think in this situation, you're in Corpus Christi, Texas. You've got megacolon. You've got myocarditis. I think it starts making you add that to your differential. You look at a blood smear, and you say, "There it is."

VR: Well, this would be a good *TWiP* case, wouldn't it?

DG: It would, actually, yes.

VR: Especially if it happened in New York City.

DG: [laughs] Or they'd call me in.

VR: Yes.

DG: It's a tough case.

VR: Anthrax in hippos; they have other problems with humans, infectious diseases, but I don't like seeing the hippos dying either.

DG: No. It's not great to see the hippos die. Of course, they're also being really careful in how they're handling and disposing of the carcasses. All right. While we have basically become a neglected tropical disease country, dengue: "60 new cases in just the past week, Florida's dengue total jumps to 485," and this is from the Florida -

VR: That's a lot of dengue.

DG: Yes, lots of dengue. We're up to 485. That was 60 cases of locally acquired dengue just this last week.

VR: Well, Florida wants to protect the mosquito, so that's what you get.

DG: [laughs] Is there some effort to protect the mosquitoes in Florida? I guess so. Well, they keep electing the right government officials if that's their goal. All right. Bird flu over last weekend. Health officials in Yakima - Is that how you pronounce that? Yakima County, Washington.

VR: Yakima.

DG: Yakima. Basically, there were two more folks sickened with H5N1 avian flu, including one person who died after hospitalization for severe illness.

VR: Is this the bovine one or the D1?

DG: I'm assuming it's the D1 just because the person died, but let's take a look here. Let's see if we can -

VR: They have an outbreak in cows in Washington.

DG: Yes, when I tried to link to the page. Does the *CIDRAP* tell us?

VR: It doesn't say which - Oh, wait. This one. The cows have B3.13.

DG: B for bovine and benign, and D for ducks and deadly.

VR: They don't say what the human cases are, but I guess if the person died, it must be D, right?

DG: They are in this right above the H5N1 detected in cow raw milk tank. They talk about genetic sequencing from the virus; at least in the cattle in the nearby farms has the B3.13. All right. This one, I was showing to my daughter, Daisy. Look at screwworm. Look what's going on with screwworm.

VR: It's really moving, isn't it? Look at it. It's in Texas and New Mexico, Arizona, and it's going to move north as well.

DG: It's already starting. It's halfway up New Mexico. If you look at it, we had four cases August, three cases September, 36 in October. We've already had 24. It's the 5th of November. "Remember, remember, the 5th of November." We're up to 113 animal cases. There was a case in a cat in New Mexico. If you follow this link, I put in a link, you can actually go through and see all the different animals that have been infected so far.

VR: The Gunpowder Plot, right? That was November 5th.

DG: Guy Fawkes Day. Today's Guy Fawkes Day. I can't wait to celebrate. Remember the Guy. Do you know that poem, Vincent?

VR: I saw the movie.

DG: [laughs] "Remember, remember, the Gunpowder Treason"?

VR: Yes, right.

DG: OK, all right. Ebola. We are in over 10,000 cases, 10,563 confirmed, 5,130 confirmed deaths. You can look at the line. It's going. There's no plateau. It hasn't started to decrease in slope at all. It is a straight line.

VR: It's really remarkable that it's so much bigger than the West African outbreak was in the same number of days because that was the biggest ever. This may surpass that.

DG: It's on track. Most people are predicting that it will. Maybe in a couple of months, the U.S. can get itself back together, and we can help, which, historically, is something that we would do. All right, back to measles, and just to repeat, right? We had a death in a child in New York, first fatal case in 30 years. We had another death in Pennsylvania, and then we had a baby in Wisconsin die from measles. That's the first death there, 36 years, and we are up to over 5,000, 5,051 cases of measles so far this year.

VR: It looks like the U.S. has a rash on this map.

DG: 321 cases just this last week.

VR: Wow.

DG: Some of them are in Pennsylvania. 77 in Pennsylvania, or up to 1,467 in Pennsylvania, so a big chunk there. 210 in New York State, though. I think everyone listening, right? You're

listening. Talk to someone else. Talk to anyone who will care. This should not be happening. This is not OK. We're supposed to live in a country where children are supposed to be safe, right? They have to wear bike helmets. They have to sit in a child seat. You have to wear a seat belt when you're in a car. There's a lot of things we do. You can't shoot off your firearm in a suburban setting. Our school should be safe. We shouldn't have children dying there.

New York State launched its own respiratory disease tracking dashboard. We talked about this last week. It's really interesting. You can look at hospitalizations and cases, right? It's good to look at both. I'll leave in a link, because you can see that the COVID hospitalizations were actually kind of high, and still are higher than the flu hospitalizations. They're coming down. The flu hospitalizations are shooting up. The cases for flu are shooting up while the COVID cases are heading down. It's still in the thousands, by the way, just in New York State. I'm going to give a little primmer, primer. Kathy says call it primer, right?

VR: I think that's correct. Primer.

DG: Primer. What happens? Here you are, right? You're a *TWiV* listener. You're in the know. A runny nose. You're not feeling well. Maybe you've got a fever, maybe a little cough, trouble breathing, right? You've got, at least initially, an upper respiratory infection. It might progress to a lower respiratory tract infection. What are the ones that we worry and test mostly for? We test for COVID. We test for flu. We test for RSV. Why do we do that?

It's actually a Flu A and B. That's why we call it the quads. It got Flu A, Flu B, RSV, COVID. The main reason for testing is these are ones that either we can do something about, or we want to try to keep you from spreading it to others, right? COVID, right? We'll talk about early antiviral. Folks around you can actually get something to keep them from getting it, right? You can get post-exposure prophylaxis. Same with flu. Early antiviral, post-exposure.

RSV, you really want to avoid giving that to the little kids, giving it to the older folks. Let's say you do that flu or that COVID, or maybe even do the quad test, and they're all negative. You still have something. I ran into this this week. Person's like, "Oh, I did the test. It was all negative." I'm like, "Well, you have a fever. You're coughing. You feel crummy. You don't want to get out of bed." "No, but I did the test. I don't have anything." I'm like, "Yes, you do."

[laughter]

DG: They're like, "Well, I canceled some stuff, but I'm still going to go to this eye appointment." I'm like, "Why are you going to go to the eye appointment? Are you going to give it to the eye doctor? You think they want to feel the way you feel?" Just keep that in mind, folks. We all went to kindergarten. We learned to share, but they were not talking about illness. All right. Flu, starting to see activity, starting to see the green turn to yellow and orange.

I got Louisiana down there. This stuff is a little behind. You can say behind the eight ball, right? This is week ending October 24th. We're two weeks ahead of this. We're really seeing the flu activity start to pick up across the country. You can see COVID's going down, maybe. Flu is on the way up. Not a lot of RSV activity when you look at the epidemic trend from the CDC. Flu activity is already here, and we already had our first pediatric flu death of the year.

Actually, a bit in the news because I don't know if this was the same death, but it's the mom

of a little child that died of flu, basically being like, "Hey, I didn't know." These are vaccine-preventable deaths. People are not getting their kids flu shots. All right. We ended up with 193 deaths last year. We ended up over 200 deaths the year before in little children. All right, so get those flu shots. Then if you do get flu, there's treatment. Not only is there treatment, but there's post-exposure prophylaxis.

All right. RSV, we're starting to see some activity, but this is interesting. Let's look at this map. We've got RSV wastewater viral activity level. Normally, if our listeners, well, have been following for years, it normally starts down in Florida, then Alabama, Georgia. It moves up. You got this moderate activity in Texas, high activity in South Dakota, and low in Alabama, Florida, low in New Hampshire, very low everywhere else.

VR: Yes, it's weird. Do you see any RSV these days?

DG: We haven't seen it yet. I talked to my daughter, a pediatric ICU nurse. She's like, they haven't seen any cases yet. I haven't seen any cases yet. I was trying to look into, does this have any impact, vaccination, right? We now have RSV vaccines. We now have the RSV monoclonals for the little kids. Are we going to see a whole different pattern now that we have these effective interventions?

VR: Maybe. Yes, vaccines are good.

DG: Yes, vaccines are good. All right, you can repeat that as much as you want. All right, COVID update. Even with the blue washing, we still have quite a bit of COVID activity going on here.

VR: Yes, I don't know. This is a persisting plateau there, right?

DG: Yes, which is what we've seen in times past, which bounces around.

VR: Maybe it's going to go down now.

DG: I'm a little worried that we're going to have enough background that when everyone gets together for that turkey day here in the United States that you've got to show up. It doesn't matter how sick you are.

VR: The last year's peak ended by the beginning of November. It was down already, but we're not there. This is going to go further.

DG: That's the concern, that this is enough activity that when we get into the holidays, it's just going to go right into our winter.

VR: Well, folks, you should be prepared. Get vaccinated or -

DG: Yes, get vaccinated. People have stopped getting vaccinated. Just remember, you get vaccinated, you're going to reduce your risk of ending up with COVID, the disease, symptomatic, by about half, and also all the other things. COVID's not good, as we keep talking about. Well, let's talk about it. The article, "Susceptibility of Human Neural Stem Cells to SARS-CoV-2: Entry Mechanisms and Glycocalyx Influence," published in *PLOS One*.

These investigators hypothesized that neural stem cells derived from human ectoderm might be susceptible to SARS-CoV-2. They used pseudotyped viral particles, both wild-type

and Omicron spike variants. They confirmed efficient transduction in neural stem cells (NSCs), with Omicron variants preferentially utilizing endocytosis-mediated entry.

VR: I don't know why they have to use transduction. Why can't they say infection?

DG: [laughs] That would work. That would work.

VR: Transduction has a specific meaning. It means moving a piece of DNA from cell to cell, right? Phage-mediated transduction. This is not right. Come on, folks.

DG: Actually, you're right, because they are talking about infecting them with an endocytosis-mediated mechanism, yes.

VR: Keep it simple. It's infection.

DG: Yes, so they're infecting neural stem cells, successfully infecting neural stem cells, yes. They're concerned, right? Because if you can successfully infect these stem cells, well, who cares about stem cells? Who cares about stem cells? Little babies, developing fetuses, right? They're worried about teratogenic issue, right? That's a fancy word for birth defects, or the mom loses the pregnancy. All right. I'll leave in a link because they're beautiful pictures.

VR: I don't know what it means, though. These are cells in culture, right?

DG: Exactly.

VR: The real question is, does this ever happen in people?

DG: We don't know, right?

VR: They say here, maybe you say at the end, you should be on the lookout for - yes, these suggest future clinical studies and long-term surveillance of infants and children exposed in utero are necessary to explore neurodevelopmental deficits. I think that's a good idea anyway, right?

DG: Yes. It's obvious you should be doing that first, but this is interesting lab work, right?

VR: Yes, but as I say, who knows what it means? These are just cells in culture. You don't know. Maybe in the animal, they're not susceptible to infection. It can happen.

DG: Does the virus get to where it needs to get to even get endocytosed into the stem cells?

VR: For example, if you take a human kidney, a human who has polio, the kidney is never infected. If you put kidney cells in culture, you can infect them with poliovirus. If you did that and you infected them, you'd say, "Oh, the kidney is a site of polio infection," but it's not. That's why I'm complaining a little.

DG: Well, let's do the other study. Let's compare the risk of maternal complications and adverse infant outcomes among pregnancies with or without COVID-19 in the Sentinel System.

VR: That's a good idea.

DG: Let's look. Let's see. Is this a problem? Here, we look in *PDS*, and we have a

retrospective study that looked at basically COVID-19 infection during pregnancy. They looked at the timing, they looked at the severity, and they looked at adverse outcomes for mom, adverse outcomes for the baby. They're going to look from 2020 to 2023. They're going to look at 70,000 pregnancies with COVID-19. There was a modestly increased risk of ending up with a C-section, preterm birth, and this was seen with severe COVID-19 compared to pregnancies without.

Actually, those are nice. You can really see the preterm delivery. You've got good severe COVID, non-overlapping intervals. C-section, just to show the data there, you can actually see that there's a little bit of an overlap, but it does look like - particularly with severe COVID-19, there might be a trend towards, particularly at the very bottom, severe COVID-19. There, you get away from the overlap.

VR: Here's the study where they could have looked at neurodevelopmental defects. They could follow these kids for a while.

DG: Yes, they got this data, so that would be to go on and follow. Then somehow, you've got to separate out, is the issue because it's preterm birth. You've got to match the preterm birth somehow. Some challenges. All right. Remember, COVID, we've got some vaccines. You've got a lot of choices there. Now is the time to get your COVID vaccine as well. All right. We're going to wrap up with a few.

We've got three articles here in the post-acute sequelae, late phase. First one, the article, "Post-Vaccination Chemosensory Dysfunction: Changes Following SARS-CoV-2 Vaccination in a Global Study." This was published in *Investigative Otolaryngology*. Here, they looked at individuals with COVID-19 chemosensory impairment. Basically, folks with smell and taste issues after they got COVID-19. They're looking at, "What if we give you a vaccination dose? Is that going to help you?"

VR: You mean after they lose their taste or smell, they get vaccinated?

DG: Exactly, yes. They either lose, or it's disturbed. They go ahead, and now we're going to - We've done this, like, "Let's give you a vaccine and see if somehow, that affects what's going on." More than 90% of participants reported no change in smell or taste following vaccination. Among the folks, 10% of folks actually thought there was some kind of improvement. Of the folks that thought there was some type of improvement, there's this parosmia. Some thought that was better.

There's this phantosmia. I don't know if you know. It's people like, "I smell something burning." It's like, "No, nothing's burning." Sometimes that got better. 10% to 20%, they had the distorted taste where things maybe tasted metallic or things like that. That got a little better. 3% of people said it actually was worse after the vaccine. Not a lot of evidence supporting vaccination to improve these chemosensory distortions. If somebody's desperate, this is something that maybe, we had 10% of people getting better. Remember, 3% of people said it actually got worse.

VR: We don't have any controls here who are not vaccinated, right?

DG: I think that's the problem. Were those people just going to get better anyway? That's really what you need because a certain number of people are going to probably get better anyway. Did these people get better or worse? Yes.

VR: Of course. You need to compare it to a non-vaccinated cohort. Absolutely.

DG: Exactly, yes. All right. Now, this is a preprint. We don't do preprints a lot, but this seemed like something that gets used enough that I wanted to go through, spend some time, and share this. This is the preprint, "Low Dose Naltrexone for Post-COVID Fatigue Syndrome: A Randomized Controlled Trial," posted on *medRxiv*. I have to say, the whole thing about trying naltrexone, it's a little challenging as a provider because you've got to work with a compounding pharmacy. You start with 0.5 milligrams, and then you gradually increase it by half a milligram, finally get up to 4.5 milligrams if you can.

Here, they look at: Does naltrexone help with post-COVID fatigue? This is a decentralized, randomized, parallel group, double-blind, placebo-controlled clinical trial. Folks are randomized one-to-one to either get the low-dose naltrexone. They're going to start at 1 milligram. They're going to go up to 4.5 milligrams if they're tolerated, or they're going to do placebo. You do this for 16 weeks. The primary outcome was fatigue severity. Basically, no difference, did not help. Same as placebo.

VR: What is naltrexone usually used for?

DG: It's really pain, but at higher doses, not this low dose. That's why you have to compound it, because you're using it in this odd, off-label way. All right, this is our last one. I spent a lot of time thinking about this. I just put it in today. The article, "Metformin at the Time of COVID-19 Infection and Risk of Long COVID: A Target Trial Emulation Study," published in *The Journal of Medical Virology*.

Here, they conducted a new user analysis of metformin prescribed within six days of documented infection with SARS-CoV-2 versus an experimental control. Basically, folks were going to get metformin or fluvoxamine or fluticasone or ivermectin or montelukast. The primary outcome was Long COVID or death. Now, in the primary analysis, 4% in the metformin group developed Long COVID versus 8.5% in the control group, so about a 50% reduction.

Then, if you actually look, and I broke down so we can look at the different ways they looked at it, it really looked like you were seeing the biggest difference the sooner you got started. If you waited and you didn't start it for 14 days, not a lot of separation. If you started it right away, zero to one day, or even if you started it zero to six days, you saw this separation in the number of folks that ended up getting Long COVID.

A couple of thoughts. One is 8% seems really high; that 8.5% of folks are going to get Long COVID. This is Omicron mostly that we're seeing here. 8%, one in 12 folks. I was thinking about this when I was out running today, right after I thought about how slow I was compared to that Olympic athlete that survived polio. We don't think one in 12 people that get COVID end up with Long COVID. That seemed very high. That's always been an issue with some of these studies is that somehow, it ends up pretty high placebo numbers. I'm not sure exactly what was the dosing because, in the COVID add, it was really this complicated uptitration. I don't know. Any thoughts there, Vincent?

VR: Yes, there's an effect. It's just small, right?

DG: Yes.

VR: These other drugs, they're used as controls, right?

DG: Yes, but 4%, so that's a number needed to treat of 25. That's not terrible.

VR: No, but it's not what we need, right?

DG: Yes.

VR: I just don't know what makes you respond to this as a Long-COVID patient, right?

DG: Yes. I don't know if we have a good mechanism or a good understanding of what's going on here.

VR: You don't want to give it to everyone, right?

DG: That's a challenge. Who are you going to give it to? Some of the features here, so the COVID-OUT trial, you had to be basically obese. This was a lot broader look at people. Not everyone was obese. Also, I don't know if people are excited, like, "Hey, you've got usually about, I think, 1% or 2% chance of Long COVID. Maybe we go from 2% to 1%." This might be a hard sell. Particularly if you're using this complicated, like, "Start with this, and then gradually increase it," and then are you going to stay on it for months? People are like, "I'm done with the COVID. I don't know if I want to be on this for six months."

All right. No one is safe until everyone is safe. I'm hoping that we can embrace that, and we can start making, at least our country, a safer place for children and pregnant women and people whose immune systems are not fully there. No one is safe until everyone is safe. Your favorite time of the year, Vincent. We've switched to the *MicrobeTV* fundraiser. Actually, I should say now for November. Actually, folks, this is November until December. This is like NPR. In two-thirds of the time, we're going to raise twice the money.

VR: We're not going to go into January this year.

DG: I know. I know, Vincent. I want to get it on a quarterly system. Next year, you're going to get October, November, December, just to shift things.

VR: OK. Folks, then you have to give early, give often.

DG: Everyone gives you the money in December, Vincent. January is a dry month anyway.

VR: Really?

DG: Yes.

VR: Parasiteswithoutborders.com, folks.

DG: Click on there. We're going to double your money. We're going to help support *MicrobeTV*. As I like to say, "If you like what we do, or you just want us to keep doing it, whether you like it or not." [laughs]

VR: Yes, we'd love you to support us either way. This would really help us a lot if you think it's valuable for us to continue doing science programs. Thank you very much.

DG: Fantastic.

VR: It's time for your questions for Daniel. You can send yours to Daniel@microbe.tv. Amy writes, "Thank you for all you do. Huge fan and longtime listener. Daniel, with the greatest respect, I think you overestimate the ability of patients to change physicians if they find them behind the science or falling foul to government misinformation. In certain communities, there are so few doctors that all meaningful choice is removed, unless you can afford to travel."

"Medicare patients are particularly vulnerable. Advocating for my elderly relatives to get quality medical care is a constant struggle. The ignorant responses I received from the doctors' offices in 2021 during the COVID pandemic were particularly alarming. I'm sad to report it's worse now, as low Medicare reimbursements lead to high physician turnover, and demand quickly outpaces supply."

"Cost is also a factor. Each new doctor, test, treatment is another copay. If you can only afford a high-deductible health insurance plan like myself, this can quickly become costly. You fight so hard for health equity. I hesitate to submit this feedback, lest I sound ungrateful, because clinical update and *TWiV* give me the tools I need to advocate for myself and my family. I'm very appreciative."

DG: No, Amy, this is well-taken, and don't apologize for sending this. I spent actually early part of my career. My first job was Helena, Montana, and then I was a primary care doctor in Colorado up by the Wyoming border, and then was a hospitalist up in Alaska, so definitely been in underserved places where it's challenging. Yes, no, it is tough. Sometimes you end up in a place. That's your choice, and that's your doctor. It is tough because what do you do if that doctor is actually giving you bad information, giving you bad guidance?

My default is: If you can, change doctors, but I appreciate that is not something everyone can do. Hopefully, send people, send those doctors to *TWiV*, have them listen. If they're saying stuff that runs afoul of the truth, then advocate for what's true. Advocate for good care. Yes, I think we can also start. We've got a Democratic senator heading to Washington. Maybe we can do something to fix this system and really improve access for the folks that need it. Maybe we can do something about the health inequity that we've got here.

VR: Barbara writes, "I'm a layperson, avid vaccine supporter, and *TWiV* listener ever since being introduced by a friend during my second COVID infection at age 65. Yes, I took Paxlovid. Thank you for all you and Vincent do to keep everyone safe. Influenza A was rude enough to infect me before I could get my seasonal flu shot. Symptoms began 9/24, positive home test 9/26, started Tamiflu. I'm still working on regaining stamina, and otherwise seem to have no complications."

"My questions are as follows. One, should I get a seasonal flu shot even after having Flu A? If so, how long post-infection should I wait? Two, I got a COVID booster, mNEXSPIKE, in June. I plan to get another COVID vaccine at an appropriate time. Should I wait the full six months from my last shot, or should I try to get one sooner? Based on the idea that the next shot I get should be more protective of currently circulating variants. I have basically no underlying conditions, except for a tendency towards diverticulitis and stress due to caring for my mother with dementia, who lives in a memory care unit."

DG: All right, Barbara. First off, someone gets the flu. Do we still recommend that they get a flu shot? We do because you're going to get one particular type of flu. It might be H5. It might be H1N1. Actually, that's what we're seeing a lot of circulation at this point. Not H5,

but H1N1. Still, you might get Flu B. You might get the other type of flu. Yes, wait a couple of weeks. Wait until you're feeling better. Go ahead. Get your flu shot. That's what we tend to recommend. Now, the COVID shot. We'll maybe get into this a little bit later, but it isn't that you have to wait that six months. It's that we look at the antibodies.

We look at the risk of having symptomatic COVID-19, so the disease. That protection, that reduction, really tends to drop after about six months. It doesn't go away completely, right? There's still, as we've talked quite a bit about, the T-cell effect that might endure a little bit longer, but it really drops. As it's been more than a couple of months, it's fine for you to go ahead and get a COVID shot. You don't need to wait. We're starting to see COVID activity. We're seeing COVID activity. This might go right into the holiday season. Go ahead. Get that flu shot after a couple of weeks. Get the COVID shot at the same time. I think that's absolutely fine.

VR: Kathy writes, "I've been a faithful listener since the start of the pandemic. I'm so appreciative of what you do at *MicrobeTV*. Especially love your clinical reports and have learned so much. Thank you. I have a question about timing of flu and COVID shots, given that I'm three weeks post-op from a hip replacement. I'm taking Celebrex, baby aspirin, and several doses of Tylenol daily. I'm concerned if I get the shots now, their effects on my immune system would be dampened by the drugs. Is that a reasonable concern, or should I go and get the shots? I'm also concerned about adding additional inflammation into my system right now, so early in my hip's recovery process. Thank you for your insight and expertise."

DG: Yes, Kathy in Seattle. I don't think that the Celebrex, the aspirin, the Tylenol is going to have a significant impact on your immune system that's going to prevent you from getting the benefit from the shots. It's always a balance, right? You're going to get a little bit of inflammation from the shots, but you will get a lot of inflammation if you end up getting flu or COVID without that degree of protection. Reasonable to go ahead and get those vaccines. You don't want to have the rudeness of flu infecting you, or the rudeness of SARS-CoV-2 getting you sick before you get your vaccines.

VR: Heidi writes, "I plan to get an influenza vaccine soon and am considering the mRNA mFlusiva vaccine. Either that, or I plan to get the high dose this year. I understand the mRNA can be manufactured quicker, so it might be able to better match the strains that we will see this season. Does the mRNA vaccine and the regular protein-based vaccines protect against the very same strains? Is there an advantage of one or the other?"

DG: Heidi, this is a great question because it's going to allow us to talk a little bit about that. The mRNA has the ability to be better matched because within 60 days, you can end up with a new mRNA vaccine. That's the science of it, but that certainly is not the regulatory side of it. The mRNA flu vaccine for this season, it's done, it's approved, and it's actually the same makeup as the cell culture or the recombinant protein flu shots.

It's going to have the H1N1 Influenza A/Missouri. It's going to have the Influenza A/Darwin H3N2. It's going to have the Influenza B/Victoria, Pennsylvania, where your egg-based are going to be similar. The A's are the same, but the B is going to be a Tokyo. Even though there's this theoretical ability, if, let's say, suddenly, we realize we totally got the match wrong, the mRNA within 60 days could be revamped, but somehow, we need to have a regulatory environment that would allow that.

Now, what about approval? Who can get the mRNA shot? The mRNA shot basically was approved for Flu A and Flu B, approved for use in persons 50 years of age and older, and then it got this indication for persons 65 years and older under accelerated approval based on immune responses. They actually have this new, right? Continued approval for this indication is contingent upon verification and description of clinical benefit in a confirmatory trial. That's a new thing that was put there.

Now, you mentioned that you're thinking about, "Either I'm going to get the mFlusiva," so the mRNA flu shot, "or I might get the high dose." I'm thinking you're 65 or older. As mentioned in that approval, we haven't done any efficacy trials comparing high dose to the mFlusiva. It's all basically looking at antibody levels at this point. You're a little on your own there. Do you go ahead with the recommended high dose or the recommended senior type, or do you say, "Boy, 25% higher antibody levels compared to the standard dose," and consider the mRNA?

VR: I guess also, if you're very reactogenic with mRNA vaccines, it's another consideration.

DG: That's definitely a good point because, yes, as we've noticed, the mFlusiva, the mRNA flu shots, can give you more reactogenicity. You're going to notice it if you're a person that reacts to the mRNA vaccines.

VR: Steve writes, "Thank you so much for doing all the work you do to produce *TWiV*. I have been a listener since mid-2020 and a supporter for a few years. I really enjoy the science, the stats, and weather reports. You will be happy to know. My favorite temperature is 82F, 28C. In the latest clinical update of 2nd October, I thought Dr. Griffin said that COVID vaccines should follow the flu model, i.e., once a year. Did I hear that correctly, or should we continue with a COVID vaccine every six months? My wife and I are COVID virgins and would like to keep it that way. Thanks for all your work. I would like to know if there are any updates to the mRNA flu vaccine."

DG: OK. Well, I think we hit the flu vaccine, the mRNA one, so that's good. It's up there. Let's talk about this. What is the story? Remember, as I mentioned, we live in a regulatory environment. I actually went. I'm going to paste in. What is the FDA approval for the current mRNA shots? We'll talk about Comirnaty. I'll leave a link. It's basically the same for the others.

Comirnaty, that's the Pfizer-BioNTech. This is approved, and it's approved to be administered as a single dose. You get it. The only exclusion is you can't have gotten another dose within the last two months. That's interesting. You go ahead. Let's say it's November, because it is; it's November. Get a shot in November, early November, 5th of November. Maybe this will be the 7th by the time you hear this. Then November, December, January, February, March. Now, it's April, and there's a lot of COVID activity.

As I've mentioned, the shot that you got this November, if you were to get another shot in the spring, again, you're going to get that 50% reduction in clinically attended COVID-19. Also, some reduction in the severe outcomes. The science is still there, but that's the packaging. The packaging now is this one shot, but there will be certain high-risk folks. Just realize that six months from now, there's potentially a reason to go ahead and get a second shot.

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

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

[music]

[00:53:01] [END OF AUDIO]