This Week in Virology

TWiV 1148 Clinical Update

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Guest: Daniel Griffin

Aired 14 September 2024

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

[intro music]

VR: From *MicrobeTV*, this is *TWiV*, *This Week in Virology*, Episode 1148, recorded on September 12, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: I see on your bow tie there's spikes. There's some virus on your bow tie, but I can't see it very close.

DG: Actually, it's interesting. If you were to zoom in, this is actually my fungal bow tie.

VR: Oh, my gosh.

DG: Yes, this is like a close-up of the conidia and there are little spores. The nice thing is you can wear it different ways. You can actually end up with it other - This is like a bow tie you can bring with you when you travel, and depending on how you put it on, it's got a lot of red and blue or a lot of green.

VR: All right.

DG: I'm reviewing today, just coincidentally, after putting this on, I was reviewing fungal therapeutics and resistant genes and ergosterol and the echinocandins.

Let's get right into it. Actually, I guess, speaking about red and green, a quote from F. Scott Fitzgerald from *The Great Gatsby,* "So we beat on, boats against the current, borne back ceaselessly into the past"

VR: I remember that pretty much.

DG: It's interesting. I feel like I've even used this one before but sometimes I feel this way. [chuckles]

VR: Do you think that sometimes we're just pushed back all the time?

DG: Yes, sometimes I feel like, as much as we try to move forward, there's this current against us. You have to reteach, no, this is what is actually true, despite all this effort to undo what we've learned. All right, let's jump in with a little more optimism. Maybe optimism, I don't know if that's the right description for this first paper, [chuckles] but right up front, the article, "Farmed Fur Animals Harbor Viruses with Zoonotic Spillover Potential." Maybe it was that harbor reference that got me thinking of *The Great Gatsby* because actually in the book Jay Gatsby is looking across our harbor right here in Port Washington. He's over there in Great Neck looking across Manhasset Bay at Port Washington, East Egg, where I live.

This article, which was published in *Nature*, is a situation where the investigators performed single-sample metatranscriptomic sequencing of internal tissues from 461 individual fur animals that were found dead due to disease. They characterized 125 virus species, including, as they say, 36 that were novel and 39 at potentially high risk of cross-species transmission, including zoonotic spillover. What are you thinking so far, Vincent?

VR: I love it. Great.

DG: All right. They identified seven species of, what are we thinking? Coronaviruses. Oh my gosh, who's heard of those? Documented the cross-species transmission of a novel canine respiratory coronavirus to raccoon dogs and bat HKU5-like coronaviruses to mink, bat to mink, present at high abundance in lung tissues.

Three subtypes of influenza A virus, H1N2, H5N6, H6N2 in the lungs of guinea pig, mink, and muskrat, multiple known zoonotic viruses, such as Japanese encephalitis virus and mammalian orthoreovirus in guinea pigs. Raccoon dogs and mink carried the highest number of potentially high-risk viruses, while viruses from the *Coronaviridae, Paramyxoviridae*, and Sedoreoviridae families commonly infected multiple hosts.

We got a nice - Really, I like this map. They give us a map. This is China, China, Mongolia. You can see the fur animals in all these different areas. I even like they've got this little close-up where you can see the different animals.

VR: I think many countries have fur animals. I think if you looked in any of those locations, you'd find viruses of some kind.

DG: It's interesting because there is definitely a lot of human interaction with these -

VR: Yes, for sure.

DG: - fur animals.

VR: If you remember, during the beginning of COVID, the mink farms in the Netherlands, the minks got infected from humans and it was spreading like crazy. They culled all the mink in the Netherlands. They got rid of them because it was a threat.

DG: Yes.

VR: I think the point here is interesting, that raccoon dogs, of course, were also sold at the Huanan Seafood Market for eating and they are highly likely to have contained SARS-CoV-2. You have to be careful with these animals.

DG: Yes. I think as we keep talking about it, I think at this point, the preponderance of evidence really supports that there were infected animals that were brought to that market. The spill over into probably raccoon dogs or other animals that were then brought to the market occurred wherever they were being bred, one of these cases, not being farmed for their fur, but being farmed for their meat. Then you bring them to this place where then, you interact with lots and lots of people and then comes across. Just another reason, maybe, why we shouldn't be farming animals for fur.

I think the other, and this is really important, is this whole don't keep your head in the sand. They're right here. We've been saying for decades, we've been saying, the whole community of scientists, virologists, infectious disease specialists, that these pathogens of zoonotic pandemic potential, they're out there. They're there. The coronaviruses, the influenza viruses. It's important for us to under and appreciate this because there's this odd idea that, oh, if the scientists don't look, they're going to - Pandora's box will stay closed. We're messing [chuckles] with these animals on a regular basis.

The next one, we're moving back into mpox. It's been actually a lot, I had to select what I thought was the most important here, but the article, “Comparison of Protection against Mpox following mRNA or Modified Vaccinia Ankara Vaccination in Nonhuman Primates,” published in *Cell*. Here, the researchers used a clade I monkeypox virus, Zaire, challenge model to assess the protective efficacy of an mRNA lipid nanoparticle vaccine, mRNA 1769. Sounds familiar, right?

VR: It does. I bet those are the amino acid numbers or something like that, right?

DG: They're going to look and they're basically going to say, "How does this mRNA vaccine work?" This mRNA vaccine is expressing optimized version of the four monkeypox viral antigens of interest, and that's A29, A35, B6, and M1. They're going to compare this to the modified vaccinia Ankara. That's the Bavarian Nordic JYNNEOS vaccine, which is a replication-deficient vaccine, which expresses all the viral antigens, protein, nucleic acid-based vaccines. The animals received either the MVA or the mRNA 1679. All the animals were completely protected from lethality of infection. Five out of the six in the PBS group succumbed to infection.

Now, what they're really going to basically contrast is the lesion number. We're going to see a little bit difference here, fewer lesions with the mRNA vaccine compared to the number of lesions that we saw with the Bavarian Nordic, the JYNNEOS vaccine. They do point out that there was a little bit of duration of disease reduction as well but a few limitations they point out. Because it was really interesting watching this. Bavarian Nordic stock goes down because now there's an mRNA alternative and look, it's a little bit better. They point out, a couple of things I'll point out, one is they point out that we don't know about longevity.

This is short follow-up. Is this going to be - Because what we really want to do, and this is sort of the smallpox history, the JYNNEOS history so far, is we really want to give this vaccine

maybe as a one or two dose and then be done with it. Will this have that durability? What we think is decades. The other is cost. Right now, this is a vaccine that has a certain cost. Is Moderna going to come in with an mRNA vaccine for mpox that's actually going to be less expensive?

VR: Daniel, there still were lesions in these animals, right? There were?

DG: Yes, there still were lesions, they still saw lesions and it was really - when they compared the number of lesions it was about a 90% reduction. The MVA, the JYNNEOS immunized animals, they got up to a maximum lesion count of about 600 where the other animals ended up with a peak lesion in the 50s. You did see a reduction in the number of lesions.

VR: It may still allow transmission? It may -

DG: I think it does allow transmission, yes. Once you're getting lesions, we would think that there's - But that would've been great. I would've loved that part. Then we took these animals and put them in with other animals. I know with primates, that's a really expensive ask, but you could have even just gone ahead and done some plaque assays, right?

VR: Yes. I mean -

DG: Does the monkeypox virus plaque?

VR: I'm sure it does, yes. The measles vaccine does prevent lesions, correct?

DG: It's great at preventing lesions and then even if someone with measles gets some degree of disease, we've talked about, it's about a 400-fold reduction in the transmission. Because that would be a great thing because we're trying to control an outbreak here, you could say, "Oh, this vaccine may cost twice as much, but it blocks transmission." That's huge.

VR: The MVA, does it prevent lesions at all? Do you know?

DG: We still see people who, post-MVA vaccinations, still get clinical disease, they still get lesions. There is that phenomenon, they tend to get less disease, they tend to get fewer lesions, and they end up with a really big impact on severity. I think in the study that we saw, that was down in the DRC down in Africa, we actually saw it, no one ended up hospitalized if they got vaccinated.

A lot of interesting stuff going on there. Briefly, the article, "A Cross-Sectional Evaluation of the Virtual Outpatient Management of People With Mpox," published in *Open Forum Infectious Diseases*. Can we just use telehealth? Should we use telehealth? Can we successfully do that? This is actually a description of the successful use of telehealth to manage mpox. I will point out, we really used this model heavily during the early days of the mpox.

Actually, just to describe our experience, what we would do a lot of times is we work closely, the urgent cares, other providers in the Tri-State area for access to the tecovirimat or the TPOXX and enrollment in the STOMP trial. There was one required in-person visit that we

would coordinate. Here, among confirmed cases and end up 221, 86% were managed exclusively on this virtual ward as they call it.

Fourteen percent did require admission treatment for concomitant sexually transmitted infections was provided to one-quarter of the patients. Antibiotics for other infective complications, about 16%, some symptomatic relief, 27%. They actually conclude, and I agree because we had the same experience, that this virtual ward model facilitated safe and holistic outpatient management of mpox while minimizing admissions and really serves as a model for future outbreak responses.

VR: Whenever you say tecovirimat, I think of the automat. Do you remember those?

DG: Oh, I do, [chuckles] yes. I think this is great, people bemoan like, "Oh, we're less prepared for the next pandemic than we were going into this last one." Actually, I have to say that the real ramp-up of telehealth facilities is the idea that you can actually take care of folks at a safe distance. Here, we're orchestrating the diagnosis and treatment of other sexually transmitted infections, there's antibiotics, there's symptom care.

We're really minimizing the number of people that actually need to end up in a hospital, so really minimizing the burden on our acute care facilities. That was a big issue, I didn't cover the article this week, but they actually predicted about 20% or suggested about 20% of the deaths during the first year of the COVID-19 pandemic were due to the facilities just being overwhelmed, so if we can somehow mitigate that.

VR: Also, in this case, you're not going to have in-hospital transmission, which is a big problem.

DG: That's a huge issue because you have an individual with mpox, they end up in the hospital, how are you going to deal with keeping them safe? You're tying up that room preventing in-hospital transmission. Unfortunately, we still to this day, someone shows up in the hospital for something else, but someone is there admitted with COVID and now that person gets COVID. In-hospital transmission is a challenge.

All right, this is a letter that, I say people send letters, they send it to me personally, they send it to PWB, they send it to daniel@microbe.tv. That's what they're supposed to do.

VR: Correct.

DG: They also send it to somewhere else, which we won't mention because they'll send them there [chuckles]. Here was a letter sent to Parasites Without Borders: Dr. Griffin was asked by a listener where to refer patients for mpox vaccine. I was surprised he did not advise the listener to contact the NYC Health Department, the first place to turn to. [chuckles] However, for patients in New York, State Health Commissioner James McDonald has issued a statewide standing order allowing pharmacists to administer the two-dose mpox vaccine without a doctor's prescription. The Department of Health announced Friday, I'm not sure which Friday this was,

"My standing order allows individuals to get their JYNNEOS vaccine from a pharmacist without seeking a physician, greatly increasing access to this important layer of protection as we remain vigilant and continue to monitor mpox in the United States and abroad," McDonald

said in the statement, "Pharmacists are an important component of our overall healthcare system and remain a center point of accessible care in our communities." I'm going to actually say thanks to our listeners and this person. We'll put in our show notes a link to the NYC Health and Mpox Finder. There's basically in vaccinefinder.nyc.gov.

You go there, it's interesting. There's two panels, one is finding the mpox vaccination, and then that has a robust list of places that have it. Actually, phone numbers, addresses, the rest, and then there's another tab for COVID vaccine and that gives you a blank page, just saying. [chuckles] All right.

A little bit more on RSV, this really seemed timely when I was quoting some of the trial data last week, and this is the article, “Nirsevimab and Acute Bronchiolitis Episodes in Pediatric Emergency Departments,” published in the journal *Pediatrics*.

This data from Spain, and so back in the 2023-2024 RSV season, that's the last, last year. Spain became one of the first countries to introduce the universal RSV prophylaxis. That's the nirsevimab, the Beyfortus, that's you're getting the monoclonal antibody.

Locally, most Spanish regions also immunized infants younger than age 6 months at the start of the season, this extended catch-up. The aim of this study was to assess how RSV prophylaxis affected the number of infants presenting to pediatric emergency departments with acute respiratory infections. A retrospective study was conducted in 15 Spanish pediatric emergency departments from nine different regions.

Here we have actually the published study published in *Pediatrics,* "A comparison with the average rates for the previous epidemic seasons revealed a 57.7% decrease in episodes of lower respiratory tract infection in 2023–2024, a 59.2% decrease in episodes of acute bronchiolitis, and a 63.1% reduction in acute bronchiolitis-related hospital admissions, a 63.1% reduction in PICU, pediatric ICU admissions." Just really some good real-world data about the efficacy we saw here.

VR: Daniel, they don't look at deaths at all or is this not an issue?

DG: I think the death rate tends to be so low that they're focusing on larger numbers. You'd end up with a really wide confidence interval.

VR: Good.

DG: I think in our entire country, in the U.S. we see - I think the number is 100 to 300 deaths per year. You'll look at a country, you're going to see just a few handful of single-digit deaths in Spain from RSV season in the pediatric population.

VR: Presumably, nirsevimab will prevent that, right?

DG: You would think the majority of deaths it should prevent. Exciting. All right, and COVID, Vincent. [chuckling]

Daniel: Have you heard of COVID?

VR: I have.

DG: Looking at our map, what stands out to you?

VR: We had this incredible peak at the end of the summer, which was unprecedented in the previous summer, and now it looks to me that it's going down.

DG: The wastewater data is going in the right direction. It seems to be coming down. Our late indicators, that's what we're seeing now. We may be off the peak. Actually, the peak in some areas was as high as it was last winter, actually. Interesting how high it was.

VR: There was not an August peak last year.

DG: It wasn't quite -

VR: It's very interesting. I'm on record as saying this will replace the winter peak. We'll see.

DG: We're going to see. We'll be here. You and I will be here in January. The COVID deaths. In the hospital, we're still seeing a large number of people in the hospital and deaths. This weekly, we're actually seeing Georgia has got into that 4% to 6% of all the deaths in Georgia are due to COVID. Kentucky is still there. New York, actually, I say majority, probably about half the country, 2% to 4% of all the deaths we're seeing right now are COVID-related deaths. We're expecting that to trend better in the coming weeks.

Unfortunately, I'm hearing news from the universities. They've got their pledge week, their rush week. I think they give it a new name now. Lots of COVID at our university campuses. The variants, KP.3.1.1 is taking the lead. I think it's 40% up here in the Northeast, but pretty moving across.

VR: JN is nowhere to be seen.

DG: Yes. I always like to keep my lineage in mind. The JN.1, which is really the parent of this lineage of the KP.3.1, that's basically, it's we're not really seeing. It's less than 0.3% across the country, the JN.1.

VR: We could call all of these the JN.1 clade, right, Daniel?

DG: Yes, as we talked about in our livestream. We're now seeing JN.1 clade taking everything over. Yes, this is all JN.1 clade.

All right, Vaccination, I'll make sure at the very end of this, just to give some updated recommendations. I just keep getting asked those. It makes me wonder if perhaps my close family and friends are not all listening to our weekly update. The article, I have to say, Vince, I found this really interesting. Hopefully, we can have a little discussion about this. It was the article, "Association Between SARS-CoV-2 Viral Load," we should call that RNA copy number, by the way, "and COVID-19 Vaccination in Four Phase 3 Trials," published in *JID*, *The Journal of Infectious Diseases*.

For this analysis, four randomized placebo-controlled phase 3 COVID-19 vaccine efficacy trials were really included. We'll go through what we're looking at. We're going to look at the

mRNA-1273. That's the Moderna mRNA vaccine. That'll be our mRNA representative. We're going to look at the AstraZeneca and the Janssen vaccines. That's going to be our chimp adeno and our adenovirus vaccines. We're going to look at Novavax, which is our protein subunit vaccine. What they're going to do is they're going to look here at the, they say viral load, but the RNA copy number, so copies per ml. They're going to compare.

These are people who end up getting an infection who either got each specific vaccine or they got a placebo. These are the these are these placebo-controlled phase 3 vaccine trials. This is data from a little bit back that they're now analyzing here. I'll go through it a little and then we can talk about it. They talk about the estimated vaccine effect on the RNA copy number. You can actually see the estimated vaccine effect on RNA copy number. You're using almost as baseline, pretty similar to placebo, your Janssen, and your AstraZeneca. Then about a three-log reduction with Novavax. about a two-log reduction with the mRNA vaccine.

VR: Many questions, Daniel.

[chuckling]

VR: First of all, what's the match between the vaccine and whatever is circulating?

DG: It's the same, it's the same point in time. We're looking at a reduction two to three months following the last vaccination.

VR: These were the original vaccines, right?

DG: Yes, this is the original vaccine efficacy trials.

VR: Roughly, when was were this data collected? This would be 2021.

DG: Really 2020-2021.

VR: The other thing is, this is RNA copy number. I don't know what this means. I would like to know the infectivity. It's not so hard to do, right?

DG: Yes.

VR: It's clear there is a reduction that's better with Moderna than any of the others. Novavax is pretty good too.

DG: Novavax, there's overlap. I don't want to oversell. A 2.1 versus a 2.78 for Novavax. Novavax has a trend towards a little bit better. Really overlapping confidence intervals. Really compared like statistically significantly different compared to the AstraZeneca or the J&J.

VR: Nevertheless, AstraZeneca and Janssen were clinically significant protection against severe disease, right?

DG: Yes.

VR: It tells me that this doesn't mean anything, maybe. [chuckles]

DG: Yes. Part of the part of the discussion they had was, is this important for onward transmission?

VR: We don't know because, first of all, we don't know what the reduction in infectivity is. Even if we did, we don't know how much you need to transmit. This is always the problem.

DG: That's again, is it the threshold? If you're above the threshold. I only got shot once in the chest. Yes, it doesn't matter. That's enough. That's the issue. It's a binary with you. You got infected. We don't we don't think there's a dose to like, "Oh, but I got really infected."

VR: There's a challenge trial in the UK where they give people 10 to the 5 TCI 50 or whatever. They put a pipette right in the nose. They put a paperclip on their nose. That's not natural transmission. I think those numbers are irrelevant, right?

DG: Yes. That's also tough, too. Yes. Here, what would be, say, more interesting to me, and we'll actually mention this in one of the other studies we're going to talk about, is what if you look about secondary cases in households? They could have gathered that. I don't know if they were set up to do that. I would love to know, two to three months later, the different people got the different vaccines, what were the secondary attack rates in those households? That would be even more compelling for me.

All right. Passive vaccination, remember Pemgarda, and we'll keep a link to the pemgarda.com infusion center locator. COVID early viral phase. We have the NIH and the IDS guidelines, but I am going to start off with the article, “Health Outcomes Three Months and Six Months after Molnupiravir Treatment for COVID-19 for People at Higher Risk in the Community (PANORAMIC): A Randomized Controlled Trial,” published in *The Lancet Infectious Diseases*. Here are results. They're not really the results, but they're results from the extended follow-up of the PANORAMIC trial.

We had the early results and now we have the follow-up results of PANORAMIC. PANORAMIC was a randomized, controlled trial to evaluate the effects of early antiviral therapy on long-term health outcomes at three months and six months after randomization. This extended part of the PANORAMIC, this is part of that multi-center primary care, open-label, multi-arm prospective randomized controlled trial conducted in the UK. The participants were eligible if they were, really, eligible for treatment. You had to be aged at least 50 years or 18 years with a comorbidity, unwell, and five days or less with confirmed COVID-19 in the community. It's not hospital.

This is in the first five days. In this study, participants were randomly assigned to the usual care group or molnupiravir group plus the usual care. That was molnupiravir 800 milligrams twice a day for five days. The results of this, it was a pre-specified analysis, not just going back and data mining. We actually see that people who are randomly assigned to molnupiravir, early antiviral during the acute phase of COVID-19, had better outcomes at three months and six months. What were those better outcomes? A lot of this was questionnaire-related.

In general, they related better well-being, remember, this is blinded, well-being, fewer and less severe COVID-19 associated symptoms, less visits to the doctors, less healthcare utilization, less absenteeism from work or study, and overall on the scale, they're using improved quality of life. The conclusion based on this data is that in a - This was mostly a

vaccinated population, by the way. In a vaccinated population, people treated with early antiviral therapy, in this case molnupiravir, for acute COVID-19 felt better, experienced fewer and less severe COVID-19-associated symptoms, accessed health care less often, and took less time off work at six months.

VR: Daniel, Is the implication that this is impacting Long COVID because of that?

DG: That's basically what this was. This was a trial looking at Long COVID, three months and six months. We're actually seeing more data, a growing body of data that early antiviral therapy provides a benefit for folks in terms of Long COVID.

VR: Vaccination does, and on top of that, even if you're vaccinated, take an antiviral and that'll add to it.

DG: Yes. All right. What are the recommendations? Number one, PAXLOVID, number two, remdesivir, three, molnupiravir, and in some cases, convalescent plasma. All right. The COVID early inflammatory week, just a reminder, this is that bad week. This is when the viral replication is on the way down, when we're starting to see the inflammatory phase, steroids at the right time in the right patient, anticoagulation guidelines, pulmonary support, remdesivir still in the first 10 days, and in some cases, immune modulation. We don't do a lot of that here in the U.S., but I was surprised in Taiwan, that's really a part of the standard that they do. We have discussed the data on that.

All right. I'm just going to wrap us up here with what I thought was really an interesting, another microbiota alteration article in our Long COVID section. This is the article, "Adult Outpatients with Long COVID Infected with SARS-CoV-2 Omicron Variant. Part 1: Oral Microbiota Alterations," waiting for part 2, I guess, published in *The American Journal of Medicine*. These results are from a prospective, nested case-control study that evaluated the differences in oral microbiota in individuals with or without Long COVID, symptomatic and asymptomatic groups. Where's Michael Schmidt?

They were assessed with 16S ribosomal RNA sequencing on tongue coding samples, 108 patients were included. There are 54 in the symptomatic group. The symptomatic group had, interesting enough, higher diversity and microbial dysbiosis with increased diversity and relative abundance of pathogenic bacteria. These would be the *Campylobacterota,* the *Coriobacteriales*, the *Pseudomonadales*, and the *Campylobacterales.*

The real challenge, I have to say, is they keep changing the names and some of the names are so darn similar. You're wondering, did I say that twice? They found out that these particular marker bacteria were associated with Long COVID symptoms. Really interesting is that there were distinct variations in the oral microbiota between COVID-19 patients with and without Long COVID, a discriminatory finding here.

VR: The question is whether these patients had dysbiosis before Long COVID and it predisposed them to it or if this was a consequence of Long COVID.

DG: Whether messing with this can have a benefit for folks with Long COVID.

VR: It's funny that it's just the oral microbiome. Because the gut is another big one.

DG: Yes, I don't think it's so much just as we're finding it here too. Because we have some studies that there's a gut microbiome dysbiosis associated with Long COVID. I suspect there's also a skin microbiota as they were seeing your oral cell.

VR: Even a brain microbiome.

DG: Actually, that would be really interesting, right?

VR: It's there.

DG: Yes, there is a CSF microbiome. All right, so as we've been saying for a while, actually four-plus years, no one is safe until everyone is safe. Appreciate all the people who jumped on the *Office Hours* livestream that we did last night. Vincent and I did last night live, jumping on and helping support the work that we do. I'm hoping a number of you will pause the recording right here, go to parasiteswithoutborders.com and click Donate. Every bit helps. We're in the middle of our Floating Doctors fundraiser where August, September, and October, we'll double those donations up to potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. This first letter has the rebound word in it, Daniel.

DG: Oh my gosh.

VR: All right. Robin writes, "Any updates on possible longer courses of Paxlovid? I saw Paxlovid's data that a longer course in immunocompromised patients lowered viral load and prevented rebound more effectively than a five-day course. Would it make sense that a longer course for everyone would do the same? Would it be more effective at decreasing post-acute problems potentially by further lowering viral load?" Oh my gosh. “Thoughts?

[chuckling]

DG: All right. You got all the little catch things in there. Let's start off first with a request. We always harped when people talked about efficacy. You said, "What kind of efficacy?" What would you talk about? When you say rebound here, are you talking about symptoms? Are you talking about RNA copy number going from 10,000 to 100,000 but not up to millions? That's one of the things, I guess, I'll first mention is a lot of doctors will say, "I see my patients and 20% of my high-risk people, they have this rebound. I would say no, they don't actually have rebound. They have symptoms during that second week.

Symptoms during that second week do not correlate with RNA copy number. RNA copy number during that second week does not correlate with symptoms. What really is rebound and what is the point? As we talked about, too, are you thinking like, "Boy, if I treat everyone for 10 days, I'm going to keep that RNA copy number down below transmission." We don't see transmission in that second week. You're really not going to accomplish any impact on transmission.

Two, as I mentioned, there's no correlation there between that RNA copy number during that second week and symptoms. You're not going to get symptoms any better by treating people for 10 days versus five. If anything, you get an extra five days of whatever potential side

effects they might be having, another five days of being off the medicine. You got to really ask, what is my goal? What am I trying to accomplish? It makes everyone feel good to have a negative antigen or a low RNA copy number. Is it worth it?

In my days when I was in medical school, we still were treating people with pneumonia for 21 days with antibiotics because we wanted them to be "all better" before we stopped. We now know that was actually harmful. That's how you breed resistance. That's how you cause problems. That would be the first. As you mentioned, lowering viral load. We're not measuring virus. We're just measuring RNA copy number. RNA copy number, as we're saying here, once you get out to this latter part, past day seven or eight, you're below transmission anyway.

VR: Frouke writes, "I was wondering whether you could speculate on whether there may be a link between the IgG4 class switch observed after a third dose of mRNA vaccines and the reduction in the risk of Long COVID after the booster. I understood that IgG4 is less inflammatory than IgG1 to IgG3 and that a similar class switch in beekeepers seems to keep them safe from an anaphylactic shock. As Long COVID seems to have an autoimmune component to it, could more IgG help prevent Long COVID?"

DG: I don't know. [chuckles] It's really interesting. There are certainly a lot of people out there who think they do know. This is interesting and there are certain autoimmune diseases that are IgG4 autoimmune diseases. There's this interesting phenomenon that you describe where there's actually, the IgG - Give an overview.

The antibodies or immunoglobulins, we have different classes. We've got IgE that's involved in, let's say, allergies and parasite clearance, and we have the IgM, that is our first antibody that we make. We have an IgA, which we think of as a mucosal. We have our IgG. That's really the bulk of our antibodies. Then the IgG has four subclasses, so IgG1, 2, 3, 4, and then there's even like, within the different ones, there's the different like IgG2a and b, et cetera. There's a lot of different variety here.

One of the things that was noticed at one point was this elevation of IgG4, this class which observed after the third dose of mRNA vaccines. Some of the anti-science people jumped in, "Oh my gosh, this is the harbinger of doom. This is the worst thing in the world." We really have seen nothing negative here. It is interesting. We have seen that repeated vaccinations can be a therapeutic for Long COVID.

This is interesting speculation. Maybe what they were seeing as a potential warning sign may be that repeated vaccination. Maybe this is a potential thing to look at. Maybe we are modulating some of that immune dysfunction by modulating the different IgG subclasses. This is all speculation and we need to do the science.

VR: Lori writes, "I'm a 62-year-old female, day nine after SARS-CoV-2 infection. Symptoms were sore throat, achy body, tired. I started Paxlovid day three. I started having periods of nausea around day four. By day seven, nausea was all day. I started having abdominal pain. Pain is now constant enough to keep me awake. Acetaminophen helps. I read that it's not uncommon to have GI symptoms after COVID. How long can I expect this to last? I've started on a clear liquid diet to help with symptoms. Is this a good idea?"

DG: This is a challenge. A lot of times, during the first week, you can have GI symptoms as part of acute COVID and GI symptoms can continue. There was this idea early on that, oh, people only had respiratory symptoms. They didn't have GI symptoms. I remember starting to ask patients and they all had GI symptoms, but they're like, "Yes, but that's the least of my problems, Dr. Griffin. I can't breathe." GI symptoms are actually quite common during COVID. They're often overshadowed by other symptoms, but in some folks, no, that's the biggest issue.

The first patient I saw with acute COVID at one of our hospitals, this is back in early March, came in with diarrhea, no respiratory symptoms. Now, in some folks that can continue past the acute period, past the seven days, past the 14 days, even a little bit longer. What you're doing is great. Just take it easy, clear liquid diet, advance that slowly. In most cases, this should resolve. I hope that's what you experience.

VR: Laurie writes, "I'm a pediatrician and I often have to get hep-B titers on young adult patients who are applying for nursing school or similar and/or I am testing due to high-risk sexual behaviors. Increasingly, more of my patients are seronegative and I offer them the option of redoing the three vaccines and not retesting or giving one vaccine and retesting. Some programs require the three vaccines and then testing, although I don't know what they'll do with the non-responders.

I've always been taught that the memory T cells would kick in with a new exposure and not worry too much about the serology, although the school programs do. Now I'm beginning to wonder if that may not be true and perhaps I should be screening all my young adults for hep B serology when I test their lipids in other young adult labs. Are these young adults protected? What are your thoughts? Have you found that many of your patients are non-immunes when you test their hep B serology?"

DG: I'm one of these. I, over time, lost my hep-B titers. When I was back in medical school in the last century, one of the ways you can make extra money was sign up to get vaccinated and get your blood drawn. Hepatitis A, hepatitis B, anytime there was a vaccine, I was there. Yes, hepatitis A and hepatitis B, I was one of those early testing the different regimens. Then, decades later, my serology tests were negative, and shot after shot after shot, they're still negative.

We do think that it's T cell-mediated, so I'm not sure I really understand this me getting a completely another series and again. This is what they do. Don't let the fact that an administrator or a program requires the serology testing and these repeated shots to change your understanding of immunology.

VR: Russell writes, "My wife and I are in the midst of a bout with COVID, which was confirmed by a rapid test. We were planning to get the latest vaccine a couple of weeks before we traveled to Norway to visit our granddaughters, lower the chance of infection and transmission there. Now, according to the guidelines, we will not need to be vaccinated for that purpose. I'm not sure we would have tested were it not for the decision around timing the next vaccination. Would you consider this scenario as a rationale for testing (while symptomatic), that is, timing of vaccination?"

DG: I think there are several reasons why you might want to test when you think you might have COVID. One is, yes, this, am I getting a boost and should I be delaying that vaccination by three months? Which I think makes sense. If you have COVID right now, then you're going to delay. You're going to say, "I'm going to wait three months before I get my new vaccine this fall." The other is if you might be a candidate for treatment, you might say, "Oh, I want to test to see if I'm going to potentially benefit from treatment." Then the other is you want to know about potential transmission risk to others. This makes a lot of sense.

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

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

[outro music]

[00:44:46] [END OF AUDIO]