**This Week in Virology**

**TWiV 1158 Clinical Update**

Host: Vincent Racaniello

Guest: Daniel Griffin

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

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From, *MicrobeTV* this is *TWiV*, *This Week in Virology*, Episode 1158, recorded on October 17, 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:** - who's wearing some repetitive pattern on his bow tie.

**DG:** Yes. I don't know if you can zoom in on this. Can you see that, Vincent?

**VR:** I can.

**DG:** I think it would do Dickson proud. That's a hint.

**VR:** Is it Trichinella?

**DG:** Yes. It's not a doctor cell, it's a -

**VR:** Nurse cell.

**DG:** Nurse cell.

[laughter]

I was a little disappointed because I was wearing this today in the ICU, and everyone just seemed baffled. "What is that?" I'm like, "Oh my gosh, they're not teaching parasitology in the medical schools anymore."

**VR:** They're not?

**DG:** Really, it's just such a minimal amount. It's a shame. So many other things have filled that part of the curriculum. When you think about this world that we live in, how many people are suffering from parasitic diseases?

**VR:** Dickson used to teach a lot of parasitology to medical students.

**DG:** There was a whole course, and actually, our listeners may or may not know, but Dickson was one of my parasitology professors at NYU. When I was at NYU School of Medicine, there was a whole section. People used to love it. Then it slowly got shrunken down into some visiting person comes and gives maybe eight lectures, and then you move on.

**VR:** It's the whole thing of U.S. centrism. They don't worry about parasitic infections in the rest of the world.

**DG:** Yes. We got plenty of our own here, but let's jump into it. I have two quotations this week. Two for the price of one. One by Ray Bradbury and one by Abraham Lincoln. Let's start off with Ray Bradbury. "People ask me to predict the future, which all I want to do is prevent it. Better yet, build it. Predicting the future is much too easy anyway. You look at the people around you, the street you stand on, the visible air you breathe, and predict more of the same. To hell with more. I want better. The most reliable way to predict the future is to create it."

**VR:** I like that very much.

**DG:** You and I are talking about what's going to happen this winter. It's within our control. People can make smart decisions. We've got tools. Let's jump into several things to talk about today. Mpox. October 14, the WHO announced the approval of Bavarian Nordic's mpox vaccine JYNNEOS for adolescents aged 12 to 17. Actually, Kathy Spindler sent me an email earlier today with some of the data on this.

We read in CIDRAP, I'm going to give a plug for CIDRAP here, that the move comes as the outbreak in the Democratic Republic of the Congo is still raging and infecting children at high rates. I want to point that out. This is ongoing. It's not over. As we pointed out, with the current outbreak, this is predominantly infecting children. We also read that we are not doing such a great job outside of Africa of diagnosing cases of mpox with the study.

A seroprevalence study indicates a high proportion of clinically undiagnosed mpox infections in men who have sex with men in Berlin, Germany. This was published in *BMC Infectious Disease*. They do this seroprevalence study to say, "OK, so how many people actually got infected? Then let's see how many people actually got diagnosed." We only diagnosed about 7% of the people that had a positive serology. Over 90%, we're just missing it.

Then I'm going to leave in a link here to the WHO Africa Mpox Surveillance website. Not only can you see that the number of cases is just rising, but you can actually see that it isn't just the DRC anymore. You can actually see a lot of other countries starting to join here. Then we even have a nice map. I'll leave in links to this too. You can see really where's active outbreak in all different parts. It's actually covering a good swath of Africa currently with active outbreaks.

Marburg. This is a challenging situation here. Last week, we had 58 confirmed cases. Now we're up to 62. Really jumped in quickly here with the attempt to get a vaccine study up and running. The real challenge is will there be ongoing cases? Will we be able to figure out whether the vaccines work or not or is this just going to pop up the next time? Were we quick enough with those vaccine doses?

**VR:** Notice, they only distributed 700-plus doses. That's not a lot.

**DG:** It's really not a lot. It's not a lot. I feel like that needs to be part of pandemic preparedness. Particularly diseases that we know about. This is the time when you just - the vaccines need to be there right away.

**VR:** Yes. In this case, for Marburg, you hardly see any infections, which is pretty rare. No company wants to invest. This is something where governments have to engage in partnerships.

**DG:** Yes. Definitely. Whopping, whooping? How do we pronounce that? Whooping cough.

**VR:** Whooping cough.

**DG:** Whooping cough or pertussis. Actually, it's important to know the two names because a friend of mine was looking to get vaccinated. He's like, "They don't have pertussis, but they do have this whooping cough vaccine." I'm like, "That's it. You go get the tetanus, diphtheria, whooping cough vaccine." I want to point this out, and get people aware of this. Still plagued with worst U.S. whooping cough outbreak in a decade. It has infected thousands.

So far we've got over 16,000 cases this year. It's already four times what we had last year. There's a fun, interesting NPR article where they ask the experts and experts say there are a number of possible explanations for the size of the current outbreak. I was curious what were people's thoughts. One, and I agree with this, doctors are testing for whooping cough more. You let people know, "Hey, this is out there. If you don't test for it, you're not going to diagnose it." People test for it, they make the diagnosis.

We're identifying more cases. Actually, I have to say kudos to a lot of the docs in our local area because we're seeing a lot of whooping cough, we're recognizing, we're diagnosing whooping cough here. A lot of pediatric cases. I thought you would like this one, Vincent. It's possible that the bacterium that causes the disease has mutated.

**VR:** Oh my God, that's such a cop-out.

**DG:** Of course, it's mutated. That's what they do as it really [crosstalk].

**VR:** That's the point. It always mutates. What you're saying is a mutation of consequence has occurred. Say it --

**DG:** Yes. Oh my gosh, that would be a little too sophisticated. [chuckles] No, that's really what they're saying. Maybe the bacterium has changed in some way. Also, and I think this is clear, I didn't include a recent *MMWR* where they just talked about how the anti-science is taking hold and less and less vaccines in our kindergarten and younger. No, people got behind on their vaccines during the pandemic, they haven't caught up, and people are not doing as good a job of getting vaccinated.

Another quotation from this NPR article, "One of the challenges that we have with the vaccine that protects against whooping cough is that it is a five-dose series over the course of the first six years of life. It does require regular visits to the primary care." This is from Dr. Eric Chow,

the chief of epidemiology and immunization at the Seattle and King County Public Health Agency. As I was pointing out, there still is a lot of vaccine hesitancy and anti-vaxxers out there that will not vaccinate their kids. This is from Tina Tan, a pediatric ID physician at Northwestern University and the president-elect of the ID Society of America.

**VR:** Daniel, when I was 8, my family went to Italy to visit my father's family and they stuck me in a room with my cousin. I was 8 and she was probably 7. She had whooping cough and she coughed all night. I'm like, "Mom, why are you putting me in there? Isn't this contagious?" I guess they had faith in the vaccine, but she sounded like she was whooping. Oh my gosh, I'd never heard a cough like that in my life.

**DG:** Yes. Really, it's a horrible cough and often it can be so severe that we talk about this post-tussive, post-coughing vomiting. Just cough, cough, cough to the point where you end up vomiting. Then another nickname for this is the 100-day cough. You get this and the amount of post-infectious inflammation is such that you cough for three months. It's really hard for us to do anything about this. It's a miserable infection.

COVID. I've got the map right up here. I was a little shocked when I saw the numbers this week, particularly Vermont.

**VR:** Look at that.

**DG:** Yes. In Vermont, this is as high as it goes. Over 8% of all deaths in Vermont this last week were due to COVID.

**VR:** COVID.

**DG:** I'm going to point out, I'm going to say due to Omicron, because no one's really dying anymore. Oh my gosh. Apparently, they are. Out there in Iowa, 4% to 6% of all deaths are due to Omicron. In Vermont this last week, over 8% of all deaths, more than one in 12 deaths, due to COVID. I was preparing for a Medscape live talk that I'm going to do on, I think it's November 8 with this British physician. We're just talking about all these perceptions.

That's a lot of people dying. A large percent of people that are dying are dying from COVID. Why aren't our ICUs full? Why aren't we seeing that visual that we had last time? We were talking about the fact that during the early days in the pandemic, let's say you have an ICU with a 20-bed capacity, we would put 20 people in there and then they'd be in there for two to three months. Maybe less than 10% of them would ever make it off the ventilators.

Every day you walk in the ICU and it was a full ICU, full of people with COVID. Now what we realize is, "Hey, 90% of the time we were doing nobody any favors." When you look at these deaths, these are not people who ended up in the ICU with bells and whistles and alarms. These are elderly people, tend to be people over the age of 65. They tend to be people with some sort of a medical problem. They end up getting COVID. They end up getting hypoxic.

Maybe they even get through that and now they have a cardiac event or they have a stroke. We don't put them in an ICU for two to three months, so to speak, on display. We really make a decision about what's the best thing for them. For a lot of people, not surviving and spending the last two months of your life on a ventilator in the ICU was really not the best choice. I just

want to point that out. Now, in a sense - more than in a sense, death is a late indicator with COVID. We had our peak earlier.

Apparently, they're still pretty high over there in the UK. If we look at our wastewater, we really can see that we're heading into this lull that you and I were predicting, Vincent. The big is how wide will that trough be? I think that's our question. It's really come down. This week, I actually put up because you can go to this site, this cdc.govwastewater, and I'll leave a link in, and you can actually zoom out, go all the way back to January 2022, and see the pattern over the last two years.

You can see, do we get two peaks? Do we get a hump and a peak? You can see this year, we had a peak that started back in November, came down really into March. Then in June, it started to go up, came down. We're still on our way down at the moment. We'll see where that goes.

**VR:** In the previous year, it came up, looks like late November started rising. We'll see about the future, Daniel.

**DG:** Yes. This was what prompted me to think about my quotation. The wastewater, we may not be able to do a tremendous amount about this, but we can do a tremendous amount about people that end up in the hospital and end up not surviving. We'll talk a bit about that. I will mention, we're also starting to see influenza. I had a gentleman in his 40s, really sick with influenza type A. The variants were all in KP.3.1.1 territory. That's making up the bulk.

I'll say an article, I want to discuss this, "Relative Effectiveness and Waning of a Third Dose of mRNA COVID-19 Vaccine in Medicare Beneficiaries Aged 65 Years and Older during the BA.1/BA.2 Omicron Period," published in *JID*. Here, the authors are going to look at the third dose of vaccine. We've been talking for a while about the idea that these are really three-dose, not just two-dose vaccines. What about some recent data here?

Here, they used Medicare claims data to conduct a retrospective cohort study in U.S. community-dwelling Medicare fee-for-service beneficiaries. These are all folks 65 and older. They're looking at BA.1/BA.2 Omicron period. We're going back in time to December 2021 through 2022. They're going to look at this, and they're really going to ask this question, this relative vaccine effectiveness, three-dose versus two-dose with the mRNA vaccine.

Also going to get a little comparison between the Moderna and the Pfizer–BioNTech vaccines. They're going to look at 8 million eligible beneficiaries, 73% get three-dose. They're going to look at a couple of different periods of time. I think this is important. You're going to look at 14 to 60 days since vaccination. When they look at that, they're actually going to tell us that a third dose provided significant added benefit above or against COVID-19-related hospitalization.

Our relative vaccine effectiveness here, our RVE is for hospitalization, 77%. I do want to point out, you got the two doses, and this is another drop. You're already getting a benefit, this is an extra benefit. For the Pfizer–BioNTech for that 14 to 60 days, also 72.5%, so greater than 70% benefit. A little bit of comparison between the two. Then we go out a little farther. Now we're going to look at greater than 120 days. For those with prior medically attended COVID-19 diagnosis, what if they get that added vaccine?

We did see with Pfizer–BioNTech, there was an added benefit for 120 days, while Moderna also provided some added benefit for greater than 120 days. That added benefit was higher against death compared to less severe outcomes.

**VR:** Daniel, these vaccines were the original vaccines, I presume.

**DG:** Let's go back here. Yes. That's actually a good point, too. Another thing I had - and we actually have some data here we can talk about, where we follow these over time. In the UK - I think this was really an interesting comment that the doc was making, because we're talking about here in the U.S. and other parts of the world. Do we have JN1? Do we have KP2? How close are we to the current variant?

He's like, "We got a whole bunch of vaccines we bought a while ago, and we're still going through those before we move on to any of these newer ones." He was saying it's been quite a while since we dealt with variants that those vaccines target, but we still seem to be getting protection. Can you imagine what he was attributing it to? Not B-cells, but some other type of cell, the T-cell, because the T-cells don't really care that much how close you are to the variant.

**VR:** I just think the issue here is too, given the paper we did last week, there's probably no memory B-cells being generated by these vaccines or by infection. It's not surprising that after 60 days, you see reduced effectiveness because you're simply not making antibodies. Then you're totally dependent on T-cells. If you're older, and that's this population, these are 65 and older, they have trouble making memory T-cells. If you don't make antibody, you can't blame the variant for immune evasion.

**DG:** It's really true. Yes.

**VR:** The T-cells will always work because they're not affected by the variants. Yet, if you're older, you're not really having memory T-cells.

**DG:** Yes. I think this is good. It's interesting. There's still the B and the T-cells. You got to be in a camp. You got to be on a team. No, I think that as time goes by, we're starting to really appreciate that.

**VR:** I think they work together, right Daniel? Ideally at the most.

**DG:** Imagine that.

**VR:** Imagine that. Working together.

**DG:** I think this is really helpful because, sometimes people just say stuff. I think it was Mark Twain, when people say things long enough, pretty soon, there's this crowd echo. If you find yourself agreeing with the crowd, then you may want to rethink what's going on. A lot of people say a lot of things about, "Oh, these antigen tests these days, such and such." Let's look at some actual science. This is the article, “SARS-CoV-2 Antigen Rapid Detection Tests: Test Performance During the COVID-19 Pandemic and the Impact of COVID-19 Vaccination.”

This was published in *eBioMedicine*. I see this title and I'm thinking, "I don't know." Ideally, the way to really look at this would have been if you had the foresight back in 2020 to set up a study and say, "You know what we're going to do? We're going to follow this for who knows how long this is going to go on, but we're going to look at one center, we're going to keep all the variables the same, and we're going to follow the performance of these tests over the next several years." That's what you got to do. I'm like, "All right, but I'll read this anyway."

Then I start to read this article and wow, here we read that they actually performed a prospective assessment from 12 November 2020 to 30 June 2023 at a single center, tertiary care hospital, looking at the sensitivity and specificity of the RDTs. These are these rapid antigen tests from three manufacturers. They're even looking at three manufacturers and they're going to compare these to the PCR as a reference standard. I'm pretty impressed.

I'm like, "Well, yes, that's great. It all sounds good, but you're going to have to do a lot of tests to really convince me here." I look at this, and check this out, they analyzed almost 80,000 paired results. Interesting enough, we actually find out that what we've been saying for a while is actually true. They confirm that a higher RNA copy number and being symptomatic, having COVID-19 symptoms, directly and significantly correlate with the likelihood of getting that positive antigen test.

Now, what about age? What about sex? What about vaccination status? What about, oh, the Omicron variants? Those did not correlate. Let's just make sure everyone gets the memo here. We're confirming what we know and pointing out that certain speculations are not supported by the data. What do we know? Right up front, we have high RNA copy number is where we have the best sensitivity to those rapid tests. We also confirm that this is a great test for people who are symptomatic.

People are saying these other things, saying, "Now with these new variants, the tests just aren't as good." That's not true.

[laughter]

There's no science that supports that. Also, "Oh, now that people are vaccinated, these tests, they're just not as sensitive." Again, that's not true. I'll leave in the link to the article. You can actually go through. They have a really nice figure where you can actually look at sensitivity with all these different variables. Basically, if someone is symptomatic and you're testing them right early on when they have a high RNA copy number, you're going to have great sensitivity, particularly if you do what we recommend is you test that first day of symptoms, remember? Day zero is when you start to feel off.

Day one is that next day you still have symptoms. If that test is negative, 48 hours, you repeat a test again. That's OK because remember, all our data on improved outcomes is starting treatment relative to the day of your first positive test. People get all upset. They say, "Oh, my gosh, I started feeling a little crummy Monday night. I was negative on Tuesday. I didn't test positive till Thursday." You start your early antiviral on Thursday, you're going to get that greater than 90% reduction.

**VR:** Best way to dispel myths is to get data.

**DG:** Yes. There's the science. Leads right into what do we do if you get that positive test? In the UK, they do not have COVID guidelines. They don't have these wonderful national guidelines that we have. Now, we have these guidelines, but you know what? We don't follow them. What's better? We'll leave in links. We got those NIH COVID-19 treatment guidelines. We got the IDSA guidelines. I do want to point out that *Fox News* and *New York Times* do not have guidelines.

Follow the guidelines. Number one, Paxlovid. Number two, remdesivir. Three, molnupiravir, convalescent plasma in certain circumstances, and as we've been talking about for a while, isolation. The first five days is when you see the most transmission. We don't see much transmission after day five. I was just talking to a physician today who was doing an antigen test to test out of that isolation. Remember, as I said to them, based upon some previous work, if you have a positive antigen test, day six through 10, 50/50 chance you're going to have a positive viral culture.

If you have a negative antigen test, 50/50, you're going to have a positive viral culture. Really not giving you the information that you think it gives you. Early inflammatory week. We have a little bit new here. I think this is going to be an important one because early on we had really rapidly changing guidelines. I think people were dropping everything they were doing to have these meetings and follow the grade criterion.

Now we only meet so often. Even when we meet, it takes a while for someone to do their end-note references. Then even when you try to publish it, I don't know what's happened with peer review, but everyone's too busy to review papers. It takes forever. What do we know? One, steroids at the right time, right patient, right dose. This is when a person starts to become hypoxic, the saturation is less than 94%. Anticoagulation guidelines, pulmonary support. What about remdesivir? Has this changed?

Early on, we had data that if you got your remdesivir in the first seven days, it really made a difference. We had the pine tree data with about, 80, 90% reduction in progression. What about current day? A couple of updates here with the two articles. The first article is going to be, “Remdesivir-associated Survival Outcomes Among Immunocompromised Patients Hospitalized for COVID-19: Real-world Evidence from the Omicron Dominant Era,” published in *CID.*

Here, they identified adult patients with immunocompromising conditions hospitalized for COVID-19 between December 2021 and February 2024. Really coming up to the wire here. Primary outcome was all-cause inpatient mortality examined in propensity score-matched patients. We're looking at remdesivir versus non-remdesivir groups. We're even going to do some subgroup analysis, patients with cancer, hematological malignancies, solid organ versus hematological stem cell transplant recipients: 28,966 patients included in the study. We've got 16,730, so 58%, receiving remdesivir during the first two days of hospitalization. They're going to do this propensity score-matching. We've got 8,822 in the remdesivir, 8,822 in the non-remdesivir group. What do we find? Hospitalized patients, remdesivir is associated with a significantly lower mortality among patients who didn't require oxygen. Our 14-day adjusted hazard ratio, 0.73; 28-day, 0.79. A 27% and a 21% reduction in the folks that came in and were not on supplemental oxygen.

Among those who were already on supplemental oxygen, we had a 25% and a 22% reduction. As they tell us, looking at subgroups, remdesivir was also associated with lower mortality in subgroups of patients with cancer, hematological malignancies, solid organ, and stem cell transplants.

**VR:** This is quite late in the infection, right, Daniel? It just shows that you can treat later.

**DG:** Yes. I wonder what's going on. Is there actually a viral cytopathic effect here or is this just still we're getting in there and in getting the virus down, we're helping with more of the inflammation? I'm not sure I know the exact mechanism, but it's not too late. Also, we have the article, "Remdesivir Effectiveness in Reducing the Risk of 30-day Readmission in Vulnerable Patients Hospitalized for COVID-19: A Retrospective US Cohort Study Using Propensity Scores," published in *CID*.

I have to say, Vincent, I'm going back for this COVID-19 narrative review for *JAMA* and reviewing all the clinical updates, just as I did for the Long COVID paper. I just came across that part where I'm discussing with my wife how I was just put off by the clapping out. Remember, they would clap people out. It's all great. They sent them out the door with no follow-up because no one was doing outpatient and then they would get readmitted. This is that issue is nobody likes readmission.

The hospital doesn't like readmission. The patient doesn't like readmission. I don't like readmission. Here, they performed a retrospective study looking at 326,033 patients hospitalized for COVID during the study period. They end up including 210,586. Of these, about half, so 52%, were treated with remdesivir. What do they see? Lower odds of 30-day COVID-19-related readmission. They take that 4.2% readmission rate and they drop it to 3.3%, so a 22% reduction.

They looked at the elderly population, a higher-risk population. They dropped that from 4.7% to 3.7%. They also looked at those with underlying immunocompromising conditions, point out that was a 6.2% readmission. They dropped that to 5.3%. This was consistent, didn't matter whether they came in needing oxygen, not needing oxygen.

**VR:** What's the latest after-symptom onset that you would give a patient remdesivir?

**DG:** We really use 10 days as a cutoff from symptom onset, but sometimes it's hard to get that history. Just such a safe medicine, no drug-drug interactions, no renal issues, really turns out not a lot of hepatic issues, we won't monitor that, but a lot of times we'll probably err on giving it, even if we're not sure about the timing. Remember, it's five days when you're past that first seven.

We have a couple here in the Long COVID section, more than a couple, but number one, "Measurement of Circulating Viral Antigens Post-SARS-CoV-2 Infection in a Multicohort Study," published in *CMI.*

In this study, plasma serum samples were collected from adults participating in four independent studies at different time points, ranging from several days up to 14 months post-SARS-CoV-2 infection. The primary outcome measure was to quantify SARS-CoV-2 antigens, including the S1 subunit of spike, full-length spike, and nucleocapsid in participant samples.

The presence of 34 commonly reported PASC symptoms during the post-acute period were determined from participant surveys or chart reviews of electronic health records. A little bit of an issue there about how good is that data.

Of the 1,569 samples analyzed from 706 individuals infected with SARS-CoV-2, 21% were positive for either S1 spike or nucleocapsid. Spike was really predominantly what they were detecting. Among participants who reported at least one of the 34 PASC symptoms, 43% were antigen-positive, and the presence of antigen was associated with the presence of one or more PASC symptoms with an odds ratio of 1.8. They're about twice as likely if you found someone antigen-positive.

This is a fun one. This is going to be in there with inhaling coffee and some of the other things that we learned about during the pandemic, but this is driving under the influence of COVID-19. Now, they're going to do the breath analyzer and they're going to do an Eris PCR to see if you should be out there on the road, but, "Driving Under the Influence of COVID-19: Exploring the Impact of Acute SARS-CoV-2 Infection on Road Safety," published in the journal *Neurology*.

Here the investigators looked at the correlation between acute COVID-19 cases and car crashes across seven states. They also looked at vaccination rates. They found an associate between acute COVID-19 and increased car crashes. Really, are you ready for this just to put this, I think, in a good context. Driving around with acute COVID was comparable to driving under the influence of alcohol, which is really interesting, because, you do these telehealth visits. Then we tell that patient, "Oh, we really want to start you on that Paxlovid. They're like, "Oh, I'll just drive drunk, basically, over to that pharmacy."

No, don't let them drive. You got to get this delivered to the home. We don't want people driving around basically drunk.

**VR:** That's very interesting.

**DG:** Then this is going to be our last one. We have the article, "Long COVID Facts and Findings: A Large-scale Online Survey in 74,075 Chinese Participants," along with the commentary, "Long Covid is a Significant Health Crisis in China Too." I'm going to leave links to both of these. This was published in the journal *The Lancet Regional Health - Western Pacific*. The first sentence of the commentary, I think, is really powerful.

"Long COVID, the constellation of long-term health effects caused by SARS-CoV-2 infection, is a significant global health crisis affecting at least 400 million individuals worldwide, with a cost of $1 trillion, equivalent to 1% of the global gross domestic product." They quote this first line from the article, "Long COVID Science, Research and Policy," that was published in August in *Nature Medicine*.

The article itself is a retrospective study where they used an online questionnaire to investigate SARS-CoV-2 infection status and Long COVID symptoms among 74,075 Chinese residents over a one-year period. They analyzed almost 70,000 responses. They found somewhere in the range of 10% to 30% reported Long COVID symptoms. They're including some folks in there with repeated infection. The most frequent Long COVID symptom was fatigue. That was 30%. Memory decline, 28%.

Decreased exercise capacity, that's 18%. Brain fog, 17%. I'd say consistent with what we know so far, women were more likely to experience Long COVID. Symptoms varied by age group, except we were seeing sleep disorders, muscle, joint pain more common in the older folks. What were risk factors? Underlying disease, alcohol consumption, smoking, and the severity of that acute infection. Yes, reinfection may have been associated with milder symptoms, but it led to a higher incidence and severity of Long COVID.

Vaccination, particularly multiple boosters, significantly reduced long-term symptoms by 30% to 70%. I will wrap us up. No one is safe until everyone is safe. We're still in October. There's about two weeks left. We're in our Floating Doctors fundraiser, August, September, October. We're hoping to get up to that level where we can double those donations up to a maximum donation of $20,000.

**VR:** It's time for your questions for Daniel. You can send yours to Daniel@microbe.tv. Lisa writes, "My husband and I are both over 70, live in Canada. We've been vaccinated six or seven times against COVID, and I've had COVID twice. Our latest vaccination was six months ago. After that, we got COVID at the end of June. We got Paxlovid. Here in Quebec, the government's not offering Novavax. If we wish to get vaccinated, is it worthwhile to get another mRNA dose?

We understand disease will not be prevented. Aside from age, I have asthma. My husband has arthritis. We'll get the flu shot for sure, but I'm not convinced that a seventh or eighth vaccine dose is timely."

**DG:** What are our thoughts? What are our recommendations? This is a scenario that a lot of people are dealing with. There have been vaccinations in the past. There was an infection during this summer-spring peak, but that was back in June. July, August, September, October. We're about four months out from that. What we're thinking is these mRNA vaccines may not trigger the development of these long-lived plasma cells in our bone marrow, but they do, for a period of time, boost the antibodies.

There is a temporary reduction in the risk of symptomatic COVID. Also, as we talked about in our data, there is a temporary reduction in your risk of severe disease above that baseline. We've already got a baseline. We've got a baseline of immunity, which you have this hybrid one, but we're recommending particularly for higher-risk folks, but really, I have to say, here in the U.S., we're recommending across the board that everyone get a boost this fall. Hopefully, that's going to prevent this winter peak that I am predicting, and Vincent, with his optimism, is hoping never happens.

**VR:** Jason writes, "During *TWiV 1156*, the three-season efficacy of the GSK RSV vaccine was discussed with a marked drop in efficacy by season three. These results led to comments that a booster would be needed at some point. It was reported in a press release by GSK in 2023 that a booster after one year did not change observed efficacy in the vaccine versus unboosted. If a booster one year doesn't change it, why would that be? What might that say about the efficacy of boosting later than one year? Do you think that the information we have so far about the vaccine might hint towards limitations in the long-term efficacy of this vaccine, even with boosting?

**DG:** These are good questions. Really, the question has a lot to do with what are we boosting and what's the durability. So, you get your GSK vaccine, and we've talked about the GSK and Pfizer being these fusion protein-based vaccines. See, your immune system sees the fusion protein, two things are going to happen. Your B cells are going to make the antibodies. Your T cells are going to create some degree of memory. A year later, still going strong.

You get a booster. That doesn't matter at that first year because you're still there. We'll use 2020, I'm going to say. So, 2020, let's say we started. 2021, whether we boost or not, we're doing great a year later. 2022, you're two years later, still doing well. Now as we're seeing 2020, that third season, we're really dropping to less than 50% protection. Do we boost, not necessarily one year in, because we were still going strong, but do we boost every two years? Does that give us a two-year durability?

These are the things that we'll find out going forward. I hope there isn't some sort of, "You only get your window, and then you're done and you can't boost going forward." We're hoping that this could be just something where it's an every two-year shot, for instance.

**VR:** Michael writes, "Love the show. Never miss it. Contributor to *MicrobeTV*. Full-time primary doc here. I use Paxlovid frequently. Today, I had a 67-year-old male, well known to me, fever, 100.6, myalgia, headache, non-toxic in appearance, normal PE, COVID rapid antigen-positive, for years on ustekinumab for Crohn's. As I went to prescribe Paxlo, I realized I had prescribed it to him just 22 days ago. Same scenario. In that episode, he defervesced quickly. He did, against my recommendations, repeatedly recheck his rapid antigen test at home and states, 'I saw it gradually go neg, and confirmed neg twice after that.' He's an engineer.

He returned to work with a mask about day six. He was fine until yesterday. I confirmed negs of strep, flu, and RSV. He never had a cough. I sent off for PCR this morning. Because of the IL-12/23 inhibitor, I elected to repeat Paxlovid. Would you? If this is all one infection, why a late fever without any other findings? Is the IL-12/23 inhibition important to explaining the course?"

**DG:** This is a great email because it's that whole detective part of being an infectious disease doc, trying to figure out with the clues what may or may not be going on here. You don't always have the clues. As I see here, you went ahead and you said, "Well, let's send off for PCR." Maybe you can even get somebody to read you the CT values, which might help sort this out. I'm reviewing all these clinical updates going back.

I'm back in the period of time when we were having this discussion, can you get reinfected? It really took something to prove it was really a reinfection, and we're "Who's got the sequence of the first infection? Because you can't get a repeat infection." You can get repeat infections. Unfortunately, you get repeat infections as soon as three weeks afterwards. We don't know at this point.

Is this just one of those early reinfections, this individual got infected, and then boom, they got hit with another infection, or is this just that ongoing medium COVID inflammatory phase, and now they're shedding cells, which just happened to maybe have antigen or maybe have

an RNA? Maybe that CT value is going to help you out. Because this is an acute COVID, we're going to think CT values in the teens, we're going to think millions of RNA copy numbers.

If it's just that inflammatory shedding, which we see, then maybe that's going to be lower. I've got patients who really have the same clinical course, PCR is negative, and it really is just this ongoing post-COVID inflammatory, medium COVID that we see. Was it a mistake to give Paxlovid? I actually think it's reasonable pending that PCR. Better to give it to someone who needs it, immunocompromised person, than to keep it in your pocket or leave it on the shelf where it doesn't help anyone.

**VR:** Ann writes, "I was interested in the recent discussion about the fact that the mRNA vaccines may not provide protection against infection that lasts as long as we hoped. In 2022, I timed my booster to protect me on vacation, only to catch it anyway with a positive test seven weeks after the booster. In 2023, did the same, tested positive seven weeks after vaccination. Does this indicate that the flaw is my immune system rather than the vaccine, or does it imply that the virus is unusual or something else? I just got home today and waiting to see whether I've broken the cycle of testing positive the weekend after I return home."

**DG:** I don't think this says anything's wrong with you. The thing, Ann, we keep pointing out is that vaccines prevent disease, and particularly severe disease. They don't necessarily prevent infection. The wonderful model for that is the injectable polio vaccine. You're just as likely to get replicating virus in your gut and shed. The big thing here, and I think the thing you have to say is you may have gotten COVID, but we're anticipating, we're thinking that the severity of those infections is reduced by your vaccination. Don't feel like something is wrong with you. I'm hoping you broke the seven-week curse cycle that you seem to be in.

**VR:** DJay writes, "No medicine here, just a word nerd commenting. Doff and don from “doff thy coats” come from do off and do on. On a related note, when I lived in rural Labrador, people also said, 'doubt the lights' for 'turn off the lights,' also a contraction of 'do out.'"

**DG:** Oh, I love that. [laughter] Great.

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

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

**[00:44:57] [END OF AUDIO]**