This Week in Virology

TWiV 1118 Clinical Update

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Guest: Daniel Griffin

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

[music]

From MicrobeTV this is *TWiV*, *This Week in Virology*, Episode 1118, recorded on May 30, 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. Joining us today from Sweden, Vincent.

VR: Yes, Stockholm, Sweden, the home of the Nobel Prize, where I have been lecturing and doing a couple of podcasts before heading to a virus meeting in Finland. Next week, we'll be recording from a small town in the north of Finland. We'll see how that goes with the internet. [chuckles]

DG: Oh, gosh.

VR: What do you have on your bow tie today, Daniel?

DG: What do I have on my bow tie today?

VR: Looks interesting.

DG: Oh. Let's see. There are these viruses and they have these spike proteins. It almost looks like a corona.

VR: Oh, it's a corona virus. I thought it might be a pox virus. They're kind of elongated, but yes, OK. Do you have a pox virus tie by any chance?

DG: I have to look and see. [laughs]

VR: Next time you talk about mpox, you should pull that one out.

DG: I should. I got to do that.

VR: All right.

DG: It just occurred to me, there's a little gap between our pre-recording banter and now that you and I are officially nerds, Vincent, just in case anyone was doubting it, because here you are in Sweden, you're at the Karolinska, right? Instead of us talking about sailing and Sweden, what are we talking about? HPV. We're talking about COVID. [laughs] That's what I want to know.

VR: I tell you, there are a lot of nice sailboats here. Stockholm's on the water and there are lots of docks and things, and you would probably like to sail here.

DG: I would, actually. I have a good friend who actually was, I did some research with, who's actually probably back there at the Karolinska, so I've got to go visit him. I'll do it during that six-week August vacation. Which, I remember, when he came here, and he was working there at the Karolinska and the head of the lab he was in was the chair of the committee. I think that's changed, right? He was like, "I don't understand. I don't get my six weeks off to sail in the summer? How does this work?"

[laughter]

All right, let's jump in. I'm going to jump in with a Jared Diamond quotation. "Science is often misrepresented as the body of knowledge acquired by performing replicated, controlled experiments in the laboratory. Actually, science is something broader. The acquisition of reliable knowledge about the world."

VR: I never heard you say laboratory before. You say laboratory.

[laughter]

VR: It's like a British pronunciation, right?

DG: Is that what it is?

VR: I think.

DG: I'm heading to the lab for some laboratory experiments. I guess, yes, I guess that is British. I just think it's, sometimes I feel like as exciting as science is, the goal is to get reliable knowledge. It's not just to basically put your head down and just do experiments over and over. There's a point to it all. It's exciting to acquire this knowledge, to be a pioneer, acquiring new knowledge, which then moves us forward with our understanding.

VR: Daniel, everything we have is based on science. Just look around you. The buildings, your cellphone, your internet, your computers, your health, it's all from science. Anybody who wants to be a science denier, you're basically throwing your life away.

DG: Yes. It is funny. They post their science denial on social media using their smartphones and their computers, but OK. [laughs] All right. Some fun stuff today. I'm going to start off with a comment about parenting. I have three children and they're growing up. One part of parenting that I think is important is when we teach our children not to pick up dead animals. [laughs] Yes, certain children apparently without a bit of guidance in this area will touch dead animals with their bare hands.

Now, dogs, moving on to dogs in general, seem not only interested in touching dead animals, but they often put that dead animal in their mouth or for some disturbing reason, thinking about my dog Pippin, they will roll about, rubbing their entire body against the dead animal. Now, perhaps Angela Mingarelli can come on, our trained veterinarian. She can explain what is going on here.

Why do I bring this up? Now, apparently, it gets worse. There are people that train their dogs to put dead birds in their mouths. There are even dogs called retrievers. Apparently, the best ones apparently are referred to as the Golden Retrievers. They are taught to run out, take hold of dead birds, and bring them back to their owners in their mouths. Yes. In the time of highly pathogenic avian influenza, H5N1, this is still going on.

Now, I understand, to our listeners, this might sound a bit farfetched, and we're going to leave in a link. You can verify this is really true. A link from the American Kennel Club explaining that not only does this go on, but as they say on their webpage, all retrievers must be bred to have a mouth soft enough to pick up and hold game, like ducks, without damaging them. The Golden's mouth is so soft, it is said they can carry a raw egg in their mouth without cracking the shell.

Now, I grew up with a lovely Golden Retriever named Daisy, who may or may not be the reason my oldest daughter is named Daisy, despite my wife explicitly telling me that we would not be naming our children after any of my dogs. What could go wrong with all this? I'm not talking about the naming of my daughter, but with dogs running out and having dead birds in their mouths. We have the dispatch in *Emerging Infectious Diseases,* "Antibodies to Influenza A(H5N1) Virus in Hunting Dogs Retrieving Wildfowl, Washington, USA."

Now, in this study, the investigators collected blood samples from 195 dogs identified by owners as having engaged in this activity, this bird hunting or bird hunt testing and training over the previous 12 months. There is a figure, but it had a whole bunch of boxes and no cute dog pictures, so I skipped right over that. Apparently, in Washington, the state, not the district, this is such a thing that they have a season where all the owners and their dogs engage in this activity from mid-October through February.

Now, the investigators collected blood from the jugular veins of these dogs and screened the serum samples. They report that they detected antibodies to the H5N1 subtype influenza viruses in 2% of the dogs. They do report that they detected these high levels only in hunting dogs that were involved in the bird hunting and waterfowl retrieval. Now, although that finding suggests transmission of this highly pathogenic influenza viruses, HPIAV H5N1 from waterfowl to dogs can occur, it was a low prevalence. There was a lack of reported disease in the seropositive dogs and lack of evidence for dog-to-dog transmission among the dogs, even if they were sharing households, sort of, I think, encouraging that this is not particularly well adapted to dogs.

Perhaps the question on the minds of our listeners and Vincent is, what about the sialic acid? Both alpha 2,3, that's the bird and the alpha 2,6 human sialic acid-linked influenza virus receptors, they've now become virus receptors, have been detected in all organs of dogs, and an alpha 2,3 sialic acid-linked influenza virus receptor extended from the upper to the lower

respiratory tract. Alpha 2,6 sialic acid-linked influenza virus receptors were also identified, detected in the respiratory tract, but at very low levels.

VR: I wonder, Daniel, if these dogs are now immunized against HPAI, H5N1 virus.

DG: That is one of these things that people have brought up. If you drink the raw milk, if you put the dead bird in your mouth, if you get a certain amount of exposure before this virus has adapted, become human-adapted or dog-adapted, are you left with some sort of immunity?

VR: Yes, because it's a naturally attenuated virus, right?

DG: Yes.

VR: The question just is it, do they have high enough antibody and T-cell levels, probably those are important too, to prevent severe disease? That would be the key. I can imagine you're going to be talking about a study in mice. It'd be interesting to know if those mice are immune to challenge.

DG: That is a really interesting question. OK, so you get antibodies, you're able to say, "OK, it looks like there was some sort of exposure, but yes, are those antibodies high enough to be protective?" Because we do actually have canine influenza vaccines that certain dogs get. Is it attenuated too much to prevent you from getting a protective T-cell response?

VR: I don't think people should try and drink unpasteurized milk to immunize themselves. That's not a good idea because you just don't know if the virus would change in you to cause more damage. We just don't know that. It's not a laboratory-tested, attenuated vaccine. In dogs, it may be one thing, but in humans, another. I'm just curious, if getting that amount - First of all, I don't know how much it's reproducing in dogs. We don't know that. Whether the dogs are immune to challenge would be interesting to know, I think.

DG: Yes, and the fact they're not spreading it to other dogs, it doesn't really support the idea that there's a lot of viral replication. I also don't like the idea of people doing this because, oh, maybe you're fine, but you do it in enough people and you're just giving the virus the opportunity to become human-adapted.

VR: Yes, and also, not pasteurizing milk has other risks, right, [chuckles] as we've talked about before?

DG: All right. Now, Vincent, sometimes I worry that not everyone listens to *TWiV*. When I spoke to my daughter, Daisy, the one who is in no way named after my favorite Golden Retriever, she was not aware of the bird flu situation.

VR: Oh, my gosh. Now, wait, Daisy is becoming a nurse, correct?

DG: Can you believe that? Yes, the one becoming a nurse.

VR: Why isn't she listening to her dad on *TWiV,* at least? That means she'd get free education.

DG: It should be required for all nursing students, so I will bring that up.

VR: It should be required for all Griffin family members, too.

DG: [chuckles] Apparently, they claim because I'm around and talk about this stuff, they don't have to listen but -

VR: Ah, interesting.

DG: Perhaps now with the *MMWR* early release, "Outbreak of Highly Pathogenic Avian Influenza A(H5N1) Viruses in U.S. Dairy Cattle and Detection of Two Human Cases - United States, 2024," everyone, including my daughter, Daisy, will be alerted. Yes, this is really kind of a recap for our listeners, but here we read that on October 1, 2024, the Texas Department of State Health Services reported that a dairy farmworker had tested positive for highly pathogenic avian influenza A(H5N1) virus after exposure to presumably infected dairy cattle. CDC confirmed these laboratory findings. They say the patient only experienced conjunctivitis, but, oh, my gosh, was that conjunctivitis scary looking. This was bright, fiery red, so every PowerPoint in the future is going to have that, that talks about H5N1.

No other signs or symptoms. They said you isolate, you take the Tamiflu, they get better. No other illnesses identified among the household members. Everyone else got some Tamiflu, too. Now, a week later, the USDA reported a multistate outbreak of the H5N1 viruses in dairy cows. The H5N1 viruses were also detected in barn cats, birds, other animals, one raccoon, two opossums that lived in and around the human habitations and that actually died on the affected farms.

Genetic sequencing of the virus from infected cattle and the farmworker identified this clade 2.3.4.4B. Just of note, this clade has been detected in U.S. wild birds, commercial poultry, backyard flocks, and other animals since, you ready for this? January of 2022. Go back a couple of years. Now, on May 22, 2024, the Michigan Department of Health and Human Services reported a case in a dairy farmworker on a farm confirmed to also have that H5N1 virus in the cattle. This person, so second person, we got a Texan, now we've got a Michiganer, this investigation is ongoing, but this person also had only eye symptoms.

These are now two cases, the first known instances of cow-to-human spread of avian influenza A virus. Now as of May 22, 2024, approximately 350 farmworkers with exposure to dairy cattle or infected raw cow's milk have been monitored. As we keep bringing up, pasteurization, it inactivates the H5N1 virus. The commercial milk supply is safe for consumption. Importantly, the risk to the public might change, but only if these viruses acquire genetic changes that increase their, like this transmissibility to and among humans, which could increase the risk of an influenza pandemic. There's no transmissibility above humans, so it would be an increase from zero at the moment.

Now, if my daughter is not reading the *MMWR*, what about *The New England Journal of Medicine*? Here we have the correspondence, "Cow's Milk Containing Avian Influenza A(H5N1) Viruses - Heat Inactivation and Infectivity in Mice," was published in *The New England Journal of Medicine* this last week. Here we read that to further assess the risk of these positive milk samples, these investigators orally inoculated mice with infected milk. They're not squirting it up the nose, they're actually, they're drinking a little dropper thing and they get a few drops of the milk.

Now, the animals actually showed, these mice showed signs of illness starting on Day One. They had ruffled fur, they had lethargy. Now, all the animals survived until Day Four, so I'm thinking, "OK, good mice, you made it." Then, they euthanized them to determine virus titers in multiple organs. They detected high virus titers in the respiratory organs and moderate virus titers in several other organs. Findings, as they say, consistent with the systemic infections typically caused by HPAI H5 viruses in mammals.

They go on to comment that detection of virus in the mammary glands of two mice was consistent with the high virus load in the milk of lactating cows, even though these mice were not actually lactating. I thought it was interesting. Now I wanted to - That next question that you sort of brought up preemptively there, Vincent, when we talked, do these mice transmit it to other mice? I will recommend a deeper dive into this paper on *TWiV* 1117. I think this is the title from Alan," Pol Dances with the RNA that Brought it."

VR: Sure is. It's an Alan title. This is interesting because in the cows, this is not a respiratory infection, right? It's a mammary gland infection. In the humans, the two humans who got infected from the cows, it's conjunctivitis. It's not a respiratory tract infection. In mice, the respiratory tract appears to be infected. I don't know if it's pathogenic or not. They didn't do any lung function tests. Already, you see mice are different from cows and humans. I don't know what that means, but I think what we learn in humans is important. Those are accidental infections. This is not a respiratory pathogen any longer. If something's happened in the traveling from the bird to the cow to the human, that now makes it not respiratory tract. People need to back off a little and stop worrying so much.

DG: Yes. I was curious here, they're getting the mice to drink it, and I almost would like somehow to get it directly into the stomach, just making sure it's not somehow, you're putting the drops in the back of the throat. Is some of it somehow getting up into the respiratory system?

VR: Oh, I'm sure it's aerosolizing, and going up into the nasopharynx and infecting there. Yes, if you put a tube into the stomach and dripped it in, I bet you wouldn't see as much infection, because the stomach is pretty -

DG: Yes. I'm curious, is it, do you get a viremia? Is that how it gets into the lung? Just want to -

VR: Yes , sure.

DG: - pin down the science. All right, and I'm going to close out this section with the USDA Animal and Plant Health Inspection Service announced May 28, that tests have confirmed this H5N1 avian influenza in alpacas at an Idaho farm where the virus was in the poultry flock. Currently, H5N1 has been detected in 67 dairy herds across nine states. We got a few more detections over the last week. Another in Idaho, another in Texas, other in Michigan.

I'll have people just give another plug for *TWiV* 1117 and this like, what are we going to do? Are we going to vaccinate the cattle? I thought it was really an interesting issue. You say, well, "Boy, it would make sense. It would keep us safe. Oh, but it might impact intercountry commerce. They might not want to buy our milk if we have vaccinated cows," which, really

crazy. I'm just thinking about some sci-fi movie where the world all ends because we want to continue to sell our milk overseas.

VR: People don't need milk. Remember that.

DG: You're going to get more hate mail. "They need milk. They need their cheese." [laughs]

VR: I can't get any more hate mail than I already get.

[laughter]

DG: All right, let's move into COVID. Weekly COVID update, the percentage of provisional deaths is still 2% or less across the country, but the wastewater, what are you guys doing out West? We are now seeing an exponential rise in the wastewater just out West. Everyone else, we're doing OK. National looks OK, Midwest, South, even here in the Northeast. Yes, out in the West, we're starting to see a rise.

VR: What is this y-axis? You have 0, 1, 2, and 3. Is that a log scale or linear? [chuckles]

DG: Yes. No, that's a good question. It's this wastewater viral activity level that they're using. Yes, it'd be nice to have just some kind of like - Yes.

VR: Yes, because from one to two is not a big deal, right?

DG: Yes.

VR: I don't know what this is. You go on to the next topic, maybe I'll try and figure it out.

DG: Yes, you can, the nice thing, people will leave a link, but you have the ability to look at this in 45 days and you can go out to like all time, a year, six months. You look at it in different scales and get a different sense of activity. Vincent, you be distracted by that while I talk about the article, "Risk Factors for Pediatric Critical COVID-19: A Systematic Review and Meta-Analysis."

Yes, these are the results of a meta-analysis that looked at critical COVID-19 defined as invasive mechanical ventilation, intensive care unit admission, or death. We're talking about kids here. They're looking at 70 studies, published from March 2020 to August 2023, and they found a nearly tenfold increased risk in kids who had two or more underlying medical conditions. They looked at 172,165 children, adolescents, and young adults with COVID-19 in 45 countries, and reported that in healthy children with no comorbidities, the absolute risk of critical disease for COVID-19 was 4%. Now, that's about one in 25. That seems high to me. Then we read that compared with no comorbidities, the pooled odds ratio for critical disease was 3.95 for the presence of one comorbidity, so four times, and 9.51, so almost ten times as high for children with two or more comorbidities.

VR: Now, Daniel, this data are delayed six weeks, so -

DG: Isn't that a problem? Yes, we're already seeing, like when I give data, we're talking about - Well, I had it up to 5/18/24, so, yes, that's about -

VR: This y-axis is simply, I think it's RNA copy number, so, we're talking about one, two, four, so the peak of activity was 14 copies per mil. Not a lot, right? Sewage is highly diluted, so that's probably OK. We're talking about, in your little chart there, an increase from one to two copies per mil. These numbers are quite stable, so if you look from April through the present in many areas of the U.S., it's just between one and two. It seems to be rather stable. This is a real increase between one and two, but I just don't know how much it really matters clinically.

DG: Yes. You sometimes worry when they say, "It's double." You're like, "Double, like I just doubled my risk of winning the lottery." Like, "Yes, OK."

[laughter]

DG: Still going to lose. Yes, we'll keep an eye on it, but so far, we're still at low levels for the moment. All right, ventilation, transmission, so I'm not sure how many Noah Kahan fans we have, but he is the singer with that song, "Stick Season." I don't know if you know that song, where the line goes, "The doc told me to travel, but there's COVID on the planes." I was listening to that earlier today. [crosstalk]

VR: Daniel, I know it sounds good as a lyric, but there's probably no COVID, but there's SARS-CoV-2 on the planes, right?

DG: You're right. Let's try that. "The doc told me to travel, but there's SARS-Co -" No, it doesn't work.

VR: It doesn't work. I know.

[laughter]

DG: There's COVID virus on the planes, maybe that. I don't know. No, it's got to be - I'll shoot Noah a correction. Yes, Noah is sort of correct then I'll say. There's SARS-CoV-2 floating around. The article, "The Risk of Aircraft-Acquired SARS-CoV-2 Transmission During Commercial Flights: A Systematic Review," was published in *Environmental Research and Public Health*. These are the results of a systematic review and analysis of articles published prior to vaccines being available. From the 24th of January 2020 to the 20th of April 2021, to identify factors important for transmission.

I have an overlap in my mind when those vaccines came out, like end of December, beginning of January, so 2020, 2021. Now articles were included if they mentioned index cases and identifiable flight duration, and excluded if they were talking about non-commercial aircraft, they were doing airflow or transmission modeling, cases without any flight data, or if they couldn't really determine in-flight transmission.

They finally narrow it down, they've got 15 articles selected for this in-depth review, 50 total flights. They analyze these for flight duration, both as categorical variables. Short, less than three hours, medium, three-to-six hours, or long, greater than six. Compared to short flights without masking, medium and long flights without masking were associated with a 4.66-fold increase and a 25.93-fold increase in incidence rates, respectively. We're looking at those different. Long flights with enforced masking, no transmission reported. Then they break this

down. For every one-hour increase in flight duration, you get a 1.5-fold increase in the incidence rate ratio of cases.

VR: Daniel, I thought the HVAC in the planes took care of all this. Apparently not.

DG: That's what I was told.

[laughter]

DG: This seems to challenge what Alan Dove has been telling us from his -

VR: Yes. I thought that once you push back and that high-velocity air system comes on top to bottom, and then it's filtered through a heap of filters, I thought it took care of it, but yes, they're not right. It is transmitting, so you should wear a mask on planes. In times when there's a lot of community transmission because people are getting on the planes. They're not infected. You're not going to transmit. Right now, as you just showed us, the transmission is very low in communities, so the risk is lower.

DG: Yes, but I think this challenges some of what I thought made sense. I go to the crowded airport, I got the N95 on, I'm waiting to get into the plane, and the crowded waiting, and going down that narrow, crowded area. Then I had this idea, once everyone's seated, the plane takes off, everything's fired up, I thought I was OK for a while, but this -

VR: No, you're not.

DG: Yes. This science says that, not so good.

VR: It's funny, on my flight here from New York, there were two people wearing masks the whole flight. I felt like saying, "Hey, don't you know the air system is really good on these planes?" I'm glad I didn't.

[laughter]

DG: OK. All right. COVID active vaccination, a little more data, not the data I wanted, but a little more data on those new vaccine doses or boosters with the correspondence, “Durability of XBB.1.5 Vaccines against Omicron Subvariants,” published in *The New England Journal of Medicine*. Here, the investigators are using a cohort of approximately 1.8 million persons. It's from Nebraska Electronic Disease Surveillance System and the Nebraska State Immunization Information System. They're looking at four endpoints. They're looking at infection, hospitalization, hospitalization or death, or then death alone.

We see in this study that overall, the XBB.1.5 vaccines were effective against Omicron subvariants, less against JN.1. The effectiveness was greater against hospitalization and death than against infection. It waned moderately from its peak over time. The ramping and waning patterns were broadly similar to those of the bivalent booster. They have some really nice figures, and I'm going to just go through these a little, but I'm going to comment about why it isn't the data that I wanted.

What I really wanted to see was people that had gotten two shots. People who'd gotten a first shot on or before October 25th, so they have people that got that. Then I want to see those same people get a second shot in March and see if that affects. We get several panels. First we look at infection and then infection according to date of vaccination. We see this vaccine effectiveness waning relative to infection, but not falling off a cliff, just sort of peaking and then dropping.

Vaccine effectiveness against hospitalization, maybe holding a little steadier and a little bit higher, sort of dropping over time. Hospitalization or death, and then death actually seems where we're seeing the most significant decline over time from this vaccine effectiveness peak of 70%, dropping down to maybe like 30% as we get out to 23 weeks.

VR: I'd really like to know the age stratification here, because I wonder if this waning is principally in older people, where they just don't respond well to vaccines of any kind, right?

DG: I think that's also helpful, because we have this recommendation, "Hey, boost if you're over 65." You want to know is that the population that is seeing the most decline? Also, is that the population that if you do that, do we get ourselves back up? If we do, for what period of time?

VR: The thing that's interesting here is that you do have some really good protection against hospitalization, even with a different subvariant. The original vaccine, as you said, is XBB1.5. Then some of these people are infected with JN.1, but there is good protection until time passes. It seems to me, it's not the variant that's the issue, it's the durability of the vaccine. Maybe these, I presume these are mainly mRNA vaccines, maybe the durability isn't that great, and you have to rethink it.

DG: Yes. I do like the way they do these figures, because they basically have like, "Here's XBB, other XBB variants." Then, as you start to see JN.1 come in, there's no cliff. It's just nice slope, stays right along, so we're not really seeing a variant impact here.

A little update here on COVID, passive vaccination, Pemgarda. That's our new passive vaccination. You get the antibodies, and actually, this week I tried to - We'll see how well this goes, I tried to prescribe my first Pemgarda. There is an infusion center locator website, pemgarda.com. It's terrible, whoever makes Pemgarda out there. We were trying to use it, something was coming up. Here's where we think the infusion center, it's in some residential neighborhood. I tried it locally. It comes up at one of our preschools. I don't think the preschool or the elementary schools are giving out Pemgarda. Yes, I put in, "Contact me. Help me with this. Let's get this working." Because yes, you can't use it if you can't figure out where to get access.

All right, moving on to the early viral phase. Remember those guidelines, the early effective antiviral, so Paxlovid, remdesivir, molnupiravir, convalescent plasma, in isolation so we don't get everyone else sick. Second, early inflammatory week. In the right patient, right time. We've got steroids, anticoagulation, pulmonary support, maybe remdesivir, still in the first 10 days, immune modulation.

Moving on, we've got a bunch here in late phase, PASC/Long COVID. I am almost done. I say almost done being about 95 hours into my 100 hours of my Long COVID review paper. Sort of realizing, "We really have been covering a lot, but this is nice."

We have another article, Post-COVID Conditions Following COVID-19 Vaccination: A Retrospective Match Cohort Study of Patients with SARS-CoV-2 infection," published in *Nature Communications* demonstrating, again, pre-infection vaccination was associated with reduced risk of several post-COVID condition outcomes and may decrease the long-term consequences of COVID-19.

We see here vaccinations associated with a greater than 10% reduction in the risk of the following, lower risk of sensory problems, circulatory, blood and hematological, skin subcutaneous, and then even nonspecific COVID-19-related disorders. In general, associations were stronger at younger ages, but mostly persisted regardless of the variant period. It's always better with three or more doses versus one to two vaccine doses, and also time since vaccination.

In my review, I just might say, "There's a list of papers. This is a consistent finding." Now the article, "The Importance of Including Long COVID Outcomes when Developing Novel Treatments for Acute COVID-19," was published in *JID*, really arguing that we should be looking at Long COVID as an outcome when we study treatments. They give us what they call seven compelling reasons. I feel like I'm on *The Johnny Carson Show*.

Number one, Long COVID's not rare. Number two, Long COVID is debilitating to individuals and has a high societal cost. Three, those at high risk of severe COVID-19 are also at higher risk of developing Long COVID. Four, treatments for acute COVID-19 may reduce the risk of Long COVID. Five, measures exist to track Long COVID. We have the technology to do this. Six, Long COVID considerations are potentially important for acute COVID-19 treatment decision-making, something we can do in that acute week that prevents Long COVID. Number seven, deaths and hospitalizations due to COVID-19 are getting to be less common, increasingly rare, creating an opportunity for other important clinical endpoints to be considered.

All right, this week in *Nature Communications*, we have the article, "Cerebral Microstructural Alterations in Post-COVID Condition are Related to Cognitive Impairment, Olfactory Dysfunction, and Fatigue." We've discussed several times that some individuals with post-COVID sequelae report neurological symptoms such as cognitive deficits, olfactory dysfunction, fatigue.

Now here the investigators employed MRI, magnetic resonance imaging, to conduct a comparative analysis of cerebral microstructure among patients with post-COVID conditions. They looked at healthy controls, individuals that got COVID but said they were fine. They detected widespread alterations in cerebral microstructure attributed to a shift in volume from neuronal compartments to free fluid associated with severity of the initial infection. Correlating these alterations with cognition, olfaction, and fatigue, they found distinct affected networks, which they report were in close anatomical functional relationship with the respective symptoms.

They have several nice figures where one can see in detail, which parts of the brain are being impacted, turned into fluid instead of good healthy brain tissue? The discussion is extensive in this paper and goes into limitations, other studies in the area, a bit on potential mechanism from the authors. These show that COVID-19 leads to microstructural changes in the brain, which differ between participants with and without PCC symptoms. A correlation between functional status and imaging data were identified, whereby the presence of PCC symptoms was associated with the affection of specific cerebral networks suggesting a pathophysiological basis for this syndrome.

Just a couple more Long COVID ones here. “Prevalence and Co-occurrence of Cognitive Impairment in Children and Young People up to 12-months Post-infection with SARS-CoV-2 {Omicron Variant),” published in *Brain Behavior and Immunity*. Yes, we are talking about young people, children here. The investigators report the prevalence and characteristics of children and young people, CYPs, children and young people. All right, we need a three-letter acronym for that. Those that reported brain fog 12 months post-PCR-proven SARS-CoV-2 infection, and they tried to determine whether differences by infection status exist, and they explored the prevalence of CYP, children and young persons, experiencing cognitive impairment over a 12-month period post-infection. They also looked at cognitive impairment, poor mental health, well-being, mental fatigue, sleep problems.

At 12 months post-testing, 7% of first positives and 7.5% of the reinfected CYPs actually had cognitive impairment. A bit higher than I would have thought. At all-time points post-testing, the CYPs experienced cognitive impairment, more likely to score higher on all strengths and difficulties, questionnaire subscales, scoring higher. They're also using the Chalder Fatigue Subscale for Mental Fatigue. They're using the Short Warwick-Edinburgh Mental Well-being scale. They're also seeing issues with trouble sleeping. We're seeing issues here, and also, this is a nice link in case providers or patients want to do, say, specific testing to document these impacts.

VR: Again, most of this is self-reporting, right?

DG: That's actually the challenge with a lot of these. I like this stuff before where you do an MRI and you look at this, "Oh my gosh, your brain is turning into liquid." This stuff is always tough when it's a questionnaire.

VR: Sure. No, I don't question that everyone has some symptoms, but I'm not sure that it needs to be COVID-specific, right? If you've had COVID, it's upsetting, and so it may not have a pathophysiological basis. It may just be that you're upset, and therefore, you have a brain fog. Now, in this paper, they do some testing, which is great, but I just worry these are high numbers, 7% and 7.5%. We've seen much lower numbers in other studies where it's less self-reporting and more bring people into a clinic and test them for various things, so like the POTS test, right?

DG: Yes. Yes.

VR: I think this is a real challenge.

DG: I always worry when you try to put a number on this stuff. It's okay for me to say, "OK, yes, there is this issue of cognitive impact in children," and then what percent. That number,

I think, is going to be a challenge. How do you do it? Who do you recruit? Who are you looking at?

All right, and this is going to wrap us up as far as articles this week, "Long COVID Symptoms after 8-Month Recovery: Persistent Static Lung Hyperinflation Associated with Small Airway Dysfunction," published in *Respiratory Research*. Now here, the investigators looked at small airway dysfunction, SAD, and static lung hyperinflation, SLH, in patients with post-acute sequelae of COVID-19.

Sixty-four patients with PASC were enrolled between July 2020 and December 2022 in this prospective observational cohort. They did pulmonary function tests, impulse oscillometry, IOS, symptom questionnaires performed two, five, and eight months after acute infection. We read that the CD4/CD8 T-cell ratio was significantly correlated with residual volume to total lung capacity ratio. Serum CD8+ T-cell count was negatively correlated with forced expiratory volume in the first second, that's FEV1, forced vital capacity, FVC. Of the patients with SLH at baseline, static lung hyperinflation at baseline, the majority continued to have persistent issues after eight months of recovery, those tending to be older and having dyspnea and fatigue. The SLH, so that's that static lung hyperinflation, was correlated with reported fatigue.

VR: Here we have measurements, that's good. Furthermore, I'm not surprised that there are respiratory problems in people with a severe respiratory infection. All this makes a lot of sense to me.

DG: Yes. I think when we start testing these folks, if you do formal, full pulmonary function tests, if you do a CAT scan, you start to see abnormalities. You start to see fibrosis, hospitalized, adeno hospitalized. You don't always see abnormalities. Sometimes we certainly see respiratory issues without finding the objective data. We're finding the objective data in a large percent of these folks.

All right, no one is safe until everyone is safe. We are doing our Floating Doctors fundraiser, May, June, and July. We're about a third of the way in there. Those donations need to come in a little faster, folks, if we are going to get to our potential maximum donation. We're going to match your donations up to a potential maximum donation of $20,000 for the great work that Floating Doctors are doing.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Terri writes, "I got COVID the first time on May 1st. I had fever and body aches for days. I took Paxlovid and started on Day Four. On May 22nd, I noticed a rash under my left breast. As of today, May 27th, the rash has spread to both breasts, almost down to my belly button. Now I have patches showing up on one shoulder and my neck. Just wondering if this might be related to my COVID case. If you've seen this, just wondering how you might have treated it."

DG: Yes. This will be the might-be-related, because it's always tough. Just the fact that you've had COVID is this, but that's definitely have been described. One of the issues we're seeing after COVID is what we call the immune phenotype of post-COVID. This is where people have issues with new onset rashes, increased sensitivity to things. Some of this is mediated through histamine-related pathways. Some people will start taking a Claritin or a Zyrtec or an

antihistamine once a day and seeing if that helps with these. We certainly see things consistent with this.

VR: Mindy writes, "I'm a healthy 40-year-old woman who just had anaphylaxis for the first time to my only allergy, mosquito bites. The only significant health change since my last bite last year was my first case of COVID this winter. It was a doozy, the sickest I've ever been. I also had new mild allergic rhinitis since having COVID. I'm starting to read about the increasing risk of allergy post-COVID and post-COVID mast cell activation. What's the current consensus on how COVID may have escalated my mosquito allergy from a vigorous local reaction to anaphylaxis? Does the COVID factor inform testing or treatment options? I have an upcoming appointment with an allergist and I want to come armed with any relevant information. Having a severe reaction to a common exposure has me spooked."

DG: It's great that you bring this up. As I mentioned, I'm working on this review. Really, what it is, it's like everything we've talked about for four years on *TWiV*. If you listened, it's just going to be a recap, right? You don't even need to read the paper. There are studies showing the relative risk of a new diagnosis of allergic rhinitis, the relative risk of a new diagnosis of asthma, the relative risk of a lot of these allergic situations is significantly increased after COVID compared to people that didn't. These are tough because everyone's had COVID, so where do you find these “no-vids” by comparison? Some of it is a timing that's also persuasive.

Mast cell activation, a lot of folks started noticing early on in the Long COVID community that symptoms that they were having were suggestive of a mast cell activation syndrome, so MCAS. Huge challenge there is that a lot of people outside the immunology, allergy immunology field really not familiar with MCAS, and what's going on there and how to do it, how to treat them, how to address it. Even how to diagnosis. Is not an easy diagnosis.

Putting all that together for you, you're going to see your allergist. That's the right person to talk to. They're trained in this. They understand mast cells and what they do. They may understand certain things about low histamine diets and antihistamines and things like that. We could go into the right place. Let the allergist know about COVID. Let them know about this history that you just shared with us. Yes, don't be spooked. Talk to your allergist and hopefully, they can guide you through this.

VR: Cathy writes, "I'm a 60-year-old biomedical scientist living in the UK. I've not had COVID to date. I've deliberately done my utmost to avoid it due to a 30-year history of relapsing/remitting ME/CFS. I've had four COVID vaccines, two AstraZeneca, one Moderna, one Pfizer bivalent BA. My last was in October ‘22. Unfortunately, I am one of the rare individuals who suffered cardiac inflammation after mRNA shots. I'm considering buying a Novavax booster privately, but I'm aware that myocarditis and pericarditis are rare side effects of this vaccine also.

If a person has suffered cardiac inflammation after an mRNA shot, is Novavax likely to be a cardiac risk? I wonder if there are data on this issue and specific individuals' susceptibility to cardiac inflammation after COVID vaccines."

DG: Yes, appreciate your situation and yes, definitely understand with the relapsing, remitting ME/CFS, not wanting to get COVID and not potentially wanting the COVID to compound that.

Yes. Also, yes, rarely we have seen cardiac inflammation after mRNA shots. It tends to be in adolescents at a higher rate, but yes, you're over 60 and you had this, Novavax makes sense. Here you've got to decide what are your exposures, what are your risks. If you're one of these hermits who's just going to stay and not get COVID, not get infected with SARS-CoV-2, that's one thing, but most of us, you've got to present your findings, you've got to interact with others, things are low right now, but in the fall, winter, we will probably see an increase in cases, more virus circulating.

Then, in that situation, Novavax would seem to make sense. Yes, I would love to steer you towards the article where they take people just like you and they study what's the incidence with Novavax. I don't think we have that data.

VR: Anonymous writes, Thank you for reading my letter on *TWiV* last week regarding type 1 diabetes and COVID and traveling. Just wanted to give you an update. I have Paxlovid in my hands, even though my doctor said some wacky things. See list below. Things my doctor said: No one has died from COVID since 2022." Hmm. I guess they're not listening to *TWiV*, right?

DG: I'm thinking of the map from the CDC. If you have like a zone which is less than 1%, less than 2%, 1% to 2% of deaths across the country are due to COVID and that's current data. Yes, people are still dying.

VR: "Told me about Paxlovid rebound, even though it's viral rebound. She told me, since the beginning of Paxlovid's existence that she can't find it at a pharmacy. Meanwhile, my local Walgreens filled the prescription within two hours after she told me all her facts in quotes and said, I said, 'I understand, but I still want to take Paxlovid with me to Europe.' She said, 'Well, then I guess I am prescribing it for your mental health.' Had mentioned I was anxious traveling to Europe knowing Paxlovid isn't as readily available there as in the U.S., but why would you say that to someone? I have a PhD in epidemiology, but I knew I couldn't argue the science with her during my visit or she might not have helped me, so I will send her some studies later. What do you think? Time to find a new doctor? LOL."

DG: Yes. What do you think, Vincent? [laughs]

VR: Yes, I would. This doctor is not well-informed, but as you have also said, it's not easy to find a new doctor, but yes, I would try as hard as I could because this person is not helping you.

DG: Yes. Not evidence-based and oh my, that bedside manner. [laughs]

VR: That's *TWiV* Weekly Clinical Update with Dr. Daniel Griffin. Thank you, Daniel.

DG: Thank you, and everyone, be safe.

[music]

[00:50:54] [END OF AUDIO]