This Week in Virology

TWiV 1116 Clinical Update

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Aired 25 May 2024

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

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VR: From MicrobeTV, this is TWiV, *This Week in Virology*, Episode 1116, recorded on May 23, 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: OK, Daniel, your bow tie is a little blurry. What do you got on it?

DG: Oh, is it blurry? OK. Hopefully, the quality on YouTube will be higher than the quality you're seeing, Vincent. People will not be surprised when they start to listen, why I am today wearing my influenza bow tie -

VR: Oh, my.

DG: - with all these different RNA segments. Let's jump into it because we've got a lot to cover today. I'm going to start with a quotation from Frederick Nietzsche, who I am certain I have quoted before. Actually, dare I say my favorite dog, Zarathustra, was taken from Frederick Nietzsche reference. I thought this was appropriate, actually. I think maybe it's sort of a caution for our times. "The surest way to corrupt a youth is to instruct him to hold in higher esteem, those who think alike than those who think differently."

VR: I love it.

DG: I think, with all our social media, we sort of like, "I don't want to hear from people who disagree, I want to hear people that agree with me." Maybe our skin needs to be thick again so that we can connect with those, shall we say, across the aisle, those with different opinions. Let us start off with a little more on H5N1. In the words of Taylor Swift, welcome to New York. The article, “Detection of Clade 2.3.4.4b Highly Pathogenic H5N1 Influenza Virus in New York City,” recently published in *Journal of Virology*. Now, in this study, the authors conducted surveillance of avian species in the urban environment in New York City.

The details are actually, I have to say a little fun, but they report, "We detected highly pathogenic H5N1 viruses in six samples from four different bird species, and performed whole

genome sequencing." When you read the details, you find out that one of the parks, they found some domesticated chicken that had escaped that was wandering about in one of the parks. What is the importance of this study? The authors tell us that while surveillance programs for avian influenza viruses are often focused on migratory routes and their associated stopover locations or commercial poultry operations, many bird species, including migratory birds, frequent or live in urban green spaces and wetlands, not inside those urban farms.

This brings them into contact with a highly dense population of humans and pets providing an extensive urban animal-human interface. I like that concept, the urban animal-human interface, in which the general public may have little awareness of circulating infectious diseases. How did they collect these samples? We read that they looked at birds known to get infected. Dickson would be great because he would tell us about each one of these. They start off with the Anseriformes. Those are the ducks, geese, and swans. The Charadriiformes, those are the gulls, the terns, the auks, and other shorebirds.

I don't know if people know New York City is really an island as far as Manhattan goes. Then, Queens, Brooklyn, western end of Long Island, Staten Island in the name, the Bronx really on the water there. Really a lot of exposure here to the water environment. Now, this is important to think about dates here. Samples for this study were collected from January 2022 to November 2023. Probably before a lot of people were even thinking about H5N1. Just the importance that we've got this science going so we don't suddenly scramble at the last minute.

In total, 1,927 samples were collected and processed for this study. One hundred twenty five environmental fecal samples were collected from New York City parks and green spaces, they say, using proper personal protective equipment, masks, and gloves. In addition, professional animal rehabilitators at the Wild Bird Fund, the WBF, and veterinarians of the Animal Care Centers, ACC of New York City, provided four water samples and 1,798 cloacal and oropharyngeal and fecal swabs from urban, wild, and domestic birds. Just for context, cloacal, what is that? Birds have this common opening, cloacal opening, where one hole does it all in terms of feces, sperm, and egg release.

This is in contrast to, say, a rectal swab, which might be what you're doing in other situations. From these 1,798 samples from 895 birds, six were found positive for the HPAI, the highly pathogenic in avian influenza H5N1. They have a nice actual figure where you've got a map, and you can actually see where these birds were found. We've got one northern Manhattan, another detection up there in the Bronx. Then we've got some down in the Queens, Brooklyn. Actually, you look at the map, and you see, oh my gosh, yes, this is right on the waterways there.

A few different ways that I can see people taking the study. One is, to be honest, it's a fun study. Many of us find birds fascinating and beautiful from that perspective. Lots of fun to read about these birds. One might be reassured, as we are seeing that back in 2022 and 2023, there are some birds flying around with H5N1, and here we are all in 2024, still doing all right. Also, just a few birds, so I think that's important. My takeaway that I hope others embrace is we need to keep our eyes open and our surveillance system in place. Let us not have the

gambler's fallacy where that roulette ball lands on black, and now we are surprised that it did that again.

I'm referring to the recent COVID-19 pandemic, and that doesn't mean that now we're done with that for our lifetime, so we do need to keep our eyes open. I'm going to share a preprint, Vincent. This is a preprint, "The Avian and Human Influenza A Virus Receptors Sialic Acid (SA)-α2,3 and SA- α2,6 are Widely Expressed in the Bovine Mammary Gland." Our listeners are probably getting familiar with the fact that avian influenzaes preferentially bind SA-α2,3. Human influenzaes preferentially bind the α-2,6. There's also a duck sialic acid where we have the SA-alpha-2,3-Gal-beta-1,3 and the chicken, there'll be a test at the end, the chicken SA, which is an SA-α2,3-Gal-β1,4.

It just gets more interesting as we talk about the SA modification. This is sialic acid, and then it's modified with different sugars. Here, the investigators are looking at beef calves in Copenhagen, Denmark. Lots of interesting results, but they put all together in a really nice graphical abstract where we see, I'm going to put my glasses on for the fine print, but we see, as I mentioned, the human, α2,6. We see the chicken, SA-α2,3-Gal-β1,4. We see the duck, which is the sialic acid, SA-α2,3-Gal-β1,3. Then they actually look at the distribution of those receptors in the different bovine tissues. You actually can see that we have a mix in the bovine tissue. Rather interesting, actually. We have a mix in the brain, and actually, we have quite a mix with really dominant SA-α2,3-Gal-β1,3, the duck sialic acid in the mammary glands.

VR: Yes. This is explaining why the mammary gland can be infected. The receptors are there for H5N1. I suggest people take a look at *TWiV* 1113 with Richard Webby, where he talks about this more extensively. This is an unusual place to be infected. We all don't think about influenza virus infecting mammary glands, but that's what it's doing in the cow, and maybe, as a consequence, it doesn't infect people very well because there haven't been all that many human infections.

DG: All right. Now, why do we keep talking about H5N1? This matters for a couple of reasons. First is that according to the U.S. Department of Agriculture, or the USDA, the virus has now been detected in 52 herds, and the outbreak is thought to be even more widespread. I'll talk about why we say that. I'll leave a link to the USDA website and where to see this information, but we get a map. For those that are map-challenged, they even put in the little state abbreviations so you can see confirmed affected states. We've got Idaho, Colorado, New Mexico, Texas, Kansas, South Dakota, Michigan.

They've got Michigan and the Upper Peninsula. I don't know if that means it's identified in both, or if it's just that, hey, Michigan has an Upper Peninsula. Ohio, North Carolina. We are seeing this distributed about. As one might not be surprised, we read in *The New York Times*, actually, I read this originally in *STAT News*, so I'll link to that as well, but there's a *New York Times* article by our friend, Apoorva Mandavilli, and Emily Anthes, "A Second Dairy Worker Has Contracted Bird Flu, CDC Reports." As my wife asked, "You told me people couldn't get this," and as I responded, "You can get it in your eyeballs, dear."

Maybe that will be the new expression. "It's all fun and games until you get bird flu in your eye," or, "This is about as much fun as bird flu in the eye." OK, perhaps that won't catch on, but we read that a Michigan man who is a farm worker had mild symptoms and a nasal swab

from the individual tested negative for H5N1 virus, but an eye swab the agency received on Tuesday tested positive. Veterinarians have reported that some farm workers have developed flu-like symptoms, but here's the rub. Few farmers and farm workers have agreed to be tested for the cause.

In Michigan, farm workers exposed to infected animals have been asked to report even mild symptoms. Testing for the virus has been made available, but as of Wednesday, we're recording this on Thursday, the CDC has only tested about 40 people. We go on, it's not surprising as we read in *STAT News*, both the USDA and the CDC have admitted that farmers have been reluctant to allow testing of their cows or their workers, afraid of the stigma attached to being associated with the outbreak.

VR: This is more important to find out what's going on than a stigma. This somehow needs to be overcome, but what I wanted to say was if you're wondering why it's an eye infection in humans, that's where there are alpha-2,3-sialic acid receptors, and nowhere else in the upper tract, so that makes perfect sense for this kind of infection.

DG: Yes. I think that hopefully, that will be a takeaway why we keep hitting on the numbers, the different sialic acids that we've got. Just remember 2,6 for human-adapted, 2,3 when we're looking at the chicken and the duck-adapted. All right, moving into COVID, we still get some numbers from *BNO News*. We're down to average deaths about 500 or so a week, so we're under 100 a day. We can look across the country, and I actually like this percentage of provisional deaths due to COVID-19 in the past week, we're really seeing everywhere it's under 2% due to COVID-19.

Really, what a dramatic change from previously. Continue to track the wastewater viral activity for COVID-19, and in the future, I'll even leave a link into the influenza A wastewater charting, which is now available. If we look at the big screen, wastewater is now down to about levels that we saw this time last year, 2023. I did zoom in a little because everyone seems to be moving in the right direction except for those folks out west. Actually, when I zoom in, I'm starting to see the trajectory out west rise. We'll definitely keep an eye on that.

VR: Daniel, we're about 500 deaths a week. Do you think we're going to get close to zero or not before we go into the fall respiratory season?

DG: Looking at history as a harbinger of what's going to happen again, we're about that level that we were in May and June of last year. It plateaued for a little bit, and then it rose up again. We may be at the plateau. This may be as good as we get. If it could go all the way to zero, tremendous, but no, it's still smoldering along here. All right. The article, I like to say how quickly we forget the article, “Estimates of SARS-CoV-2 Hospitalization and Fatality Rates in the Prevaccination Period, United States,” published in the journal *Emerging Infectious Diseases*.

These results are based upon, big number here, 2,479,423 cases from 21 jurisdictions with hospitalization information reported to the CDC from May 1, 2020 to December 1, 2020 to create a hospitalization dataset. Think about that, that's in the first year, so we've got May to December of 2020. The authors also analyzed 4,708,444 cases from 22 jurisdictions for a death dataset. We've got a hospitalization dataset, we've got a death dataset during the same

timeframe, and this is huge. The case hospitalization dataset covers about a quarter of the U.S. population, and the case fatality dataset covers over 40% of the U.S. population.

Before the mid-December 2020 introduction of COVID-19 vaccines, the pandemic caused approximately 480,000 hospitalizations, so almost 500,000 hospitalizations, and 350,000 deaths in the United States. The overall case hospitalization rate during that period was 5.7%, and it's broken down a little by male and female, a little higher for males at 6.2%, 5.2% for female. The hospitalization rates were lowest for children ages 5 to 14, that was 0.6%. Then highest in case patients 75 years and older, that was actually 25.9%. We read that during the pre-vaccine period, 18% of hospitalized patients and 44% of those admitted to an ICU for COVID-19 died.

Really dramatic. All right. In ventilation and transmission, this is a soapbox thing, I'm going to just warn everyone. In this section, I wanted to include the article published in *CID*, "Doff Thy Gown - Shedding Contact Precautions for COVID-19." This is an invited commentary where the authors point out that SARS-CoV-2 is predominantly transmitted through the air. However, the U.S. Centers for Disease Control and Prevention continue to recommend the use of contact precautions, a gown, and gloves for the care of patients with COVID-19. They go on to say that infection prevention guidelines should reflect the current science and eliminate this wasteful practice.

It's only four pages in total, so a short accessible read, but it really raises issues with doing things that are costly, cumbersome, not evidence-based, and contributes to trashing our environment for no good reason. I just finished my teaching stint there at Columbia, so people that have watched *House, M.D.,* you've got this entourage. We've got the two medical students, we've got the intern, we've got the resident, we've got me. There's the five of us, and we're going to go into the room to see a COVID-19 patient. Five of us are putting on these useless yellow gowns, we're all putting on our gloves.

That stuff costs money, and that just all ends up in the landfill. The populace has stopped putting their groceries in the garage for 72 hours. We've come to realize that this is very rare for there to be fomite or contact transmission, so I'm on board with these authors. Time to stop doing things that are not evidence-based.

VR: Daniel, when you go into that room with a COVID patient, you just need to wear a mask, is that correct?

DG: That is correct. These rooms, you're in a hospital, so there's a certain amount of ventilation, air exchanges per hour in the different rooms. Your risk is breathing in the virus, so we are wearing properly fitted, well-fit tested for N95s when we go in the room. That makes sense. That's the science. That's how you stay safe. We wash our hands before we go in. We wash our hands after we leave. I like to lather up a lot of that alcohol-based sanitizer. I think part of it, a little bit, gets into my system and makes the day a little more enjoyable, but no.

VR: Daniel, wouldn't you wash your hands anyway, no matter what the patient was?

DG: We do, yes, before and after every patient. Yes, yesterday I was at, I will refer to it as an event, and I shook several people's hands. Then I was like, "Where is my alcohol-based hand

sanitizer?" Just becomes such a habit. All right. We've talked a bit about COVID active vaccination. Actually, you weren't there Friday on the last Deep Dive *TWiV*, but the gang was having a discussion about these self-replicating mRNA vaccines, and so rather interesting. I'm going to direct people, it's very interesting to enjoy the back and forth there.

COVID active vaccination, COVID passive vaccination, but let's move right into the COVID early viral phase. I've been leaving in links each week to the COVID-19 treatment guidelines from the NIH, the IDSA guidelines. I'm also going to now leave in the COVID-19 drug interactions checker, the Liverpool drug interaction checker. Number one, Paxlovid, but what about these other medicines we've been hearing about? Just an update on ensitrelvir, and this is a product, make sure I put my N in there, this is a press release from the company on the SCORPIO-HR trial.

“Shionogi Provides Updates from SCORPIO-HR,” high-risk, “A Global Phase 3 Study of Ensitrelvir for Non-hospitalized Participants with COVID-19.” Just a reminder, it's another antiviral. Ensitrelvir is a 3CL, it's a protease inhibitor created through joint research between the Hokkaido University and Shionogi. Just nine bullet points that we get. The primary endpoint of this study was time to sustained symptom resolution, the first day of two consecutive days with complete resolution of 15 common COVID-19-related symptoms. Here we go on to read that although ensitrelvir demonstrated a numerical reduction in the time to symptom resolution compared to placebo among participants treated within three days of symptom onset, the difference was not statistically significant.

A predefined supportive analysis of resolution of six symptoms for one day using a statistical method similar to that used in the SCORPIO-SR, standard risk study, yielded a significant difference into the time to resolution of symptoms. Seeing some sort of directionality there. Ensitrelvir did demonstrate a potent antiviral effect for both viral RNA, and, yes, culture, compared to placebo. My favorite topic, symptomatic viral rebound, was not observed in the study, supporting a previous finding. Ensitrelvir did not demonstrate a statistically significant reduction in the proportion of participants with post-COVID-19 symptoms, Long COVID, at three months.

I will comment, as they do, there was a tendency for a higher proportion of participants to report having returned to pre-COVID health and felt no fatigue compared to placebo. There's going to be further analysis at six months. No dysgeusia, no drug-related abnormal taste was reported. I wonder who they're poking with that comment. No metal mouth. No deaths were observed in either group up to Day 29 of follow-up. Very few cases of COVID-19-related hospitalization were observed in either arm.

VR: Daniel, given these results, doesn't seem like this is going to be any better than Paxlovid.

DG: This is not encouraging. This is not really, saying, oh my gosh, we got to get this out there. Their rationale was we're moving into a time where it's really people are looking for an option that's going to get them better, feel better quicker. We're not really seeing anything compelling here, so yes, we'll wait for the detailed results.

VR: There's no ritonavir here, so that may be an advantage, right?

DG: That's potentially an advantage, yes. It's just one drug. It's pretty simple dosing. It's one drug. It's three pills Day 1, then one pill a day for the next four days. It's a little easier. It's almost - What was I going to call this? They're going to market it as Xocova. I was calling this the X-Pak as opposed to the Z-Pak. Three pills in that first blister and then you've got, Day 2, 3, 4, et cetera. I don't think they'll pay me any royalties on that wonderful, brilliant suggestion. Anyway, number two, remdesivir, molnupiravir, convalescent plasma.

Remember, if you're sick, you can give the virus to others. That's the biology. Remember the good old days, Vincent, when we had monoclonals for the treatment of acute COVID-19? Perhaps not the good old days. Those were not good days when we had those. As we may be in a situation again in the future where we need monoclonals, I thought it was important to share this article, which I think is educational. The article, "Characterization of Treatment Resistance and Viral Kinetics in the Setting of Single-Active versus Dual-Active Monoclonal Antibodies Against Severe Acute Respiratory Syndrome Coronavirus 2," published in *JID*.

Here's this issue. If one antibody is effective, is that fine? Should you be giving two? Here they're going to compare those two approaches. It's an interesting study, and compared with single-active monoclonal antibody therapy, dual-active monoclonal antibodies led to similar clinical outcomes, but significantly faster viral load decline and a lower risk of emergent resistance. Maybe the lesson here is for the future is that we may want to be thinking about cocktails instead of just single active monoclonal antibody therapy.

All right, moving into COVID, the early inflammatory week, we're still seeing this. The median time to symptom resolution is suggested to be about six days, but there's still probably about 20% of folks feel better, you're going to have that inflammatory phase during the second week, sometimes severe enough that you'll become hypoxic, may even end up in the hospital. We have recommendations regarding steroids, anticoagulation, pulmonary support, remdesivir if you're still in the first 10 days. In some cases, immune modulation with agents such as tocilizumab.

All right, and a little bit of meat today on the late phase PASC/Long COVID.

To start this section with what I think is, I'm going to say really encouraging information with the article, "The Global Clinical Studies of Long COVID," published in the *International Journal of Infectious Diseases*. The authors tell us that after searching the WHO International Clinical Trials Registry platform, 587 clinical studies were identified as Long COVID studies. Among these, more than half, so 312 studies, 53.2% are testing potential therapies. Most of the Long COVID trials are being conducted in the United States, followed by a number of trials in India and trials in Spain.

A lot of investment, a lot of work going on, understanding Long COVID and trying to understand potential therapeutics. Now, right after throwing out that a lot of us take this seriously and are doing what we can, unfortunately, I am aware that there are many out there, including physicians, that continue to be dismissive about Long COVID. I make a point of sharing articles that demonstrate objective abnormalities in individuals that report Long COVID. This week, we have the article, "Cardiopulmonary Exercise Testing in Children with Long COVID: A Case-controlled Study," published in the *Pediatric Infectious Disease Journal*.

These are results from a prospective, single-center, case-control, observational study conducted at the - Shall I have you pronounce this?

VR: Sure.

DG: Policlinico? Yes, go for it.

VR: Policlinico Agostino Gemelli.

DG: Thank you. In the period between- and you'll jump in for all future-between May 2021 and September 2023, in which pediatric patients, so aged less than 18 years were enrolled and underwent cardiopulmonary exercise testing, CPET, in the presence of persistent symptoms compatible with the definition of Long COVID, according to the WHO definition, which is currently requiring symptoms that last at least two months and cannot be explained by an alternative diagnosis, and symptoms have a negative impact on daily life. The CPET, the cardiopulmonary exercise testing, was conducted with an electromagnetic brake cycle ergometer. Those bikes that you might see at the gym if you go.

The CPETs were all performed on the ERGOSTIK TM Geratherm cardiopulmonary device, was equipped with "Blue Cherry software," regularly calibrated for gases and volumes before each test with breath-by-breath data acquisition, using a suitable face mask size, continuous 12-lead ECG monitoring, finger pulse oximetry, manual blood pressure detection at baseline, and every two minutes during cycling. Really a lot of objective data here. They studied 90 patients, 90 kids, pediatric age group. The age of the patients was between 12 and 15, so average age about 13, so adolescents.

It breaks my heart as we're talking about little kids here, and we all know about the myth that little kids don't need to worry about COVID. Many of these kids were not protected with vaccination. They found that children with Long COVID have a reduced VO2 peak, so that's the oxygen uptake at peak of exercise, abnormal cardiovascular efficiency, a pathological VE/VCO slope, and just that's indicative of possible presence of ventilatory inefficiency, pulmonary vascular commitment, and abnormally reduced slope of the VO2 work. They note that many children, in fact, were not able to even finish the test and suggest that these events during Long COVID are more probably due to poorly characterized functional events like autonomic dysfunction or other unknown factors, rather than macroscopic heart damage.

They referenced studies in adults that suggest autonomic dysfunction as an underlying abnormality. A couple last ones to wrap us up. We have the article, "Assessment of the Impact of RNase in Patients with Severe Fatigue Related to Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): A Randomized Phase 2 Trial of RSLV-132," published in *CID*. It's an interesting article. What's going on here? This touches on this, say, idea, this finding of persistent genetic material left behind after SARS-CoV-2 infection, which might be triggering ongoing symptoms of Long COVID.

They looked at this RSLV-132, which is a drug composed of a catalytically active human RNase1 fused to human IgG1-Fc. They're basically trying to digest extracellular RNA. They hypothesized that removal of the SARS-CoV-2 viral RNA might improve inflammation, neuroinflammation, and fatigue associated with PASC. Here we get the results of a Phase 2, double-blind, placebo-controlled, randomized clinical trial in participants with a 24-week

history of PASC, severe fatigue. The primary endpoint of the trial assessed the impact of six intravenous doses of this RNase, this RNA-destroying enzyme, on the mean change from baseline.

Mixed results. While fatigue was not statistically significant improved at Day 71, earlier time points did show statistically significant improvement in fatigue and physician global assessment. The data suggests eliminating latent viral RNA by increasing serum RNase might, I'm going to just put a big, might improve fatigue in PASC patients. At least in this analysis, there was some suggestion that women may respond better to this approach than men. Just very preliminary, but interesting.

VR: Very interesting approach to put an RNase on a long-lived IgG. That is cool. What I want to know is, is this just in the blood, or are these antibodies going into tissues and acting as well? That would be interesting to study that.

DG: Yes, that's an excellent point, Vincent, because we don't really think it's the circulating genetic material. We think it's, the RNA is getting into the cells, and that's triggering these innate sensors, it's turning on inflammation. I'm not sure I understand. It's interesting that we're seeing some signal that is encouraging. Yes, interesting.

VR: I think to do that kind of study would be hard in people, but they could certainly use animals to say, "We'll put this RNase in the blood, and let's see if it gets into tissues, to what extent, to give us an idea of what might be happening in people."

DG: I would love a Long COVID animal model, Vincent. Just think how tremendous that would be. Then we could do stuff like that and ask those questions. All right. I'll wrap things up this week with another article focused on things that we can offer our patients with long COVID. I do want to comment, that list is growing. This is not this, oh, you got long COVID, No, we can do stuff. The article, “Potential Diaphragm Muscle Weakness-related Dyspnea Persists Two Years After COVID-19 and Could Be Improved by Inspiratory Muscle Training: Results of an Observational and an Interventional Trial,” published in the *American Journal of Respiratory and Critical Care Medicine*.

Here we see that compared with sham control, this IMT, inspiratory muscle training, improved diaphragm and inspiratory muscle function, inspiratory muscle fatigability, diaphragm voluntary activation index, and dyspnea. All right. I will wrap us up there with, as we've been saying for over four years now, no one is safe until everyone is safe. I do want everyone to pause the recording, go to parasiteswithoutborders.com, and click Donate. Even small amounts help. We are right now doing our Floating Doctors Fundraiser, where for May, June, and July, we will double your donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Mike writes, "I'm a healthy guy in my 40s. I've been vaccinated, boosted repeatedly, had COVID twice in both instances. It wasn't long after I was vaccinated, boosted, and my symptoms were very mild, similar to allergies, and I bounced back very quickly physically. However, after my last bout, my brain has felt like Swiss cheese for months. It seems to be slowly improving. If I contract COVID again, would Paxlovid act as a prophylactic against this? The studies seem

mixed, and I'm not sure a doctor would even give me a prescription based on my mild symptoms."

DG: Yes, Mike, you're obviously up to date on things, and this is the challenge. We have gotten mixed results, jumping in early with an antiviral. We have compelling data. First, the compelling data preventing death and hospitalization in the unvaccinated, and then we saw data that carried over into the vaccinated. What about, you're describing a low-risk individual, can we prevent Long COVID? Still, mixed data, so we don't know at this point.

VR: Patrick writes, "I've been listening to the clinical updates ever since they started. Even though I'm not a medical professional by any means, I very much appreciate your rundown each week, so thank you. I have a question about the way herpes simplex virus is transmitted, particularly HSV-1. I'm a 33-year-old male, reasonably healthy. Recently, I discovered that a partner of mine had an active cold sore when they were performing oral sex, so I'm concerned about the possibility of contracting genital HSV-1. However, I've also had cold sores in the past, so I know that I'm already infected with HSV-1.

Is this considered a new infection in a new site? Will it reactivate my latent infection? Will my risk of transmitting HSV-1 be basically the same as it was before, or will I be permanently a potential source of exposure to future partners, even when asymptomatic? The resources I've found online are not clear about this specific scenario, so I would very much appreciate your thoughts on this matter."

DG: OK. All right. A little primer on HSV. When people say herpes, this is what they're talking about. We've got herpes HSV Type 1, herpes HSV Type 2. When I was a kid, a long time ago, herpes Type 1 gave you cold sores in your mouth. Herpes Type 2 was the genital. I have to say, at this point, I used to joke, I'm not sure how this happened, but now we see HSV and HSV-2 causing oral disease. We see HSV-1 and HSV-2 causing genital disease. Maybe if people read this, they'll understand why that happens. Now, either can affect either place.

There is some protection from 1 for 2. There's some protection for 2 versus 1. There certainly are people that have been infected and have serological and other evidence that they were infected with both 1 and 2. Just the fact that you've got cold sores on your mouth, we don't know, in 2024, if that's HSV-1 or HSV-2 without doing testing to clarify. There is some protection against getting a genital infection with the other. If you've been infected with HSV-1, we don't really think we're seeing a lot of repeat infections with a variant of HSV-1.

If you have HSV-2, we're not seeing a lot of people that we think are getting infected with a different type of HSV-2. Yes, when you have a cold sore, and there's actually often a little bit of tingling before you have an open lesion, there's a period when you can transmit, when you can shed the virus. It's a contact transmission. People with cold sores can spread the virus. People with genital sores, and that tingling can also shed the virus.

VR: Probably a good idea not to have sex when you have a cold sore, but you can transmit without having a cold sore. That's a problem.

DG: Yes, I think that's important. That was a period of time, and still, in certain circumstances, where we'll actually do PCR screening because you can get asymptomatic transmission.

VR: Heidi writes, "I've been a faithful *TWiV* listener since COVID and consider Dr. Griffin my go-to-source for ID advice. I'm a healthy 68-year-old who's had all the SARS-CoV-2 vaccines, the last being in 5/23. I've never had COVID. I'm going to Scotland in August and planned on getting the latest booster about six weeks before the trip. However, in April, I had a rare side effect, uveitis, to a zoledronate infusion given for osteoporosis, with mildly elevated ESR and CRP. Other symptoms included unilateral headache and scalp tenderness.

The uveitis was treated with prednisone eye drops for a month and all the symptoms resolved in several weeks. My understanding is that this type of reaction was due to release of acute-phase proteins, including cytokines. My doctor recommended waiting to get any vaccines until the symptoms resolved. Is there any risk of recurrence of my inflammatory symptoms if my immune system is stimulated with another booster? Thanks so much for all that you do."

DG: Yes, no, this is a great scenario you lay out for us. For the listeners, the zoledronate, think of it as like an IV Fosamax for the osteoporosis, the bones as we get older, as the bones are not as strong. Yes, here we're seeing this inflammatory reaction. There's a couple things here. Yes, while one is having an inflammatory reaction, it makes sense not to provoke it. You really want to let that inflammation resolve. We're also talking about inflammation of the uvea, the eyes, is eye inflammation. Most of us are quite attached to our eyes and proper function of our eyes.

What your doctor is saying makes a lot of sense to me. Then it's this risk-benefit, as we keep talking about. Right now, things are a little low relative to COVID, not zero. We still have almost 100 people a day dying. We still have wastewater detection. You are going to travel, airplane, I assume, probably not going across in the Queen Mary or a vessel like that. Yes, during travel is certainly a time when there's a higher risk situation. I think what your doctor is saying makes a lot of sense. You really don't want to turn the inflammation back on when it's resolving, so I think it's a good consideration with regard to timing of when you might do your next vaccine.

VR: Mary writes, "I was listening to *TWiV* 1114 clinical update and heard you again comment negatively about practitioners that won't take the time to run the Liverpool COVID-19 drug interaction checker so they can comfortably prescribe Paxlovid early on in the viral phase of the disease. Each time I hear you sigh in frustration, I want to leap up and down with a suggestion. Finally, I'm putting fingers to the keyboard to write the following. Please put a link to the Liverpool COVID-19 drug interaction checker in the show notes every episode.

Please mention frequently that anyone at risk, even I, only an accountant, can easily use it to preemptively perform the check before they even get sick. It is easy. I did it the first time you mentioned it. I have to keep a list of all my medications because I can't take a physical without my doctor going over it and asking me what dose and how often I take each one. It was my own idea to use the checker, but my doctor could have suggested it to me and so can you. Even more frequently than sighing in exasperation over practitioners' failure to use the tool, I hear you both lament failures to even prescribe Paxlovid.

If the failures are even a tiny bit due to unfamiliarity with the tool, or, God forbid, ignorance that it exists, then you are in the catbird seat to solve that roadblock. Instead of sighing in

exasperation, give them the tool and remind, remind, remind that you need to use it. Doctor or patient, use it. Thank you." [chuckles]

DG: All right, Mary. From here going forward, we will leave in a link to the covid19-druginteractions.org/checker, the Liverpool drug checker. Yes, no, and I think, what you also do, which I think is nice is, when you jump on that telehealth visit with your doc, when you go and see your doc, yes, as you probably saw, it's very user-friendly. Have a list of, these are the drugs I'm on. These are the ones that got flagged on my Liverpool checker. Here's what we need to do. Thank you, Mary. You can take credit for this.

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

DG: Oh, thank you, and everyone, be safe.

[music]

[00:46:56] [END OF AUDIO]