This Week in Virology

TWiV 1162 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]

VR: From Microbe TV, this is TWiV, *This Week in Virology*, Episode 1162, recorded on October 31, 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, and happy Halloween.

VR: Happy Halloween, Daniel. Now, your tie is orange. Is that some Halloween thing?

DG: It's orange, and those that zoom in can see there are black bats on there in tribute to the bat zoonoses that plague us. All right, so let's jump right in. Then a Halloween appropriate Edgar Allan Poe quotation, "Believe nothing you hear, and only half of what you see." [chuckles] I thought that was very appropriate for the skepticism that we should bring to things as scientists. We got a bunch today so let's hit the ground running as they say, I think they say that *Mycoplasma pneumoniae*, an alert from the CDC that we are seeing an increase in cases of what people may know of as walking pneumonia.

Mycoplasma pneumoniae infections have been increasing. I'll leave a link into that. People can actually get quite sick from *Mycoplasma pneumoniae* so just I want that on people's radar. The only way you're going to make the diagnosis is if you think about it, if you test for it. Polio, not good news here. Northern North Gaza polio campaign postponed due to violence as WHO. We read in Reuters, I'll leave in a link that the polio vaccination campaign in north Gaza has been postponed due to Israeli bombardments, mass displacement, and lack of access.

The final phase due to begin, well, it's supposed to start Wednesday, the 23rd of October, aimed to vaccinate more than 119,000 children in Palestine, but the current conditions, including ongoing attacks on civilian infrastructure continue to jeopardize people's safety and movement in northern Gaza making it impossible for families to safely bring their children for vaccination and healthcare workers to operate, the UN agency said in a statement reiterating its call for a ceasefire.

Mpox, we now have the first imported mpox clade 1b case in the UK. The case was detected in London. The patient was transferred to the Royal Free Hospital's High Consequence Infectious Disease Unit. The UK is now the fifth country to receive an imported case of clade

1b monkeypox. They say case, but that should be clade 1b Mpox, an infection with clade 1b monkeypox virus. This is added to Sweden, Thailand, Germany, which we mentioned last week in India.

VR: Last night, Daniel, on the live stream, someone noted this, and they say, "Should we worry?" I said, "You should already be worried for the people in Africa because we're all in this for the people in Africa because we're all in this together." Then someone else said, "No one is safe until everyone is safe."

[laughter]

DG: I appreciate that. We're all in this together. The entire world is less than a day plane flight away from each other. We're part of this global community. Hopefully, when horrible things happen in the U.S., like when we had 2,000 deaths a day from COVID, hopefully people didn't just say, "Oh, should we worry here?" Also, and this is going to be good news here in the mpox arena, Bavarian Nordic, I bought some stock there, I don't know if it's doing well, but I feel like I'm part of this, Bavarian Nordic announced Tuesday, October 29, that the first patients have been vaccinated in a clinical trial to assess the safety and immunogenicity of the JYNNEOS vaccine in children aged 2 to 11 years old.

The trial is expected to enroll 460 participants, mainly in the DRC, but with some sites to be included from Uganda. Really a lot of cases in Uganda. Not looking good there. Why am I so excited about this? As we mentioned last week, the deaths, the cases, this is mainly a disease of children.

All right. Marburg, pretty exciting, updated Marburg tracking dashboard, just in time I guess. Last update from the 22nd, we had confirmed cases, 62. We now have confirmed cases, 66. There's only two active cases at the moment, sitting here with 15 deaths so far, but some interesting data, we can now see the male-female gender distribution. You could see cases per age group. Interesting enough, the real peak here is the 30 to 39 group here, interesting, folks in their 30s making up 30 of the 66 total cases. Deaths also really mainly in that age group. Mainly in that age group. A couple deaths in folks under 20.

All right, flu. I got an article here, I'll just will comment. So far, not too much flu activity, but we do have the surveillance summary in the *MMWR*, "Laboratory-Confirmed Influenza-associated Hospitalizations Among Children and Adults — Influenza Hospitalization Surveillance Network, United States, 2010–2023." This is a surveillance summary for that block of time. We get really broad ranges here. Seasonal influenza accounts for as low as 9.3, as high as 41 million illnesses. We see a low of 100,000 up to a high of 710,000 hospitalizations per season. The deaths as low as 4,900 but really getting up to over 50,000 deaths annually in the United States.

Now, since 2003, this Influenza Hospitalization Surveillance Network has been conducting population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in the U.S. We end up with weekly rate estimations, descriptions with clinical characteristic outcomes for hospitalized patients. Here, we read that during each season, adults aged 65 and over are consistently the highest when it comes to influenza-associated hospitalization rates, followed by children, age zero to 4, so those little kids under 4, so it's extremes of age.

Among patients hospitalized with influenza, the prevalence of having at least one underlying condition was, say, only 37% among the little kids. Most of those little kids, so over 60% of the little kids, so age zero to 4, otherwise healthy, only about a third of them had some underlying condition. Among influenza antiviral use, this increased during the 2010 to 2011 through the 2017-2018 seasons, but then it actually decreased, so it got up above 90%. Now it's dropped down to less than 80%.

Now, admission to the ICU, need for mechanical ventilation, and in-hospital deaths, those are going to have ranges, 14% to 20%, 5% to 10%, and then 2% to 3.5%. Just to reiterate that 2% to 3.5%, those are folks that end up in the hospital, not surviving, dying from the flu.

All right, RSV.

VR: Oh, sorry, I wanted to say, this graph that you put in, so we're still pretty flat with flu as of Week 36. Right now, this is Week 44 that we're in, so there's a little delay in the reporting.

DG: Yes, there is delay in reporting, which is interesting because we saw it go up last year about Week 46.

VR: Exactly. I think -

DG: We're a little behind on the data. I am hearing from our urgent cares, and I think I mentioned that how I took care of a hospitalized patient with influenza A recently. We're starting to see a little bit of activity, so yes, we'll see where we're going.

VR: I suspect in the next couple of weeks, it's going to go up.

DG: We're about that time of year. It's been a little bit earlier than prior years. We're just about to, when this drops, it'll be November, so yes, about November, December is when we start seeing the upticks, historically.

RSV, I should start right off by mentioning we're starting to see a little bit of activity down there in Florida so this is very timely. The article, 'Mucosal Nirsevimab Levels in Respiratory Syncytial Virus Breakthrough Bronchiolitis," or post-passive immunization disease. This was published in *The Lancet Infectious Diseases*. Nirsevimab, make sure I add an N to that in my notes, monoclonal antibody with the Fc modifications to basically get it to last longer, triple its half-life. Targets the prefusion form of the RSV glycoprotein F administered intramuscularly. This is that monoclonal that reduces hospitalizations, severe forms of RSV, and those young kids. Last for about six months after administration. Here, what they're actually measuring is what are the mucosal antibody levels in these kids relative to who ends up getting disease? Actually, it's really interesting. We're seeing about less than half the level of the nirsevimab in the mucosal sites in the folks that end up getting symptomatic disease.

VR: The ones who have high levels of mucosal antibody, they get other kinds of viruses or whatever.

DG: Yes, this is that test-negative study. As they come in, they've got something going on, so you get this matching, but the ones who're actually are coming in with RSV, in general, have less than half the median levels.

VR: Is that because they're farther out from the infusion? We don't know.

DG: That's interesting. I'm not sure I see a great breakdown here. Is this a timing issue? Do we need to get the timing better? Is there something different as far as the individuals and them having something about them that ends up not getting?

VR: Because the original study was up to six months. Now, I just wonder if these are beyond six months, and that's the problem, right?

DG: Yes, it would be great to have a nice breakdown because there should be a nice kinetics. OK, so you give it, let's say we check two weeks, four weeks, 12 weeks, follow it out would be great because I can't see it realistically. We had shortages last year being something you give more often, but maybe timing becomes important because as I started to mention, we're starting to see activity in Florida, and that's how RSV sweeps up, so do you start off, we give nirsevimab to the little kids in Florida in, I don't know, let's say early October, September, and then we then, end of October we do the Northeast and the other parts of the country.

COVID, we're back to COVID, Vincent. It's here to stay apparently. The provisional deaths due to COVID-19, no orange there for Halloween, fortunately, nothing but green, so dropping down. There's a few areas where it's in that 2% to 4%. They're the swing states, if you look on the map. We've got Pennsylvania. We've got, what is that, Michigan, Wisconsin. Georgia is doing OK, by the way. I just thought it was interesting. No, in general, we're less than 2% in most of the country. Wastewater is still on its way down.

VR: Daniel, why do they have that curve labeled COVID-19, whereas for the others they got influenza, they have RSV? Why don't they have SARS-CoV-2? [chuckles]

DG: Isn't that so funny? Right, yes. Vincent is talking about this cdc.gov respiratory viruses data activity levels, and so, yes, influenza, RSV. Because we say, "Oh, what does this patient have?" "Oh, they have RSV." I think it might be the virus and disease have the same name but then they label it, respiratory virus. They should call it respiratory viral syndromes or whatever because COVID-19, yes, is the syndrome, but the virus is SARS-CoV-2.

VR: CDC should know better, right?

DG: [laughs] We're going to leave that right out there, Vincent. That's going to be a TikTok. Now, I like to compare this to the UK, which is interesting. They've got that nice influenza pattern, where they had their peak last winter, and now you're starting to see a little bit of an uptick. Their RSV, they're actually really starting to see an uptick over there for RSV in the UK. COVID just bouncing around. Actually, still pretty high at this point.

Let's move into vaccinations. We've got a few things to talk about here. While we reinforce that vaccines primarily prevent disease and not infection, it would be ideal, we can always ask for this, if they could actually do a better job of that bonus because there is some correlation in the months right after that vaccine or that booster. Vincent and I can circle back to this, but what we're really talking about here is it's abortive infection. We saw this from the challenge studies is that you really want everything to stop at that mucosal site. We're not looking at never getting any viral replication at all. We're talking about an abortive infection where your mucosal surfaces encounter the virus, but you never get sick.

We'll talk about this article here, “Repeated COVID-19 mRNA-based Vaccination Contributes to SARS-CoV-2 Neutralizing Antibody Responses in the Mucosa.” This is published in *Science Translational Medicine*. I'm going to get a counterpoint on this, so everyone, get ready for this. In this investigation, they looked at mucosal neutralizing antibody responses in a cohort of 183 individuals.

Participants were sampled at several time points after primary adenovirus vector-based or mRNA-based COVID-19 vaccination and after mRNA-based booster vaccinations. They report that repeated vaccination with mRNA boosters promoted SARS-CoV-2 neutralizing antibodies in nasal secretions. Nasal and serum neutralizing antibody titers of both IgG and IgA isotopes correlated to one another.

They investigated the source of these mucosal antibodies in a mouse model. This is interesting. Here, the mice are going to get repeated mRNA vaccines for SARS-CoV-2. These experiments indicated that the neutralizing antibody-producing cells, and what people think about, "Where are those? Are these antibody-producing cells sitting in the mucosa or maybe they're in the spleen and bone marrow?“ Actually, what do they find here? That the antibody-producing cells are in the spleen and bone marrow with no proof of tissue homing to the respiratory mucosa, despite this detection of mucosal antibodies.

The antibodies are really coming from the serum and then spilling over. Serum transfer experiments confirmed that circulating antibodies were able to migrate to the respiratory mucosa, and they say that collectively these results demonstrate that, especially upon repeated vaccination, the currently used COVID-19 mRNA vaccines can elicit mucosal neutralizing antibodies and that vaccination might also stimulate mucosal immunity induced by previous SARS-CoV-2.

VR: This is weird because recently there's a paper out of Shane Crotty's group showing if you do nasal swabs, you can actually pick up memory B-cells in the nasal mucosa.

DG: Right, yes.

VR: There's a difference obviously.

DG: We're going to hit another step. OK, so that's his question. There's this whole idea that we do. We do have B-cells in mucosal surface. It's actually a majority of our B-cells are in mucosal surfaces in the gut. This is this big thing. People have been talking about, "next-generation vaccines," this whole idea that you're going to stimulate those mucosal B-cells because that's really where you want the infection to end. You want it to be an abortive process at a mucosal site. You don't want it to get into the system. You don't want to mount systemic inflammatory response. You don't want to feel sick. That was that study.

Here's the next article. It's the same “Science Translational Medicine.” “SARS-CoV-2 XBB.1.5 mRNA Booster Vaccination Elicits Limited Mucosal Immunity.” Here the authors point out that, yes, current COVID-19 vaccines provide robust protection against severe disease, but minimal protection against acquisition of infection. Intramuscularly administered COVID-19 vaccines induced robust serum-neutralized antibodies, but then they say their ability to boost mucosal immune responses remains to be determined.

In this study, the authors show that the XBB.1.5 mRNA boosters result in increased serum neutralization of multiple SARS-CoV-2 variants in humans, including this JN.1, but in contrast to the other study in the same edition, they found that this mRNA booster did not augment the mucosal neutralizing antibodies or the mucosal IgA responses. Their data is suggesting the separation between peripheral and mucosal immune systems. What to do?

There's this commentary, “From Blood to Mucosa,” same edition of *Science Translational Medicine*, where they try to reconcile this. They say, "I don't know, maybe different cohorts, maybe the methodology was different, maybe the timing was a little bit different," but we're not really seeing that we're clear on what's going on here.

VR: There clearly are memory B-cells and T-cells, there are even germinal center B-cells in the nasal mucosa, right.

DG: Yes.

VR: That was quite a big study done by Crotty's group and so if you don't find them, then there's something wrong with your study, right?

DG: Yes, yes. [laughs] Interesting trying to sort this out, but I do see that there's a lot of work going on because that's really, boy, would that be the Holy Grail. Where you have a vaccine where you really stop the infection right at the mucosal surface without any kind of a systemic response.

VR: Realistically, if you're depending on a memory response, which you would most of the time, it's going to be delayed a few days, so you're always going to get some infection, but it would be dampened, as you say and not eliminated. Whether you shed enough to transmit would be a good question, it would be an interesting study to do.

DG: Yes, that's another really important topic that is coming back is, how much do vaccines work from a public health perspective? In certain circumstances, we've definitely talked about measles, where vaccines not only protect you and your child, but there's clearly a community difference. What was the data there where one person with measles who's unvaccinated will give it to 15 to 20 other people, where a vaccinated person gets infected, it's probably going to take 15 to 20 infected vaccinated people before you get even one case of ongoing transmission.

As excited we are about vaccines, we always need to be honest with the fact that there are vaccine associated adverse events, just so that everyone is aware that we're balanced, we pay attention to that. Here, we have the article, “Risk for Facial Palsy after COVID-19 Vaccination, South Korea, 2021-2022,” published in *Emerging Infectious Diseases*. Here, the investigators conducted a self-controlled case series to investigate the association between COVID-19 vaccination and facial palsy in South Korea. They use this large immunization registry that's linked to the National Health Information Database.

They include over 44 million patients aged 18 years and over who received at least one dose of a whole bunch of different COVID-19 vaccines. We've got the Pfizer-BioNTech, we've got the Moderna, we've got the ChAdOx, we've got the J&J in there. They're looking at people that had a facial paralysis diagnosis, and then they're going to compare the facial paralysis

incidents in a risk window, that really first 28 days after vaccination, compared to a control, which is really a remainder.

They found that 5,211 patients experienced facial paralysis within the risk window. Then this is compared to over 10,000 within the control window. They did actually find that there was an increase in facial paralysis within the 28 days post-vaccination, primarily after first and second doses, but now, there's a couple of comments, and I think this is really interesting.

First, this is not something seen in isolation. Let me just pull this out. They actually point out that there's been this noted positive association with vaccination in some other studies. They mentioned the study that was done in Israel, and that was a Pfizer association. There was another analysis in the UK. There's one that's out of Hong Kong, China. Now, here's where it gets complicated. People say, "Oh my gosh, I don't want to get that vaccine, I might get facial paralysis," but what about the risk of facial paralysis if you get COVID-19 infection and you don't have the protection of a vaccine?

Here, in South Korea, they look through this, and the annual incidence of Bell's palsy had increased from 23 cases pre-pandemic to 32.5 cases per 100,000 during the first couple of years, so 2021-2022. Now, a retrospective cohort study in South Korea indicated that COVID-19 infection itself is actually associated with a higher risk for Bell's palsy. Then you can look at people who are vaccinated. There's about a 1.2 risk, but if you're unvaccinated, it's 1.84, so a 60% higher incidence if you don't have the protection of the vaccine.

They do a little bit of a hand-waving thought experiment, thinking about what might be going on here. Why is this potentially happening? They're thinking, could the lipid nanoparticles used to encapsulate the spike antigen or the inflammation triggered by the mRNA or the viral vector be stimulating production of type 1 interferons and interferon-stimulated genes? Maybe this is resulting in a targeting by the immune system of the myelin basic proteins, and then maybe this is damaging the myelin sheath, and it's actually parallel to what we've seen when we used to use interferon therapy for certain folks and then induce Bell's palsy with that.

VR: Daniel, what is facial palsy?

DG: You've got the facial nerve that comes out. I use my hand because it's got multiple branches that come out, and so it's motor function, and the motor function gets disturbed, so you see a droop, a one-sided facial droop.

VR: Is this permanent?

DG: It depends. In most cases, it's not. In most cases, it resolves.

VR: I don't understand these results at all. Days one to 28 after vaccination, you get 5,000 cases. What if you didn't vaccinate anyone? What would you get? Would you get 5,000? What's the baseline?

DG: Yes, the way they do this actually is a little bit, because they're looking at, this period of time, so it's relative to period of time. I would have loved if they did this the way they did like cases per 100,000 persons. If they broke it down and say, "We got 28 days, so we're seeing

5,000 cases in those 28 days, and then we could use this denominator of, 44 million." Then have the others say, "Now we're looking at this 240-day observation period," but you got to break that down. You got to divide that by 10, get it close to, a nine, and then break it. I was a little troubled that I didn't get the best breakdown of the raw data to really ask. Because the other side is what if you don't vaccinate, you just let everyone get COVID without the protection? Ultimately, you end up with more Bell's palsy, more facial paralysis.

VR: I just think maybe there's a baseline rate of facial palsy. Maybe it's 5,000 per 44 million, I don't know, so it's really hard.

DG: I think at the end of the day, I come away with this like, "Yes, you may see some temporary facial paralysis from the vaccine, but you're going to get a net protection by reducing the facial palsy you get from not being protected by the vaccine."

VR: They looked at both mRNA and adenovirus vaccines?

DG: Yes, they're looking at, yes.

VR: That's unusual. It must have something to do with the antigen, I would guess, not the vector itself.

DG: When you looked at the raw data, it was actually a little higher in the viral vector than it was in the mRNA, not what most people probably thought going into this.

VR: Yes.

DG: Passive vaccination, a little bit update. I was just talking to one of my partners, Marilyn Fabry, today. At least in our local area, there's a company, Prime Infusions, so primeinfusions.com\locations. We have half a dozen locations in our immediate area that's helping us get this passive vaccination to our patients.

Early viral phase, we have our treatment guidelines. We keep putting them out there. We have an article, and this is I think, an important one. I wasn't sure. Should I put it here? Should I put it in the Long COVID section? Maybe I'll just discuss it twice. No, I won't.

[laughter]

DG: Number one, what do we recommend? Paxlovid. We recommend Paxlovid based upon the data that it's going to prevent hospitalization, death, severe disease. Here, we have the article, "Nirmatrelvir Plus Ritonavir Reduces COVID-19 Hospitalization and Prevents Long COVID in Adult Outpatients," published in *Scientific Reports*. We've talked about the fact that only 5% to 6% of studies look at Long COVID, and we really need to look at that because for most of us, most of our patients, no one thinks they're going to end up in the hospital, nobody thinks they're going to die, but they are starting to learn about Long COVID and they do not want that.

This is a retrospective cohort study where they're going to look at nirmatrelvir/ritonavir, Paxlovid, in preventing severe disease, progression, and Long COVID. Treatment was associated with, as I think reiterating, a notable reduction in COVID-19 related

hospitalizations, so a 61% reduction. We're seeing that the Paxlovid was associated with fewer Long COVID symptoms, so almost a 60% reduction.

VR: They say prevents Long COVID in the title. That doesn't prevent, it reduces it, right?

DG: It's associated with fewer Long COVID symptoms.

VR: I don't think prevent is the correct word.

DG: I think this is one of the challenges. A lot of docs say like, "Oh, there was that study, so we've got EPIC High-Risk. Then we had EPIC-SR. The primary outcome in SR was basically zero symptoms. You make it a binary. As a binary, it fails, but if you look at the issue, so does it reduce the symptom severity? Basically, yes, Paxlovid makes you feel better acutely. Here, we're seeing about a 60% reduction in the number of Long COVID symptoms. If you do it as a binary, a little bit of an issue, because people are, "I want to be 100%." I can reduce your symptoms by 60%. The binary is really the challenge.

Now, this is another one of the things we've tried that didn't quite work. This is the article, "Time to Sustained Recovery among Outpatients with COVID-19 Receiving Montelukast," that's Singulair, "versus Placebo." This was published in J*AMA Network Open*. This is the ACTIV-6 randomized clinical trial data. This is the ACTIV-6 conducted January 27 through June 23, 2023, Omicron circulating participants age 30 and older. This is going to be a one-to-one. You're going to get the Singulair, or you're going to get placebo for 14 days.

Here, the primary outcome was time to sustained recovery, so three, greater-than-or-equal-to three consecutive days with zero symptoms, so we're going to do a binary here. Really, what we end up seeing is this randomized control clinical trial: Treatment really didn't succeed in doing anything. They don't really support using Singulair for the treatment of acute COVID.

Things are still the same with the early inflammatory week, so steroids, anticoagulation, pulmonary support, remdesivir, immune modulation. We're going to round it out here with one article about Long COVID. What about Long COVID? Now, I was thinking about how we get emails with people surprised that physicians are saying that the current or the new COVID is just a cold versus that old COVID that was really bad and required treatment. Maybe the right question is what about Long COVID? We have the article, "Clinical and Functional Assessment of SARS-CoV-2 Sequelae among Young Marines – A Panel Study," published in *The Lancet Regional Health Americas*.

These investigators, this is a personal connection here, they used a cohort of U.S. Marines from a previous longitudinal prospective observational study of acute SARS-CoV-2, most of whom were enrolled prior to the infection. A panel study was established to assess for post-acute sequelae of COVID-19, so PASC. They're defining it as symptoms at least four weeks. Four weeks, we've talked about eight and 12. This is almost a medium long COVID definition. Symptoms at least four weeks after symptom onset or diagnosis. They're going to assess these with questionnaires, this validated quality of health metric. They're even going to do fitness testing, which I really liked here. They're going to compare this.

They're going to look at globally dispersed Marine participants. These are these young, healthy, robust folks. They're predominantly male, so 91.7%. Not all male, so an *n* of 825,

mostly male. Median age of 18, so really 18, 19, they're young folks. Among these participants, a quarter of them developed PASC. A quarter of these young, healthy folks had symptoms past four weeks.

What were the symptoms? This matters. The most prevalent symptoms were loss of taste and smell. I don't think a lot of us are sympathetic to that. They're like, "All right, so you can't taste and smell, you young Marines." That's 40%, but almost 40% were having shortness of breath, trouble breathing; 23% were having cough. They also were having higher issues of somatic and general depressive symptoms, issues with anxiety.

Here, this is really interesting, so compared to an historic cohort of Marines, the folks with PASC, they actually scored worse on their physical fitness assessments due to slower run times, and those who ended up with PASC continued to have decreased physical performance one year after completing their initial training. Now, I thought about this. I was talking to my wife, Jessica, about this.

I don't know if you know this joke about there's two guys, and they're up in the Alaskan wilderness. They come over this rise, and they see a grizzly. The grizzly sees them. The grizzly starts charging at them. The one guy bends over, and he starts double-tying his shoelaces. His friend's like, "Dude, I don't see what you're doing. There's no way you can outrun that grizzly." He turns to his friend and goes, "I don't need to outrun the grizzly. I just need to outrun you."

[laughter]

DG: I'm like, "Oh, what's the big deal? These Marines, they're slower than everyone else." They're slower than the rest of the battalion. They're in this bad situation, and they're like, "All right, retreat or run or wherever they got to go." You got these, a quarter of them with PASC who just can't keep up with the group. That's not OK.

VR: That's a very good cohort to do this in. It's very clear compared to the general population where it may be a little fuzzy, right?

DG: Yes, because we measure them. We like not only do you feel -

VR: Yes, we have to measure.

DG: -but then we make them run and we measure their run times and they're not keeping up.

VR: I got a joke for you from last night's live stream. This is really good. This guy said, "I never get sick on the weekends. I only get sick during the week. Saturday and Sunday, I never get ill. I must have a weekend immune system."

[laughter]

DG: Oh, I love that. I'm going to use that.

VR: You should use it. Weekend.

DG: That's going to wrap us up. As we've been saying for a long time, no one is safe until everyone is safe. Now, Vincent, this is going to get you excited because when this drops, it's

going to be November. November, December, and January is our microbe.tv fundraiser. Thumbs up. It's the year end. This is when people like to donate. I'm very confident that we're going to get up to that donation of $20,000.

We are going to double your donations to get up to that maximum donation of $20,000. And I going to give you two choices. Come here to parasiteswithoutborders.com. Click Donate. We're going to double your money for the next three months, but you can even go right to microbe.tv and give them your money directly without the doubling. I think the decision is easy.

VR: It's up to you. Make your money go longer.

DG: Just remember, no one is safe until everyone is safe as some of our live stream listeners pointed out last night.

VR: As you know, here at *MicrobeTV*, we depend on your donations to fund our activities. We don't do ads. We don't have that income. If you like this science reporting, please help us out. Go to parasiteswithoutborders.com and they'll double your donation. It's time for your questions for Daniel. You can send them to daniel@microbe.tv.

Rach writes, "I had an accident and both knees have been damaged. I was given a cortisone steroid injection in the right knee in August and one in my left knee two weeks ago. I can now walk without crutches, but I am concerned it may lower my immunity to SARS-CoV-2 or flu infections, et cetera. I'm not sure to what extent this could be a problem." She goes ahead and tells us about all her immunizations and what you can and can't do. Last night she was on the live stream and I told her to ask you, would these steroid injections in the knee be a problem?

DG: Yes. The steroid injections, these are DEPO, so a delayed action. Yes, you're technically on steroids. When someone was going to assess your risk, they'd say, "You may be 63, but you're immunocompromised. To some degree, your immune system is not where we would like it to be. I'm not sure why you can't get access to Paxlovid where you are. I guess you're Isle of Man. What are the things going to be? We've talked a little bit. One is you have got, two, three, you've gotten multiple vaccine doses. You've had COVID a couple of times in the past. The extra boosters, they're going to add on top of that, but you already have a protection against severe disease. That's probably a persistent 90% reduction. A lot is probably driven by T-cell, so we're OK there. The other is, remember that Paxlovid is going to reduce your risk from where it is right now. At 63, in your context, your risk is already reduced. Yes, I would love, if there was a situation that you could reduce that even further with Paxlovid, but yes, that wraps it all up for you. It is that time of year, try to be safe. Isle of Man, you're over where we're seeing a little bit of COVID activity at the moment.

VR: She always says on the stream that you can't get Paxlovid on the Isle of Man, which, is between England, the UK, and Ireland, right?

DG: Yes, yes.

VR: I told you that her could do molnupiravir or remdesivir. Those are options.

DG: Yes. If there's access, the reduction that we saw in the PINETREE study with remdesivir was about 90% so that's an option. Molnupiravir, we say about 30% combined endpoint, but if you looked at mortality, it was actually even better than that. No, you do have some other options out there.

VR: Amy has two questions. One, "Tis the season to gather. Before COVID, my family would celebrate Thanksgiving with a dear friends. It wasn't a huge gathering, about 13 people. I've declined the invite since 2020 because I want to avoid getting exposed. I did get COVID summer 2023, just now recovering from debilitating fatigue. My friend who was hosting Thanksgiving offered to have everyone test the day before we gather. I understand the antigen tests do a decent job detecting virus if one is symptomatic, but not great if they're not. Obviously, if someone tests positive, it's a done deal, but how much peace of mind should 13 negative antigen tests give me?" [laughs]

DG: Yes, let's start with that because we've got a couple of questions here. Probably the ideal way to do this because it sounds like you really suffered pretty miserably from Long COVID for a long period of time. The last thing you want to do is have that again, reset the clock on that. As mentioned, the tests are most sensitive in someone who's symptomatic. That's been consistent. It's really not variant-specific, it's symptom.

The other is that probably ideal is to do tests the morning, that morning of the event of Thanksgiving gathering. You can get these LUCIRA nucleic, molecular nucleic acid amplification tests, which have a better sensitivity than the antigen. You could just do antigen tests across the board. If you're going to do that, do that the morning of, not the day before. If you're going to do molecular tests, which do cost a little bit more, but have a better sensitivity, again, the timing would be, the morning before the gathering.

VR: Number two, "My dad recently developed shingles, even though he was fully vaccinated. He says he read somewhere that the COVID vaccines can trigger the dormant shingles virus to wake up and wreak havoc. Is there any evidence of this? My dad was vaccinated for COVID a week before he developed, a few weeks before he developed shingles and vaccinated for shingles a few years ago.

DG: Yes, there is an increase in shingles. In varicella-zoster the chicken pox virus coming out of latency with acute COVID. There even is a little bit of an association post vaccination. Well, people were back making these decisions, lots of people say, "Get that shingle shot, get those two shots, get those COVID vaccinations." I think the other just, Shingrix, if you're 50 and over, about one in three people are going to end up at some point getting shingles. Of those people that get shingles, about 20%, so one in five are going to get that post shingles neuralgia, that ongoing burning pain. Really, everyone, get those shingles shots.

VR: Philip writes, "I appreciate your comments about the respiratory diseases in England and your comments about the tube. My wife and I were in the UK and Ireland from October 2nd to the 22nd. We caught something while in London. We did use a lot of public transport. We've all had RSV vaccines. We updated COVID and flu vaccines just at the right time before the trip. As to pertussis, I understand at one year, protection is 70%. At four years, it drops 30 to 40%. With the drop in the vaccinated rate in general and the lowering of herd immunity is 10 years too long for Tdap boosters?"

DG: Yes, this is an excellent question. I talked about this a little bit previously. Quadruple the number of cases of pertussis here, and actually recently reviewed a poor individual actually died from pertussis, ended up in the hospital, ended up bacteremic. Occam was not a doctor. You can have that second thing going on. A lot of times that's what drives the hospitalization, and what are, looking through the recommendations for this tetanus, diphtheria, acellular pertussis all in one.

The recommendations really seem to be driven by tetanus every 10 years, but when you start looking at the quadrupling, you start going through data, the protection dropping as quickly as you're describing, yes, it does really make us need to rethink, is every 10 years a little too long actually when you're dropping down to these lower rates.

VR: Lisa writes, "I was wondering if protecting the eyes against COVID droplets, like wearing bigger glasses or wind-protecting biking glasses are useful to prevent COVID infections, obviously, in addition to wearing a good mask. In the beginning of the pandemic, medical personnel were using face shields to protect the mucosa in their eyes. Are there any data studies on this subject? If not, do you think it's a reasonable measure in any way? This practice has just been abandoned in hospitals for practical reasons, I have to buy new glasses anyway, and would choose bigger ones if it would help me avoid an infection."

DG: Yes, I remember, the history on this, which was, early on, there was a study where they looked at people that wear glasses and people that don't wear glasses. There was people wearing glasses had a lower incidence. We discussed was it the glasses or glasses a marker of intelligence, you can see that Vincent's the one wearing glasses between the two of us, I put my on periodically, and actually, there was a "droplet protection." We would end up in the hospital if we were in seeing someone who then tested positive, and we were wearing N95 and goggles, that was really what, allowed us to keep working.

There's a little bit of controversy. In general, the vast majority of the way that you get COVID-19 is by breathing in the virus. Hey, if you're going to buy some new glasses anyway, and you're going to choose some bigger ones, and they're going to work well with the aesthetic of your face, I think that's reasonable.

[laughter]

VR: Charmaine writes, "I was a bit confused listening to a conversation about Losartan. I get it that it's not to be used as a COVID treatment, but was rather alarmed at the worst outcomes. I have a friend who was just put on losartan for hypertension. I've been on olmesartan for decades. Should we not be taking ARBs for our BP and be on a different type of BP-lowering drug? I certainly don't want a worse outcome because of that, even though, of course, I've been doing and would continue doing everything else right as far as vaccines and treatment."

DG: Yes, so Charmaine, this is a good question. I was thinking about this this weekend. I actually got asked very much the same question. I'm sailing, it's the last weekend sail of the season doing this 100-mile trip with my cousin, Peter Gates, and he's on the same class of medicine, just sharing his confidential medical stuff. You want to know like, "What's the story? Is it OK? I'm on this?" I really think I will sum it down and say it is not good for treatment.

Actually, what were some of the worst outcomes? You're taking people and you're putting them on a, in a medicine that decreases their blood pressure, really at a time when that can be an issue for us. I don't really think a takeaway from the study was that people who are on this medicine for their hypertension need to be more concerned. I don't think the papers suggest that those people are at higher risk. What it does say is it's not a great time to be starting an ARB.

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

DG: Thank you. Everyone, be safe.

[music]

[00:48:38] [END OF AUDIO]