This Week in Virology

TWiV 1140 Clinical Update

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

[music]

VR: From *MicrobeTV,* this is *TWiV*, *This Week in Virology,* Episode 1140, recorded on Thursday, August 15, 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: Your tie is really dark, but I'm going to guess it's a diplococcus.

DG: So close. They are these little cocci. Actually, they're in clusters, and they are a golden color. Think of the golden grape. Can you say grape in Greek?

VR: Oh, yes, of course. I know what that is. Is that streptococcus?

DG: Yes. *Staphylococcus aureus*.

VR: Something was called diplococcus because they were pairs, right?

DG: Yes. That's Strep pneumo diplococci.

VR: You don't use diplococcus anymore, right?

DG: Some of us are old enough to remember that terminology and banter it about, but yes.

VR: When I went to graduate school, that's what we called it, diplococci.

DG: Yes, that works. That works. All right. Let's jump in. We'll start with our quotation because we have a bunch to talk about tonight. This is from Thomas Carlyle. “He who has health has hope, and he who has hope has everything” Just really, putting up there the importance of health and why we prioritize it. I think there's a famous “Princess Bride” quotation, which has a take on this, but a little more comedic. All right. Let's jump into it. We got a couple here right up front before we get to COVID. The first one is, I think, a really nice conceptual, peer-reviewed article, “Onward Virus Transmission after Measles Secondary Vaccination Failure,” published in *Emerging Infectious Diseases.*

Here we read the results of a systematic review aimed to assess transmission risk for measles after what they call secondary vaccination failure or SVF. These are going to be some new terms we're going to talk about today. We're going to talk about primary vaccination failure, so PVF. What is that? It's not breakthrough. This is a failure to seroconvert after vaccination. While this secondary vaccination failure, SVF, is something that occurs years after that initial vaccination felt to be due to waning immunity.

VR: Can I can I interrupt, Daniel?

DG: Please do.

VR: Why is it a failure? It's natural waning of immunity. Why is that a vaccine failure?

DG: Yes, it is interesting. Why do we use terms like “breakthrough,” “failure,” all these other things, right?

VR: Right. Implies something is wrong. I think it's biology.

DG: Yes. We do need we do need better terminology here. Let's talk a little bit more about this concept. Yes. The first time, and this is actually an issue. This primary vaccination failure. OK, so you vaccinate someone. You don't get seroconversion if antibodies are critical. OK, so maybe I'll call that a failure of doing that. Now, the other idea, though, is years go by. We're going to talk about how many years. Then there's this waning, and then something happens there. Primary vaccination failure results from a person's failure to produce any humoral response to viral antigen, so nonseroconversion.

This is thought to occur in about 5% of measles vaccinees. All right. 95% time, we get a good antibody response. 5% of the time you don't. Now, this secondary vaccination failure, which we need to rename, seems to occur six to 26 years after that vaccine dose. Vincent, as you bring up, it's a result of waning or some kind of incomplete immunity. This occurs in 2% to 10% of measles vaccinated persons. We can do our numbers. Ninety-five percent of the of time, you get a good antibody response off the bat. Then somewhere between 90% to 98% of the time, those antibodies keep going. And, should a person be exposed, we don't have disease.

VR: I bet after infection, you get the same numbers.

DG: It would be great to know. This is stuff people could check.

VR: I bet this fraction of people, because everyone's genetically different, a certain fraction are just not going to have long lasting antibody. It's not a vaccine failure. It's just the way it works.

DG: This is the way the immune system works. The interesting thing we're going to get out here. It is good that we're actually talking about because words do matter. We talk about failure and breakthrough, it feeds this anti-vaccine. We don't want to do that. We want to talk about what's going on. What you're going to see here is actually going to be a pro-vaccine message, which is this question. Someone gets vaccinated six years, 10 years, 15, however many years go by. We get that contraction, that waning that we see over time.

Now, somebody goes, and they get infected, they get disease. The question comes, is this really a failure? What about onward transmission? I think this is also going to be helpful in like, "Why are we trying to get a population vaccinated? How does whether or not you were vaccinated matter to me, to your neighbors, to your family, to those you love?" It's this whole concept of onward transmission, whether you're a naive, unvaccinated individual, or you're an individual that has this preexisting immunity from vaccine.

Here the investigators searched PubMed, Embase and Web of Science databases, inclusion criteria, articles describing persons who were exposed to measles-infected persons who experienced this SVF, so this late phenomenon. Across the included 14 studies, greater than 3,030 persons were exposed to measles virus from these SVF cases. Someone got immunized. Many, many years ago later. Now, they actually have a measles case. What about the people that are around them? One hundred eighty were susceptible, and we end up with this secondary attack rate of somewhere between zer0 and about 6.25%.

They identified 109 cases of SVF from these studies. This is really the meat of it. What is the reproductive number, the effective reproductive number for measles? Most of us peg that at greater than 10 for unvaccinated people. You've got a person naive, they've got measles, they're around other people. They're going to spread it in general to greater than 10 unvaccinated people. Now, one of these people who've been vaccinated before actually gets measles. What is the reproductive for them? Less than 1, calculated to be 0.063.

VR: Daniel, I think they're overlooking cellular immunity, and that's probably playing a role. They're just measuring neutralizing - They're not measuring anything. It's a meta-analysis, but they're looking for neutralizing antibodies. I'll bet these people have durable T-cell immunity, which is really doing the job.

DG: Yes. it is interesting, too, because you have this idea like, "Oh, but these people, they got vaccinated, and they still got measles." They may have still gotten measles, but it's not the same thing. Every case of measles is not the same. With a reproductive number of less than 0.1, you're really going to end the transmission. These people are not really spreading. I think this is the kind of stuff that I would love to see. It's going to be hard at this point in time to get these numbers for things like COVID.

What is the onward transmission? We talked about the Pareto principle. We had 20% of the people spreading 80%. What was the number that one person would spread to others? How many others would end up getting it? It would be great to have information now, people who've gotten a whole bunch of vaccines. What is that doing for a population?

VR: I think the bottom line here is that you shouldn't worry about it because even if a fraction of the population, their antibodies decline, they still are not going to really pass on the virus.

DG: Yes. I think this is really another very pro-vaccine message at a community level.

VR: Daniel, if a patient came to you, and you did an antibody titer, and they'd been immunized many years before, and it was zero, what would you do? Would you re-immunize or say you're not going to transmit? [chuckles]

DG: Yes, it's interesting. In the general population, we don't recommend routine revaccination. There's a couple of situations, maybe in healthcare workers. Then there were the recent issues where we talk about, "Oh, if you're going to be in an area where it's high risk, if you're going to be traveling to somewhere where there's a lot of measles." It's interesting. I do this. I traveled to these areas where there's a lot of measles going on. To get healthcare employment, they check these titers, and there are certain institutional-based recommendations.

We're really seeing here that you're missing the boat if you just check antibody levels. Now, the next one, this is something I've been getting a lot of questions about and very timely, as in today, very timely as we're recording this. August 14, 2024, so that's Wednesday, we're recording on Thursday, the 15th. August 14, “WHO Director General Declares Mpox Outbreak a Public Health Emergency of International Voncern.” We've renamed the disease mpox.

We read in a news release from the WHO, that WHO Director General Dr. Tedros Adhanom Ghebreyesus has determined that the upsurge of mpox in the DRC and a growing number of countries in Africa constitutes a public health emergency of international concern under the international health regulations. The emergence last year and rapid spread of a new virus strain in DRC, clade 1b, which appears to be spreading mainly through sexual networks, and its detection in countries neighboring the DRC is especially concerning and one of the main reasons for the declaration of this public health emergency of international concern.

In the past month, over 100 laboratory confirmed cases of clade 1b have been reported in four countries neighboring the DRC that have not reported mpox before. Burundi, Kenya, Rwanda, and Uganda. Experts believe the true number of cases to be higher as a large proportion of clinically compatible cases have not been tested. Seeing lots of cases, I'm already confirming over 100 of these.

VR: Daniel, not very long ago, mpox, monkeypox virus, spread out of Africa. How is this different?

DG: The biggest thing here is we're talking here about a clade 1b. There's clade 1, there's clade 2, and then there's variants within the clade. This is a clade 1b. Clade 1 is felt to be more aggressive, a higher mortality. Yes, this is not the same clade 2 where we - We did see some deaths in higher resource settings. This is a more aggressive virus, and it looks like we're seeing pretty significant spread. We don't live in Africa, and while this Dr. Griffin keeps saying no one is safe until everyone is safe, this “Africa Vincent,” should we be worried about this? Is this going to get out of Africa? Is it going to come to Europe?

VR: Daniel, this has been ongoing for several years. I don't know why we didn't deal with it before.

DG: That's why we're worried about it, right?

VR: This is the problem, because people don't care until it spreads out of Africa. That's not right. They should have been vaccinating the population years ago. We have vaccines. That's the role of the WHO, don't you think?

DG: Yes. This is huge. Is that the approach? Do we only care about Ebola in West Africa because, oh, it might leave West Africa, and while it's in West Africa, it's not our problem? It is the World Health Organization. It's not the Western or the entitled resource-rich countries' health organization. It's supposed to be the world's health organization. There were a lot of criticisms, even in West Africa, that a lot of the focus was keeping it from leaving West Africa, not even so much going there to really help the people that were suffering.

We've been talking about mpox for a while. Yes, all these people are getting it. People are dying. People are suffering from really a horribly painful, disfiguring disease. We seem to only be getting interested because now it's this public health concern of international concern. I think the suggestion was to really get this under control. They need about $15 million to move forward with the vaccination efforts, which in my mind seems like a very small amount of money.

VR: It's too small, Daniel, right?

DG: It seems like a very accessible amount of money. I should point out that, OK, our hands have been in our pockets too long. Because now, if you don't actually just care about people because they live in Africa, and you're worried about yourself, well, the WHO just confirmed the first case of mpox outside of Africa. The WHO today, Thursday, I'm recording this on the 15th of August, yes, Sweden. Case in Sweden. Swedish health officials said at a press conference that the person was infected while they were in Africa. People do travel. Yes, it's clade 1b, the same that's involved in this recent outbreak. The patient is there receiving treatment in Sweden.

VR: Daniel, it's my understanding you still need close contact to transmit, right?

DG: Yes. That's something we talked a lot about when we were seeing cases here in the U.S. In general, this is a very close contact spread. There was that scary healthcare worker story where a couple of healthcare workers went out to a patient's home, and they put their gloves and everything on, but they did that after they had already gotten in and only put the gloves on when they were ready to get samples. A couple of them actually got lesions on the hands. No, in general, this is very close contact. As we're seeing, this is generally spreading through sexual networks.

We've seen this in children where it's not a sexual, it's just a physical contact exposure. In general, this is not a respiratory transmission. This is a contact transmission.

All right. Moving into a respiratory transmitted pathogen, COVID, we have our map update. I put on my glasses to read the small print here because in bright yellow, Puerto Rico and the 4% to 5.9% of all deaths in Puerto Rico are still COVID. A bunch of states, 2% to 3.9% of the deaths in Texas, Minnesota, Alabama, Florida, New Jersey are due to COVID. Not only are we seeing the wastewater continue to rise across the country, in the West, it's past where it peaked last January. We're seeing continued rise in the South. Again, the South is already up where it was last December, January. Yes, all across the country, we're seeing continuing exponential rise. All right. Just keep reminding people about PEMGARDA, the COVID passive vaccination. That's that prophylactic monoclonal antibody. We've started doing that at Columbia, and actually, we're trying to get access here.

Just yesterday, I was speaking to one of our hematology-oncology docs about just all his patients who are at risk, they're pretty far out at this point for vaccination. There's also the concern that they're not going to be great responders. Remember, that's that prophylactic monoclonal treatment with about a 70% risk reduction of developing symptomatic COVID-19. Early viral phase. We have a fun article here, and it's really like a thought piece. This is the article, "Single Monoclonal Antibody Should Not be Used for COVID-19 Therapy: A Call for Antiviral Stewardship," written by some of our friends, Arturo Casadevall, Daniele Focosi, Liise-anne Pirofski, and Shmuel Shoham, and this is published in *CID.*

Here's the background. I have to say, I'm, as I'm reading this, thinking about where would I have weighed in on this back in March of 2020, where have I weighed in on this over the pandemic, and where do I weigh in now. We read that it is an axiom of infectious disease practice that the use of a single agent for microbial agents with the capacity to rapidly generate escape mutants can lead to emergence of resistant microbes. Such a lesson was painfully learned over decades of clinical experience when single-drug therapies led to the emergence and circulation of resistant strains.

I remember HIV. In the early days, I was the guy sitting there saying, because I had come from a tuberculosis background, saying why would you possibly use one medication against this virus? Then I remember when they ended up in the hospital, we would stop all their meds, and then just the virus would run amok. Here we go forward. I'm going to read from the article. For example, during a Phase II randomized clinical trial of bamlanivimab, remember bamlanivimab?

VR: Bam-bam, yes.

DG: Yes, I was actually the PI on the largest clinical trial of bamlanivimab. Very intimately acquainted with bamlanivimab. The prevalence of treatment emergent mAb-resistant SARS-CoV-2 was 7% in the treatment group versus 0% in the control group. We saw this right out of the gates. When antimicrobial drug resistance emerges due to selection for less susceptible strains, these strains - I just want to say variants here, by the way - these variants can be transmitted to others in the community and healthcare settings. This is also possible for resistance that is induced by the monoclonal antibodies.

However, it is unlikely that the demise of the first generation mAbs is solely attributable to selection of mAb-resistant variants since SARS-CoV-2 Spike protein mutations, amino acid changes, had already been documented prior to the rollout of anti-Spike monoclonals in 2021. The most likely explanation for the short clinical life of the originally deployed mAbs was that they targeted single Spike protein epitopes that were also targets of infection- and vaccine-induced antibodies. The authors here argue that while mAbs used for PrEP is justified, right, or PEMGARDA approach or Evusheld approach, they're suggesting in this opinion piece that single mAbs should not be used for COVID-19 therapy.

VR: I think that's reasonable, but Daniel, we can't even get physicians to use Paxlovid. To think they're going to use a monoclonal anyway is probably dreaming.

DG: Yes, this is interesting because where do you go with this opinion piece. For certain situations, let's take Ebola, for instance. If you've got Ebola, and someone's acutely got Ebola,

we might treat them with a monoclonal antibody. We might treat them with a small molecule. In the early days of the pandemic, so 2020, we really jumped in very quickly with convalescent plasma, also jumped in with the different monoclonal antibodies. We had bamlanivimab. It was first by itself and then coupled with the second one. We had the Regeneron cocktail, which had a couple.

A lot of the whole idea here, it was really going to be a stopgap. The whole idea that you always need to use a cocktail, it costs twice as much, there's increased production capacity, and did we really lose them because we use them one at a time, or did we lose them because you just had all these people getting infected? This was actually the same target that people were producing antibodies to, and you were getting selection pressure against just from actual wild type viral infection. I think it's an interesting piece, but I'm just not sure where we go for forward.

We're not going to probably use monoclonal antibodies in the future for acute COVID-19 therapy. We're really trying to go and get people to use the small molecules. As you point out, we're not even succeeding there. There's this whole mainstream media like, oh, in certain countries where they just don't even test, they don't even want to know, even though there's an effective therapy that can reduce progression by 80%, 90%. We're seeing ongoing issues as we point out. When 4% of all the people dying in your state are dying due to COVID, there's a problem there, because what is the biggest denominator at this point?

Everyone's got immunity. Everyone's been infected before. Everyone's had a vaccine. The people that are dying are the people that are not being offered therapy. That is a great segue into what is that number one recommended therapy by the NIH and IDSA, but?

VR: Paxlovid.

DG: Yes, people. Paxlovid. Eventually, we might have some other choices, but right now, that's recommended. Don't wait. Actually, a colleague texted me the other day, "Hey, I got a patient. They're thinking they want to wait to let that natural immunity kick in." Please don't wait. It's like waiting for something to happen with that patient having a stroke or a heart attack. What are the collaterals going to develop? No. The sooner you step in, the better effect you get. You really don't want that immune response. You don't want that cytokine storm during week two.

Paxlovid, remdesivir, molnupiravir, convalescent plasma in certain circumstances. Unfortunately, the isolation guide is because you are sick, but you can make other people sick as well. Remember, just going to reiterate this. For the first five days is when we see the most transmission. Let's say you're an elderly individual, your husband just got COVID. It's day six, and you're like, "I'm done with isolating. We're going to start sleeping in the same room." Ten to 15% of transmission is during that day six through 10, most of it day six, seven. Just keep that in mind when you're making your decisions.

VR: What is the CDC recommendation for which day are you OK? If you feel good that day five, is that enough?

DG: Day five is when they say strict isolation, and day six through 10, they say, if you're going to be around others, you're supposed to wear a tightly fitting mask. Sleeping in a room next

to your spouse without a tightly fitting mask, that's not per CDC recommendations. You're rolling the dice, and you're hoping that if you get COVID, your doc's going to get you going right on the Paxlovid. The really tough thing, and this is the public health issue that we just have to be honest about. This is great that we have this long format to say it, is: In the early days when they talked about 14 days, when they talked about 10 days, you had about a 2% compliance. From a public health, that's useless.

VR: Horrible.

DG: Yes, it's horrible. Then it was like, I say negotiating with terrorists saying, "OK, would you do five days? Would you at least do five days?" If people do five days, and even if you get 10% doing five days, yes, that's actually going to be a more effective public health intervention than 2% of the people, 98% of people not doing anything.

VR: Last night on the stream, someone said, "I had COVID. At day five, I felt great. My test was negative. Can I assume I'm OK?" I said, "No, you shouldn't. You should probably wear a mask for a few more days."

DG: I'm in the doctor's lounge, and that was this week. One of the docs is joking about, "Oh, so I understand you took a trip to Alaska," to one of the other docs. I'm like, "Oh, really? I used to work up in Alaska." He's like, "No, I'm joking." I'm like, oh, what, you weren't in Alaska?" He's like, "No, I had COVID, but it's OK. I'm all better. Today's day six." I'm like, "Where's your tight-fitting mask?"

[laughter]

VR: Especially for a health care person, right?

DG: Yes. They were wearing a tight-fitting N95. That's critical because you say, "Oh, only 10% of the transmission." The in-hospital mortality, if one of our patients is in the hospital, and then they get COVID while in the hospital, mortality is well over 20%. I was relating, I think, the story about that older woman, delightful woman who was telling us how she was going to run for president in the fall. She came with a urinary tract infection, got COVID, and then she died of COVID.

VR: The problem is if you're in the hospital for some reason, and so if you get COVID there, it's high mortality.

DG: Yes, unfortunately. OK, so during that second inflammatory week, steroids, right time, right patient. This is the early inflammatory. It's not the rebound week. One of my patients was giving me a hard time on Tuesday. She's like, "Dr. Griffin," she has Long COVID. She's like, "Ever since I got COVID in July, I felt really like a setback, took the Paxlovid bit during that first week. I started to feel better." Then I got the rebound, and I was like, "You're doing that just to torture me." She's like, "OK, we'll call it the early inflammatory response." "Thank you. You can now be my patient." During that early inflammatory week, steroids, right time, right patient, right dose.

We have anticoagulation guidelines, pulmonary support and remdesivir in some situations. We're still in the first 10 days and still some limited use of the immune modulators. A lot of challenge there is right time with those.

All right, we'll focus a lot here on COVID, the late phase, PASC, Long COVID. Really, I think I've got three articles here to talk about. First is just a mention, the article, “Long COVID Science, Research and Policy,” published in *Nature Medicine*.

Some rock stars of Long COVID in the author list here. The authors put forth this interdisciplinary review that provides a synthesis of the state of scientific evidence on Long COVID, an assessment of the impacts of Long COVID on human health systems, the economy and global health metrics, and provides a forward-looking research and policy roadmap, a rather extensive discussion of the impacts of Long COVID on individuals, health systems, economies, really a call to action to increase awareness, promote research. I thought of something, in training of healthcare providers to care for these patients.

I don't know if people know, but I'm a Swifty. I'm listening to the song “Epiphany,” where she talks about, we didn't learn about this in medical school. Somehow, if we're going to take care of these individuals who are suffering, and her song “Epiphany” is about people with acute COVID. I'm thinking of this in people with Long COVID. These are people's daughters, people's mothers, people's friends, and they're continuing to suffer. A lot of clinicians out there are really stretched. This is a tough crowd to take care of. We actually need training of healthcare providers so they really know how to care for these folks.

Yes, over 300 references and open access. I'll recommend that read. Now, a couple different things here, a couple more articles. Now, the first one, I think this is important. The article, “Differentiation of Prior SARS-CoV-2 Infection and Post-acute Sequelae by Standard Clinical Laboratory Measurements in the RECOVER Cohort,” published in *Annals of Internal Medicine*. This is just a word of caution about just doing those "routine" blood tests and finding nothing wrong. This study looked at 10,094 participants, 8,746 had prior SARS-CoV-2 infection, 1,348 were uninfected, 1,880 had a PASC index of 12 or higher, and 3,351 had a PASC index of zero.

That leads me to say, "Let's pause here. What is this PASC index?" As part of the National Institute of Health's NIH RECOVER, Researching COVID to Enhance Recovery Initiative, I'll leave in a link, recovercovid.org, this group previously examined prospectively collected data from nearly 10,000 people in the RECOVER adult cohort with or without SARS-CoV-2 infection and identified 12 symptoms that best distinguish those with prior infection from those who are uninfected.

Actually, if you dig through in the supplementary material, there is a table, Supplemental Table 1, Symptoms Included in the PASC Index. We've talked about this when this publication came out, but there's actually scores assigned per symptom. People argue a little bit about the scores and the points. For instance, if you lost smell or taste, you get eight points. If you've got brain cognitive dysfunction, you only get three. Some people are like, "Really?" Fatigue, we talk about people debilitating fatigue. I can't get out of bed. I can't go to work. You get one point.

All that being said, what they really try to do here is say, let's take people who really solidly have PASC, 12 or higher. Let's take people with a PASC score of 0, so people who got COVID who do not have PASC. Let's look at SARS-CoV-2 uninfected. Then let's basically ask the question, if we do a whole bunch of blood work, what do we find? We read that after propensity score adjustment, participants with prior infection had a lower mean platelet count, higher mean hemoglobin A1c, that's a chronic sugar measurement, and urinary albumin creatinine ratio.

They do comment that differences were of modest clinical significance. They point out that among participants with prior infection, no meaningful differences in laboratory values were found between those with a PASC index of 12 or higher and those with a PASC index of zero. What "routine labs" did they do? They did a complete blood count with differential, complete metabolic panel. They did an INR, they did a D-dimer, they did lipids, did a vitamin D, thyroid stimulating hormone, free thyroxin. They did the hemoglobin A1c, a high sensitivity CRP, a cystatin C, an N-terminal, a BNP, troponin, urinalysis, urinary albumin creatinine ratio.

Where'd they come up with these? These tests were selected on the basis of, one, routine availability. These are routine blood tests, ones that are standardized. Also, they look through the prior literature and then expert opinion, so clinical expertise of the investigators. I'm going to say there's a lot to take away from this article. One is that people suffering from Long COVID can often have normal routine blood work.

A word of caution there. While some patients seeking care might have a compelling clinical presentation, in some cases, biochemical and physiological abnormalities are consistent with Long COVID. There remain no diagnostic biomarkers, and no one can rule out Long COVID by just doing routine blood work.

VR: How did they come up with these numbers? It is a matter of frequency of these individual signs and symptoms?

DG: A lot of people were critical. There's this idea that they felt like certain characteristics were more discriminatory. When people come in, and "I got some sort of a viral illness, and I can't smell or taste." If it's congestion-related, it tends to go away pretty quickly. With COVID, it can linger.

They felt like, OK, that's pretty much if you got that, that was from the COVID. That I got COVID, and now I have this post-exertional malaise. I think it was really a goal to find discriminatory valued characteristics rather than necessarily the impact on quality of life. The fatigue, "I can't get out of bed." Giving it a point of one, people were upset by that, but there's a lot of things that can lead to a fatigue, so a discriminatory aspect.

VR: Basically, there's no common lab test that will distinguish people with PASC.

DG: Yes. You can't do a blood test and say, "Oh, you've got it. You don't have it." Nothing that rules -

VR: We knew before, Daniel, right?

DG: Yes. Just good to point out. Docs are still doing the same, "Did a whole bunch of routine lab work. You look all fine. You must be malingering." Let's not be dismissive.

VR: There are other things that are different that are not routine assays.

DG: Yes. That's some of the stuff we've talked about. We've talked about serotonin levels, serotonin levels seen in different cohorts. We've talked about this low AM cortisol without a competitory ACTH. We've talked about really off the chart EBV, CMB, and VZV serology tests, consistent with this escape from latency during acute infection. Yes, actually when my review gets published, we'll go through what would be a reasonable panel of tests to do rather than this "routine panel." All right. I think we just have two more to talk about before we get to emails.

One is, “Risk Factors for Long COVID Syndrome in Postmenopausal Women with Previously Reported Diagnosis of COVID-19,” published in *Annals of Epidemiology*. This comes from the Women's Health Initiative, or WHI, which is a landmark study dedicated to understanding chronic disease-prevention strategies in postmenopausal women. A lot of studies previously looking at just old Caucasian guys. During 1993 to 1998, 68,132 women enrolled in three overlapping, randomized, controlled clinical trials, and 93,676 women enrolled in a prospective observational study.

All the women were postmenopausal and in the age range 50 to 79 years and enrollment at 40 U.S. clinical centers. Here we're actually looking at data from this initiative. Using the WHI demographic, so that's WHI, not WHO, demographic and health data collected at study enrollment through the present day, machine learning identified the top 20 risk factors for Long COVID. Then they looked at these variables with logistic regression models. With an n = 37,280 survey respondents, 1,237 with a mean age of 83 reported a positive COVID-19 test, and 30% reported Long COVID, so pretty high.

Symptoms included an array of neurological, cardiopulmonary, musculoskeletal, general fatigue, malaise symptoms. What did they find? Risk factors for Long COVID, a weight loss of 10 pounds or more in the previous two years, sleep problems, limited physical and mobility, previous heart valve procedures, and rheumatoid arthritis. Physical function risk factors for Long COVID were a limited ability to bend, kneel, stoop. Are you ready for this? Grocery shop, as well as the use of a wheelchair, walker, crutches on level surfaces. Our more debilitated folks going into this were at higher risk coming out the other side.

VR: Certainly, some very athletic people can get Long COVID also, right?

DG: Yes, and I think that's always the thing. We're just talking about relative risk. I've talked about some of the triathletes that I have taken care of who, they've gone from being a triathlete to, "I can't walk up a flight of stairs." It hits all. It's just a relative risk issue.

To finish with the article, “Long COVID Symptom Monitoring Insights from a Two-year Telemedicine Study,” published in *PLOS One*. These investigators conducted interviews to evaluate Long COVID symptoms at the two-year mark and investigated whether patients had contracted a second COVID-19 infection between the one-year and two-year follow-ups and recorded their vaccination status.

Out of 165 patients, 84% reported symptoms at the one-year follow-up, while only 61% reported symptoms at the two-year follow-up. Seeing some people getting better. Among patients with Long COVID at the two-year follow-up, the majority, they say, had experienced Long COVID at the one-year follow-up, received the SARS-CoV-2 vaccine, and had not experienced a second infection between the two follow-ups. Both having Long COVID at the one-year follow-up and contracting a second infection were significant risk factors for preventing with Long COVID at the two-year follow-up.

Sort of that issue with getting another infection putting you at risk. My comment here, there's a couple of things here. One is, yes, every time you get COVID, it can be a setback, sharing that experience of that patient that was torturing me by using the terminology of rebound. Also, a comment here about the value of telemedicine. That was one of maybe the silver linings that came out of this pandemic, is we really got an uptick in the use of telemedicine and the introduction of telemedicine technology. It really has been a great way for a lot of people to access care. It's really been great for people with Long COVID.

For people with Long COVID, it's daunting, the idea that they're going to somehow get to a physician's office, that they're going to wait around, they're going to then get seen, somehow they got to get home. Then for a lot of them with post-exertion and malaise, now the next two days are just a disaster. For a lot of them, it's been great. Also, I guess it's great from my perspective to be able to see someone in their home, to be able to see like, "Well, what does your world look like," as opposed to just seeing them in that sterile exam room.

It's also been great for hospital discharge. Someone gets out of the hospital, and you say, "All right, I want to see you in the next couple days and make sure everything's going well." They're like, "I just got out of the hospital, I'm supposed to come to an office?" Great to be able to see them, making that transition to home. Are they on all the right medicines? Hey, is there anything going on that we need to do to keep you from bouncing right back? Really a lot of value here with telemedicine, so nice to finish with a highlight there.

VR: The last *TWiV,* Daniel, 1139, was Long COVID with Dr. Judith Bruchfeld. She talks about the experience in Sweden with Long COVID.

DG: Yes, I listened to that. That was a great episode. Yes, it's really nice to hear the experience in another situation, another context. All right, so let us say no one is safe until everyone is safe. Hopefully, a reminder in some of the stuff we covered today, but I'm hoping everyone would pause right here, go to parasiteswithoutborders.com and click on that Donate button. I hope you appreciate what we're doing, but to keep doing this, we're going to need your continued support. Right now we're doing our Floating Doctors fundraiser where for August, September, and October, we'll double your donations up to potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. DR writes, "I recently had a brief sore throat, thought it might be the beginnings of SARS-CoV-2 infection amidst this summer peak. However, two successive rapid antigen tests from two supplies were negative as was a LAMP PCR. Although I've been diligent at testing and have enough lab experience to do it right, I've never tested positive during this pandemic. What is your current clinical experience with such high wastewater levels reported globally?

Could there be lower viral loads in the respiratory system enough to evade detection while that in the GI tract is getting picked up? Does that say we should be developing urine and fecal tests for consumers? Furthermore, I saw a mention on social media of the success of lencapivir and HIV, which gives me the impression that we are sitting on our hands when it comes to developing antivirals for SARS-CoV-2 and thinking we're golden having relative success with mRNA vaccines. Your thoughts would be appreciated."

DG: Yes, so these are both great topics to bring up. The first is this issue. Let's say someone gets exposed, let's say they have one of these abortive situations, which we've talked about in that exposure study that the Brits did where they exposed a whole bunch of young people. Some of them you actually were able to pick up cellular changes, T-cell activation, things like that, but you never ever got a positive test. Sometimes are we seeing situations where that's happening? Then becomes the question of, does that affect what we would do clinically. Would those people really even benefit from getting an antiviral?

We don't know the answers to those questions. I think before we start being so aggressive in developing urine and fecal tests, you want to ask this question, does it matter? If your body is already able to keep that viral load down so low that maybe you're not even going to pick it up, would treatment even add anything to that? That's my first comment.

The next is, yes, lenacapavir. We mused a little bit about this, with influenza, if there's an outbreak in a nursing home, for instance, we'll actually put everyone on the once-day prophylactic dosing of Tamiflu, and there's some evidence showing that does something. We really haven't found success with our small molecules in doing a pre-exposure or pre-positivity. It would be interesting to keep working down that road because, yes, particularly in a nursing home, that would be a great setting to have some sort of prophylactic or pre-exposure or even early post-exposure medication to use.

VR: I think the GI RNA is a direct reflection of what's going on in the respiratory tract. You're swallowing mucus, and it's passing through. There's no replication in the GI tract. If you don't detect it in the respiratory tract, it's clinically irrelevant, I would say.

DG: It's probably true. I think, yes, it'd be great to do the studies to see.

VR: OK, Rad writes, "I'm a medical assistant at a Canadian cardiology clinic. Our clinic has been using surgical masks for all staff and patients since the beginning of the pandemic until now. We're wondering where the balance of the evidence lies in August 2024 on using surgical masks in such settings and whether the drawbacks of masking, such as impaired facial communication, environmental waste and discomfort, would be outweighed by the small but perhaps non-zero effect of masks for source control and disease incidence or severity reduction. We've been tuning into your episodes every week.

Remember you mentioning the UMD study by Lai, et.al, *TWiV* 1120, which showed lower exhaled viral mRNA in N95K and N95 cloth masks in surgical masks, where the cloth masks slightly outperformed surgical, although we don't know if 70% to 98% less exhaled viral load will be clinically significant in reducing illness severity.

We also heard of the recent Norway RCT, which showed a 29% relative risk reduction in self-reported respiratory illness over two weeks, although it seems like that study has had some

limitations, which lowers our confidence in its results. The control group reported going out more and vice versa for the surgical masking group. In other words, some have argued that this RCT tested the effect of masking as opposed to masks themselves. We know you may be unable to make broad recommendations about masking in healthcare facilities. What does the balance of evidence say to the personal and social cons of surgical masks outweigh the purported benefits in 2024?"

DG: Yes, so this is great, Rad. Basically, you're laying out the issues, you're laying out some of the evidence. This is really the discussion that different facilities have to have. Certain facilities, I'll say here in the U.S., we use thresholds. A few weeks back at one of our healthcare systems, things got to a certain point. It's interesting in their communication because they talked about levels in our patients and our team members. Maybe people listening will know which healthcare system uses team members in their verbiage, and actually making a recommendation for going back to masking.

A lot of this has to do with what kind of patients are you taking care of, how much of a contact time, what is the risk situation, what's the ventilation of your facilities and the interactions. A lot of the outpatient settings that I work in are either just using surgical masks or some situations not using masking at all. As a lot of people have pointed out, there is impaired facial communication. Sometimes there can be an issue, particularly in older individuals who really are doing a lot of lip reading. There's this huge environmental waste impact.

It still kills me that even though we know that COVID is a respiratory transmitted pathogen, we're still putting on these yellow gowns and generating 200 gallons a week per patient of this waste. It's not contact, it's respiratory. Time to get on the front page. I'm not sure about the discomfort. I think you're bringing up all the really important issues. People at facilities need to have these dialogues and make these decisions. What's really the right choice for your facility, your patient population, and your caregivers?

VR: Grazia writes, "For the past four years, I have kept abreast of the latest research, including listening to your update. I feel you have armed me with pretty good info. I'm shocked that my doctors do not hold the same views as you when it comes to antivirals. My husband is 55 and recently infected. For the first time, he attended a Seattle Mariners game, didn't wear a mask. He has Ehlers-Danlos. He called his doctor to get Paxlovid, as we have a high-risk child. The nurse tried to dissuade him from taking Paxlovid because it wrecks your GI tract and has questionable effectiveness.

While I know about the GI side effects, I also know from your show that taking Paxlovid early in that first week is important to reduce symptoms and keep you out of the hospital during week two. It may even help with forward transmission. Every doctor or nurse I have spoken with has minimized COVID and the use of Paxlovid. Why the discrepancy? Other than promoting *TWiV*, which I do, how can I change this perception among clinicians? When I asked my doctor about COVID a few years ago, she said, 'You'll probably be fine." That didn't quell my fears." Why don't you take that one first, Daniel?

DG: Let's start with this. It's really frustrating. Unfortunately, that comment about you didn't learn about this in medical school, unfortunately, a lot of physicians, and I'm saying this, they stopped learning when they stopped learning, when they finished their training. A lot of them,

oh, the *New York Times*, the *Wall Street Journal*, *Fox News,* whatever their media of choice, that's what they hear, and there's a little bit of an echo chamber they get into. Is this how we approach urinary tract infections? “You'll probably be fine. Ninety percent of urinary tract infections, they get better on their own, so I don't treat those either.”

When someone calls up a provider, they really want evidence-based guidance, and the fact that Paxlovid is based upon a really great randomized control trial, hundreds of other studies demonstrating the benefit. It's what is recommended in the NIH and the ID Society of America guidelines and very solidly in the ID Society of American guidelines.

I just ask them like, "Why are you not following the ID Society of America guidance on how to treat this infectious disease? That would be the society of the experts. Why this discrepancy? Where did you get your ideas?" Sorry. Then the other is maybe you don't even have need to have that dialogue. Maybe it's time for you to find an evidence-based provider because we're out there.

VR: All right. Our second question is about masking not in a health care situation but at home and at schools and so forth. What are you doing? Are your kids wearing masks at school, for example?

DG: Yes, this is a challenge. It's, first off, is deciding which venues you're going to attend because some crowded poorly ventilated venues I will often choose not to attend. You ask yourself do I want to be sick? Do I want to have all the consequences? It could be COVID, it could be any of the other different things. First is making a decision about the venues that you're going to attend. If for some reason you really like to go to restaurants, can you go during a time when it's not as crowded? Is there outdoor seating? Things like that. I'm going to be heading to Singapore and Taiwan soon.

Yes, I was just making sure I have my N95s proper that I'm going to be wearing. The others you got to decide how comfortable are you with the social aspect of wearing a mask because there really is a whole emotion around this. I think a lot of people have to ask what are my personal risks? What am I willing to do? Because as we're seeing, there is a societal impact to doing this.

VR: Finally, what's your opinion about the CDC's push to seasonalize the virus and the vaccine? It's not seasonal, it's not like flu. Why is the vaccine offered only once a year? Shouldn't it be every four to six months?

DG: Yes, at least, for older folks, high-risk folks, we're really getting to this realization that – like we talked a little bit with the measles as well. There may be a population benefit to the more people getting vaccinated. Even if someone gets sick, maybe they're less likely to transmit it to others. Maybe there can be a population thing. Yes, you point out correctly.

COVID is not the flu. It's not just the winter. We have a summer surge right now. Our summer surge is as bad as last winter surge. One, maybe it makes sense to get these vaccines twice a year. Then as we'll find out, maybe we put all our eggs in the mRNA basket. Maybe there's some other more durable approach that we can do.

VR: All right, two quick ones. What Laurie wants to know is if you can use Neosporin in the nose to prevent COVID.

DG: I think we studied that where there was this whole idea that you get this interferon response to shoving these - They were not just shoving Neosporin or Bacitracin up their nose. We do not condone, we do not encourage this. If you look closely at the data, it's not really clear that this is such a great thing to do.

VR: There's no clinical trial either, right, Daniel?

DG: Yes, I remember this was the Akiko one where they were like, yes.

VR: Finally Michelle says, "My 35 year old son-in-law took Paxlovid on day one. Felt better. Felt sick a few days later. Week two congested chills. Lost smell and taste. Tested positive quickly. Is he still contagious on day 12?"

DG: I'm going to say no. [laughs] Let's just go through this. As we keep saying, the most contagion is contagiousness. Most spread is during the first five days. We see some 10% to 15% day six through 10. We really have not seen spread in a 35-year-old healthy individual after day 10. I remember there was this whole CDC recommendation, and I remember it was David Ho had this preprint, which I think later got published.

Where it really was a bunch of family members and suggesting that there have been transmission in people having symptoms during that second week. It was not after day 10 if you look at that. Yes, it was confirming that you do see some transmission during that second week but not seeing transmission after day 10. If your son-in-law was day 12 and wanted to have lunch with me, I would not be worried that I was going to get COVID.

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

DG: Thank you, and everyone, be safe.

[music]

[00:55:01] [END OF AUDIO]