This Week in Virology

TWiV 1016 Clinical Update

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

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From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1016, recorded on June 15, 2023. 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: Big day tomorrow at the FDA, Daniel.

DG: Yes. I think we're hearing some rumors about -

VR: Paul Offit, last time, I saw him yesterday in Philly, he said they're going to pick a new booster to give everybody over 6 months of age.

DG: It's interesting. I've heard Paul's, and I've heard someone else's take on things. I think by the time this drops, we'll have a conclusion. It's probably going to be a monovalent XBB, and there's going to be this split. People like Paul Offit are going to say, so what is this going to offer, and then based on that, who should get it? Other people are going to just say everyone needs to get it.

VR: I'm not getting it, Daniel. I have three vaccines. I have an infection, I'm good.

DG: Let's return to that. We got to return. First, I am wearing my polio bow tie, and people will soon understand why. Also, I'll say right up front, this is one of those episodes that is going to be longer than 21 minutes. We get to 21, I'll try to give people a heads up. They can pause, break it into two 21-minute digestible components. Right off, my quotation: “There are two ways to be fooled. One is to believe what isn't true, and the other is to refuse to believe what is true,” and that's by Soren Kierkegaard.

Let's start off with polio. *MMWR*, ”Surveillance to Track Progress Toward Poliomyelitis Eradication - Worldwide 2021-2022,” came out on June 9. We've discussed before that the primary means for detecting poliovirus is through acute flacid paralysis surveillance. Waiting

till people are paralyzed, which is supplemented by environmental surveillance of sewage samples.

Now, during 2021 through 2022, among 34, they refer to as priority countries experiencing or at high risk for poliovirus transmission, only, I added the only, 76.5% met national AFP surveillance indicator targets, and the number of environmental surveillance sites increased by 31%. However, substantial national and subnational AFP surveillance gaps persist. That's what we're hearing this report. They finish by saying high-quality surveillance is critical for the timely detection of circulating poliovirus and the rapid activation of outbreak response vaccination activities to stop transmission.

They recommend countries should maintain high-quality surveillance by monitoring surveillance indicators to identify gaps, enhance the sensitivity and timeliness of surveillance activities, and guide program decision-making toward polio eradication. I'm going to just mention an article that I just ran across, and actually was enjoying this morning, that's the benefit of getting up early, cup of coffee, and the latest *Nature.*

In *Nature,* we have, "Genetic Stabilization of Attenuated Oral Vaccines Against Poliovirus Types 1 and 3." We've discussed a few times that the benefits of the novel type 2 oral polio vaccine with promising clinical data on genetic stability, not 100%, and immunogenicity quite robust. Here the authors report the development of two additional attenuated vaccine candidates against type 1 and 3 polioviruses. The candidates were generated by replacing the capsid coding region of the nOPV2, the novel type 2 oral polio vaccine, with that from Sabin 1 and 3, these or three depending, two separate ones here.

These chimeric viruses show growth phenotypes similar to the nOPV2 and immunogenicity comparable to their parental Sabin strains, but are more attenuated. Experiments in mice and deep sequencing analysis confirmed that the candidates remained attenuated and preserved the documented nOPV2 characteristics concerning genetic stability. These vaccines were highly immunogenic in the mice as monovalent and multivalent formulations. There's also some editorials in the same issue of *Nature*.

I'll pull you in, Vincent, on area that you're -

VR: Yesterday, I gave a talk in Penn called, "Can we Eradicate Poliovirus/Poliomyelitis?"

DG: Was it just one word, you just said no and walked away?

VR: No, it was 45 minutes, followed by many questions. The bottom line is we can control poliomyelitis by good immunization, but we cannot eradicate poliovirus. Now, the first article you discussed, the surveillance, high-quality surveillance. In the U.S., the CDC does not do wastewater surveillance for poliovirus. Only when there was a case last summer did they do that. I don't know how they say we need high-quality surveillance when we don't even do it here. Secondly, many countries don't even have wastewater. There's nothing to collect.

DG: A lot of the wastewater is in the stream. You're drinking the wastewater.

VR: The only surveillance you have is for AFP paralysis, and it's not good enough because only one in a hundred or 200 people are paralyzed who are infected. It's not good enough for surveillance WHO. That's part one.

Second, nOPV2 and 3, big problem. First of all, as you mentioned, nOPV2 is not perfect. It still paralyzes kids. It still reverts, remains to be seen how much of an issue that is. They made it because OPV2 is a huge problem. Whenever vaccination drops, they have outbreaks of circulating OPV2. What do they do to quell them? They go back with more OPV2. They made nOPV2 to improve that, but it's not clear how better it's going to be.

The problem with OPV2 is it's very transmissible, more so than one in three. What are they doing for nOPV1 and 3? They're using the backbone of nOPV2 to put the capsid region of OPV1 and OPV3 on it. It doesn't make any sense, Daniel. It's going to be really a big problem. That's all I have to say.

DG: Sorry, you didn't have much to say on that, but that's OK. We'll move on to influenza. I was talking to the urgent care folks, and you almost wish like publications come out at like just the right time when this is on people's radar, but it should be on the radar because right now if we look at what's going on in the southern hemisphere, we can get a sense of what might happen to us come this fall and winter.

As agreed in the U.S., flu activity is currently low as it usually is this time of year, but in the southern hemisphere, where it's now winter, cases began increasing sharply in early May. We always looked to Australia, and we hear from the Australian Department of Health and Aged Care, this marks an earlier start of the season than some years as case numbers are higher than the five-year average. Some parts of Australia are seeing a spike in illness, and the highest number of cases are among children.

As mentioned, those flu patterns could be an indicator of what's to come in the U.S. It's OK, as we say, we've got these tremendously effective vaccines. We've got this robust antiviral thing called Tamiflu. Is that true? The article," Evaluation of Oseltamivir," that's Tamiflu, "Used to Prevent Hospitalization and Outpatients with Influenza, a Systematic Review and Meta-analysis."

Here's this whole idea. If we get hit with the flu pandemic, we're just going to give everyone the Tamiflu, it's going to be OK. The purpose of this analysis was to look at whether the administration of oseltamivir to adult and adolescent outpatients with confirmed influenza was associated with a reduced risk of hospitalization. They start off by looking at 2,352 studies, ultimately include 15. The intention to treat infected, that's the iTTi, population was comprised of 6,295 individuals with 54.7% getting Tamiflu. Across study populations, we had 53.6% were female, the mean age was 45.3.

People might be saying, oh, it's a younger population. What did they find? Overall, oseltamivir was not associated with reduced risk of hospitalization within this population. We get a relative risk of 0.77, but very wide confidence interval, meaning it might be 0.47, might go up to 1.27. Then they go on to look at those older folks, what about the older folks? They go on to report that oseltamivir was not associated with reduced hospitalization in older populations, here the relative risk was right there at 0.99, not seeing much, or even in those

patients considered at greater risk of hospitalization. Within the safety population, oseltamivir was associated with increased nausea. That actually was statistically significant. Vomiting also but not serious adverse events.

One of the things I always like, I'm always a little bit back and forth about these Cochrane analyses, these meta-analyses because you pile a whole bunch of cow pies, and it turns into gold magically. I think it's the pressure effect, but if you look at Figure 2o, you can actually look at each one of the studies, and you could see. Does it favor oseltamivir? Does it favor control? Do those confidence bars just stretch right across. As you pretty much can see across the board, some favor doing nothing, some favor oseltamivir, but in every case, it just goes right across the border. They're not reaching any statistical significance.

VR: What does that mean, that it's such a wide spread, Daniel?

DG: One of these things, I had a friend when I was doing my PhD, and he said, "Listen, if you need a statistician to show you an effect, if you need to study thousands and tens of thousands of people to show an effect, it's probably not doing much. I think that's what we're seeing here is, boy, even with some of these different studies, this is not a robust effect that you can pick up with these smaller populations.

VR: Is that because the drug just isn't as good as it could be?

DG: I think there's two issues here. One that we always come across and which you lose in a meta-analysis is timing. How often are you really getting this drug in within the first 48 hours? And that's always been a comment that we've made. The others, I don't know, even if you get it within the first 48 hours, like how robust is this drug? I think we need a better flu drug.

VR: Do you prescribe it liberally, Daniel?

DG: I don't think liberally. I try to look at targeting it to a population that I think might make a benefit. If we're beyond 72 hours, I'm very honest with patients, I really don't think we're going to see a benefit there. Within the first 48 hours and it's a population that is at risk of progression, at risk of having difficulties, I'm certainly willing to this. Last thing I want to do is over-prescribe it to a young healthy person who just wants a few hours quicker recovery maybe. Let's not lose this drug for whatever limited benefit it might have in the right patients.

We will move into the COVID update, and I am very excited to share the article, “Viral Emissions into the Air and Environment after SARS-CoV-2 Human Challenge: A Phase 1, Open Label, First-in-human Study,” published in *The Lancet Microbe*. A really nice summary here where they start off with the background. This is that human challenge trial in the UK, by the way, and they mentioned that effectively implementing strategies to curb SARS-CoV-2 transmission requires understanding who is contagious and when they're contagious. Makes sense.

Although viral load, really should be RNA copy number but let's be - on upper respiratory swabs has commonly been used to infer contagiousness, measuring viral emissions might be more accurate to indicate the chance of onward transmission and identify likely routes. Now, in this study, they aim to correlate viral emissions, viral load in the upper respiratory tract,

and symptoms longitudinally in participants who were experimentally infected with SARS-CoV-2. I will mention they do plaque assays here, so this is not just PCR.

As I mentioned right up front, these results are from the phase 1, open-label first in human SARS-CoV-2 experimental infection study at the quarantine unit, at the Royal Free London NHS Foundation Trust, London, UK, where healthy adults aged 18 to 30, well previously healthy adults, who were not vaccinated for SARS-CoV-2, not previously known to have been infected with SARS-CoV-2 and seronegative at screen were recruited, and what did they do to these folks? The participants were inoculated with an infectious dose of pre-alpha wild-type SARS-CoV-2 by intranasal drops and remained in individual negative pressure rooms for a minimum of 14 days.

Nose and throat swabs were collected daily. Emissions were collected daily from the air using this special Coriolis air sampler directly into face masks in the surrounding environment. They're doing these surface-enhanced swabs. They have a kind of a cool graphic of what they're doing. All samples were collected by these researchers, and tested by using PCR, plaque assay, or lateral flow antigen test. Not just do an RNA copy number, they're actually doing plaque assays.

Between March 6 and July 8, 2021, 36 participants 10 female and 26 male were recruited, and 18, so 53% of the 34 participants became infected, resulting in protracted high viral loads in the nose and throat following a short incubation period with mild to moderate symptoms. Two participants were excluded from the per-protocol analysis, only two seroconversion between screening and inoculation that they identify after the fact, post hoc.

Viral RNA was detected in 25% of 252 Coriolis air samples from 16 participants. 43% of 252 matched samples from 17 participants, and 27% of 252 hand swabs from 16 participants, and 29% of the 1,260 surface swabs from 18 participants. Not too many participants, but lots and lots of swabbing going on. I was sort of feeling bad for those two participants that they excluded, kind of sort of looked at the serology before they squirted the stuff up the nose and then said sorry, go away now.

Anyway, viable SARS-CoV-2 is collected from breath captured in 16 masks from 13 surfaces, including four small frequent-touch surfaces and nine larger surfaces where airborne virus could deposit. Now they go on to say viral emissions correlated more strongly with viral load in nasal swabs than throat swabs. That was interesting.

This is great. Two individuals emitted 86% of airborne virus, and the majority of airborne virus collected was released on three days. Individuals who reported the highest total symptom scores were not those who admitted most virus, didn't get a correlation there. Very few emissions occurred before the first reported symptoms, only about 7%, and hardly any before the first positive lateral flow antigen test, only 2%.

More detail here with before LFA positivity 0% in the air, 2% mask, 1% hand swab, 2% surface swab missions. A couple of weeks sort of bring it together here. Those lateral flow antigens, those rapid antigen tests were catching people right when they started to be contagious. We saw the Pareto principle with a few people being the super spreaders breathing out the majority of virus and most people not contributing much to onward transmission. They

observed short windows of high airborne viral emission, with only 11% of the infected participants contributing 86% of the airborne virus, giving support to this phenomenon of super-spreading individuals or events.

I really liked Figure 2. Folks, I recommend going and taking a look at Figure 2 because they break down each participant. You can actually look, you can look at the plaque assay results for the nose swabs, throat swabs, you can look at the air sampling, and all the other sampling, and you can really see like the timing, what symptoms, when it starts, when they're putting it on to the air, when they're not. Do you have any comments there, Vincent?

VR: I just want to say this is out of the UK, which I learned yesterday. Early in the pandemic, when they found that cats were being infected, they were considering killing all the cats in England.

DG: Wow.

VR: There you go, UK.

DG: OK. I did not know that. You got to know, you start some cat lover protest -

VR: Well, they should be because there's no reason to kill cats, even if - They didn't have any idea if the cats were going to be an issue or not. How could they do that without any data, Daniel?

DG: What is that like when they say things like well, with an abundance of caution, we slaughtered all felines in the UK? I'm going to be like whenever someone throws that abundance of caution, we're not going to do the science, we're not going to really know, we're just going to do something that we think -

VR: That's right

DG: All right. Back to COVID active vaccination. As Vincent, you, and I were talking, and the wind seemed to be blowing in the direction of an updated monovalent XBB booster for the fall. I feel like we have enough science here that you and I can have a little bit of a discussion about where people are falling down on this.

Paul Offit, who I think is a voice of reason, I think, who looks at the big picture when it comes to vaccines. Because we're not just talking about making recommendations here, we're talking about the impact of that recommendation, how solid it is, and the science, what we think it's going to offer. I do think we need to be really honest here, and I look forward to Paul's comments on this, and some I've seen so far make sense.

I do think we have to ask if a person has already been fully vaccinated, whatever that means at this point, I'll go ahead with say, three shots. Maybe they've had an infection thrown in there, and a lot of people have at this point, let's say they're under the age of 50. At this point, let's be honest, low risk of ending up in the hospital, low risk of dying, probably rather low risk even of Long COVID at this point. What is the benefit to vaccination?

The other, where I think maybe it's clear is, OK, someone is older, they have a number of risk factors even just a temporary reduction in the risk of even getting an infection might have some benefit. You got to get my falling on the Paul Offit's side of the spectrum here. Vincent, any thoughts?

VR: I think Paul is cautious because he would like to have data. He doesn't do the thing you just said before in abundance of caution.

DG: Abundance of caution where we just do something.

VR: As far as I can tell, for most people, the other vaccines are doing fine. Now, we don't know if they do a monovalent XBB derivative, we don't know how that's going to do. Sure. Is it all about antibodies, Daniel? That's the key. They think HVB is going to match the current strains with antibodies, and that's all that matters, and we know that's not correct. I find there's a little bit of disingenuity or disingenuousness in the whole process here.

DG: I agree. I think that what we've learned is, OK, sure, if you can get those neutralizing antibodies, maybe for three to four months, you're going to reduce your chance of getting even infected. Maybe going to keep those mucosal levels up, but as we see with flu, you're going to get it up, and then you're going to lose 15%, 20% per month, by the end of three and four months, you're back. That T-cell protection, the idea of jumping in quickly with effective antiviral therapy, I just think, yes, we need to think a little bit about this because -

I'm about to discuss this next article, which I think is really important. I will warn people, we're right here at 23 minutes, so if you want to take a breath, take a break, come back, we're about to get into something really exciting.

This is the publication, “Has COVID-19 Threatened Routine Childhood Vaccination? Insights from U.S. Public Opinion Polls,” recently published in *Health Affairs Forefront.* This is the buzz out there, the idea that, "Oh, what we did with COVID vaccinations has destroyed vaccine confidence." What is actually going on here?

They look at 21 nationally representative public opinion polls conducted shortly before or during the COVID-19 pandemic. They're looking 2015 through 2023 that met quality standards set by the American Association of Public Opinion Research. We're looking at solid polls here not just anything they pulled up to support a confirmation bias. They reported that only a little more than one-third, so 35% to 42% of the U.S. public, believes COVID-19 vaccines are very safe for most children. Most of our U.S. public is not convinced of that. Then they suggest that these low views of COVID-19 vaccine safety have not spilled over to routine childhood vaccines.

Let me go on. Views of routine childhood vaccine safety are actually relatively high with 69% to 70% of the public believing routine childhood vaccines are very safe for most children. Thought this was interesting. Republicans and Republican-leaning Independents, 86% saying they believe, for instance, the benefits of MMR vaccines outweigh the risks in 2023, along with most Democrats and Democrat-leaning Independents, 92%. Perhaps the most compelling evidence to suggest limited spillover from COVID-19 to routine child vaccination is that public attitudes on the safety of routine childhood vaccines have actually risen during the COVID-19 pandemic.

Which is interesting from a range of 54% to 61% believing they are very safe pre-pandemic up to 70% believing this by late 2022. There's this perception, these are the traditional, these are the safe vaccines, but what about the other shoe? After approval of COVID-19 vaccines for adolescents 12 to 15 in 2021, only 40% of U.S. adults indicated high trust in public health agencies to provide accurate information about the safety of these vaccines. Only a minority share of the public has expressed high trust in the FDA or the CDC to provide reliable information about COVID-19 vaccines throughout the pandemic, with only 25% to 28% and 31% to 36% reporting a great deal of trust, respectively.

In contrast, high trust in public health agencies to provide accurate information about routine childhood vaccine safety actually increased by 17 percentage points between 2019 and 2022, from 37% to 54%.

Let me bring all this back together. In summaries, these polls suggest that Americans have not grown more anti-vaccination during the COVID-19 pandemic, but rather more anti-mandate. I'm actually going to encourage people to go ahead, we'll leave a link. They actually have Exhibit 1, where you can see the questions and responses. Because I think, as we all know, it's really important when you do these polls to look at what exactly were they asking. I'm going to recommend that people go through and take a look at that exhibit, and then we'll leave in links to the *Health Affairs* results and also to a *CIDRAP* editorial on this.

VR: I think it's good that vaccines are not going to be a political issue, Daniel. [laughs]

DG: I think that - well, let's circle back to, we'll call the Offit and the other perspective. We have to regain that trust. People don't trust the CDC. They don't trust the FDA when it comes to COVID-19 vaccinations. We can't just keep pushing without the science. We can't just err on the side of whatever they want to say and being overly cautious or whatever it is. People want to hear the science. They don't want to put something in their body unless we can really confidently tell them this is the benefit. This is the expectation. Actually, there's this disconnect as we're seeing when you force people to do something, particularly when it's new, and we don't have the amount of education that is required.

Moving on to COVID. You tested positive. Your patient tested positive. What do you do? Well, Paxlovid is now licensed, and we will discuss a little bit. I'm sure this will keep coming up, but now that it's licensed, it has an FDA-approved indication, all of the marketing by the companies will have to stick strictly to that licensing. Prescribers now have the ability to prescribe off-label as we do with many other medications. Use our judgment if we feel like it's appropriate. I want to discuss the article, which actually is off-label prescribing, the article, “Successful Treatment of Persistent Symptomatic Coronavirus Disease (COVID-19) Infection with Extended Duration Nirmatrelvir/Ritonavir,” published in *Open Forum Infectious Diseases*.

This article describes two patients with hematological malignancies, ALL, ongoing symptoms, positive SARS-CoV-2 PCR tests for months that were treated with extended duration Paxlovid with reported improvement symptoms and PCR becoming negative. Sort of interesting there. I wonder how much we will learn from that.

Two, remember we've got remdesivir, but only in certain parts of the country is there easy access to that, that three-day early IV therapy within this first week. Molnupiravir

convalescent plasma in that certain subset of immunosuppressed COVID patients, again in the first few days. Then let's avoid doing harmful things. Lots of conversations this last week about just how much macrolide resistance was generated with the Z-Paks.

How many folks we're seeing with these invasive strep infections? Now most of our group A strep is resistant to those Z-Pak. Kids, adults showing up, they've got a sore throat, they get a Z-Pak. We actually recently had a hematologist in the area who died from strep throat. If you can imagine that, after getting a Z-Pak, it progressed because basically, they weren't being treated. We got to stop doing that.

COVID early inflammatory, lower respiratory hypoxic phase, the cytokine storm. This is always that time when we're trying to figure out who's at highest risk, who's going to progress.

We have the article, "Anemia as a Risk Factor for Disease Progression in Patients Admitted for COVID-19: Data from a Large, Multicenter Cohort Study," published in *scientific reports*. These are results derived from a retrospective collection of patients hospitalized for COVID-19 in Italy. Among the 1,562 patients included in the analysis, prevalence of anemia was 45%. Patients with anemia were older, had more comorbidities, and presented with higher baseline levels of procalcitonin, CRP, ferritin, and IL-6.

Overall, the crude incidence of mortality was about four times higher in patients with anemia compared to those without. After adjusting for 17 potential confounders, we've mentioned some potential confounders, the presence of anemia significantly increased the risk of death with a hazard ratio of 2.7 and the risk of severe COVID-19 odds ratio of 2.3. I'll leave a link to that. Remember steroids in the right patient, the right time, the right dose, the right duration. We continue to get anticoagulant guidelines from organizations such as ASH. We're still meeting and working on those.

Pulmonary support, remdesivir, if early enough, immune modulation, avoiding those unnecessary antibiotics and unproven therapies. I will spend a little bit here, actually, more than a little bit, on the late phase, PASC or Long COVID. I'd always hoped that this would become a significant part of our weekly presentation as we would learn more. The first article really puts this in context.

This article captures how devastating long COVID can be for so many. This is the article, "Impact of Fatigue as the Primary Determinant of Functional Limitations among Patients with Post-COVID-19 Syndrome: A Cross-sectional Observational Study," published in *BMJ Open*. This study reported on 3,754 adults diagnosed with post-COVID-19 syndrome, PCS, in primary or secondary care deemed suitable for rehabilitation. Ninety-four percent of the patients were of working age, so they're in this 18 to 65. The mean age was actually 48. Seventy-one percent were female, 89% were white. The majority, 51%, reported losing one or more days from work in the previous four weeks; 20% reported being completely unable to work.

The headline in *CIDRAP* was, "Fatigue Can Lower Long-COVID Patients' Quality of Life More Than Some Cancers." That's what we're seeing here. Many Long COVID patients were seriously ill. Their average fatigue scores were similar to or worse than those of people with cancer-related anemia or severe kidney disease. Their health-related quality of life scores

were also lower than those of people with advanced metastatic cancers, such as Stage 4 lung cancer.

Just to put this in context, this is not just people who are feeling a little bit tired and lazy. This can be a devastating disease. I think many people are still trying to understand why one person recovers from COVID while the next suffers for months and ends up with Long COVID.

In the article, "Post-COVID Condition in Patients with Inflammatory Rheumatic Diseases: A Prospective Cohort Study in the Netherlands," was published in *The Lancet Rheumatology*. Now, this is one of those sub-studies that use data from an ongoing prospective cohort study in the Netherlands. All adult patients with inflammatory rheumatic diseases from the Amsterdam Rheumatology and Immunology Center in Amsterdam, the Netherlands, were invited to participate in the study between April 2020 and March 1, 2021.

On March 10, 2022, all the study participants received a questionnaire on the occurrence, onset, severity, and duration of persistent symptoms during the first two years of the COVID-19 pandemic, independent of their history of SARS COVID2 infection. They also prospectively monitored a subset of participants who had a PCR or antigen-confirmed SARS COVID2 infection in the two-month period surrounding the questionnaire in order to assess the COVID-19 sequelae.

Now, post-COVID condition was defined as persistent symptoms that lasted at least eight weeks, started after the onset, and within three months of a PCR or antigen-confirmed SARS COVID-2 infection, and could not be explained by an alternative diagnosis. A total of 1,974 patients with inflammatory rheumatic disease participated, 24% of the patients with inflammatory rheumatic disease and 30% of the healthy controls had a recent SARS-COVID-2 Omicron infection.

More patients than controls fulfilled post-COVID condition criteria, so 21% versus 13%. This all sounds good. Then they noted that among those without a history of COVID-19, patients with inflammatory diseases were more likely to report persistent symptoms consistent with post-COVID condition than were healthy controls, the odds ratio of 2.5. If you never got COVID, you were about 2.5 times as likely to get Long COVID. This is really a bit of a warning for those just looking for confirmation bias and not understanding.

Now, one of the challenges here is that COVID-19 reported symptoms that are commonly used to define a post-COVID condition might be part of the clinical manifestations of, let us say, a rheumatic disease. The authors point out that this highlights the limitations of applying the current criteria for post-COVID conditions in patients with inflammatory rheumatic disease and suggests that it might be appropriate for physicians to keep a nuanced attitude when communicating the long-term consequences of COVID-19.

VR: Could it also be that other diseases that people have had cause similar long conditions?

DG: I do. I think that's true. I think this was a wake-up. I saw the headlines, and then I started reading the study, and then I started going, so you got to read the study. Don't just read the headline, don't just read the title, don't just read the abstract. Spend the time it takes to really look through the article. That's what we'll keep doing for you if you don't have the time.

All right. Now, what to do when one has acute COVID to perhaps prevent Long COVID? I got one published article, one that is a preprint, and I think that's going to wrap us up. Hang in there. The results of the COVID-OUT trial that we discussed in preprint form is now out as a published article in *The Lancet Infectious Diseases*, "Outpatient Treatment of COVID-19 and Incidence of Post COVID-19 Condition over 10 Months (COVID-OUT), a Multicenter, Randomized, Quadruple-blind, Parallel-group, Phase 3 Trial." This study is getting enough attention that I already have patients asking about getting a script to have ready to go should they get COVID to use to reduce their chance of getting Long COVID.

As we've previously discussed, this trial looked at a number of different treatments, and despite not seeing any benefit to ivermectin or fluvoxamine, they reported outpatient treatment with metformin was associated with reduced Long COVID incidents by about 41% with an absolute reduction of 4.1% compared with placebo. Giving us a number needed to treat to prevent one case of Long COVID of only 25.

Now, if one wants to use the metformin as it was used in the trial, I need to point out that the dosing they used was titrated. The metformin dose was titrated over six days. You had 500 milligrams on day one, 500 milligrams twice daily on days two through five, then 500 milligrams in the morning, and 1,000 milligrams in the evening up to day 14. Now, this is important. People are like, "Oh, I'm just going to give it out." The reason this is important because the first trial that they did before this one, the TOGETHER trial, assessed a metformin dose of 1,500 milligrams per day. No dose titration. We're just going to just go right for it.

This would be expected to cause side effects in a large proportion of people, which it did. This was stopped early, really with a substantial proportion of patients not tolerating the metformin without the dose titration. If you're going to be thinking about doing it based on this study, there is a specific and a little bit of a burdensome titration involved.

Now, it is interesting if one looks at the subgroup analysis, as it looks like the only groups with a statistically significant benefit were those less than 45, the unvaccinated, and those with a BMI of greater than or equal to 30. If you got a vaccinated person, if their BMI is not greater than 30, if they're over the age of 45, so just want to point that out.

I've been musing about this for a while. Lots of discussion about why and how might this work. Why would a diabetes medicine prevent Long COVID in young, obese, unvaccinated people? Could it have some helpful impact on the immune system or be an effective antioxidant? The authors of the above paper suggest in their discussion that experimentally, metformin has shown in vitro activity at a physiologically relevant dose against SARS-COVID-2 in cell culture and in human lung tissue ex vivo, suggesting that maybe this is a poor man's cheap alternative to Paxlovid.

Here is where we get the preprint, "Metformin Reduces SARS-CoV-2 in a Phase 3 Randomized Placebo Controlled Clinical Trial," posted on *medRxiv*. This is the analysis of specimens collected in the COVID-OUT trial that we just discussed. I will be replacing viral load with RNA copy number in the results here, but they report that the overall mean SARS-CoV-2 viral load reduction RNA copy number reduction with metformin was about half a log, 0.56 log, 10 copies per milliliter greater than placebo across all follow-up with a p-value of 0.027.

They report the anti-viral effective metformin compared to placebo was about this half a log on day 5 and about 0.67 log 10 on day 10. They have a nice figure where you can see the impact here.

VR: That is our nasal syringes swabs doing PCR. Is that right?

DG: That's what it is, yes.

VR: It's a very small effect.

DG: [chuckles] It is. It is interesting. If their argument is, this is mediated by a reduction in viral load. It's working as an anti-viral. Maybe I'm a person who gets a little bit sensitive about inequity, the idea that we'll give poor people this, and then we'll give rich people the Paxlovid.

VR: If you want to show an anti-viral, you better measure some infectious virus.

DG: Yes, I would recommend that, and also not impressed with half a log difference.

VR: Half a log is not. Is error.

DG: I will throw a couple at you just before we leave. Those of you still with us at 42 minutes, the article, "Persistent Serum Protein Signatures Define an Inflammatory Subcategory of Long COVID," published in *nature communications*. I thought this was interesting as these investigators evaluated the serum proteome in samples longitudinally collected from 55 PASC individuals with symptoms that were lasting greater than or equal to 60 days, a little shorter than that, three months after onset of acute infection in comparison to samples from symptomatically recovered SARS-CoV-2 infected and unaffected individuals.

Now, the analysis suggested some heterogeneity within PASC, and identified subgroups with distinct signatures of persistent inflammation, Type II interferon signaling, canonical NF-κB signaling, particularly associated with TNF, appeared to be the most differentially enriched signaling pathways, distinguishing a group of patients also by a persistent neutrophil activation signature.

They suggested these findings might help to clarify biological diversity within PASC, identifying participants with molecular evidence of persistent inflammation and highlight dominant pathways that might have diagnostic or therapeutic relevance, including a protein panel that they proposed as having a diagnostic utility for differentiating the inflammatory from the non-inflammatory PASC. They propose a serum diagnostic panel of three marker proteins. We can't order these easily, but CCL7, CD40LG, S100A12, and have proposed that with further validation, these proteins might help to differentiate inflammatory PASC from non-inflammatory PASC.

Now the last, this is the last treatment of Long COVID. We've been talking about the importance of identifying those with post-exertional malaise, and this week we have the article, "The Relevance of Pacing Strategies in Managing Symptoms of Post-COVID-19 Syndrome," published in the *Journal of Translational Medicine.* Here, the investigators retrospectively included patients meeting the WHO definition of post-COVID-19 syndrome,

PCS, who attended the Internal Medicine Department of Angers University Hospital, France, between June 2020 and June 2022.

Followed up until December 2022, pacing strategies were systematically proposed for all patients. A total of 86 patients were included and follow-up for a median time of 10, six to 13 months. Recovery rate was 33.7%. Improvement rate was 23.2%. They reported that patients who better adhered to pacing experienced significantly higher recovery and improvement rates.

I will close it up with what I've been saying for three-plus years, no one is safe until everyone is safe. I do want everyone to pause the recording here, go to parasiteswithoutborders.com. Click on that 'Donate' button. It's your support that helps us do what we do. I think going forward, I want to continue to provide education, information about COVID-19 and Long COVID. You will not be forgotten, but we need your support, and we are now doing our Foundation for International Medical Relief of Children fundraiser. We are right in the middle.

May, June, and July donations made to PWB will be matched and doubled up to a potential maximum donation of $20,000 for IMRC.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. "January weekly update that dropped on 6/10. You mentioned how useful to have a tool for understanding how bad for one's health the smoke in the air was aside from the color-coding system. In a recent Substack post, Dr. Jetelina shared the image from Berkeley Earth, which shows Daniel at an air quality index of purple or nine. It's half a pack a day of cigarettes. In New York, it was four times worse than that.

DG: Oh, my gosh. Two packs of cigarettes if you were out there all day. Some people can't be indoors. We have a homeless problem in New York. Last night, I was hanging out with Paul Kelly, the chief vet. I was talking to him about the animals, how did they do, because what do you do with all these animals that we have in the zoos. It's a bit of a challenge for people, animals who can't get out of that. There are a few minimizer comments I have to say on Twitter, I hate to say that. Otherwise, Twitter's nothing but joy.

Out west, we would get fires, we would have issues with smoke, but I have never experienced it here. I lived 20 years in my life in Colorado, never experienced the level of smoke that we had for that Wednesday.

VR: Amy writes, "I'm an epidemiologist in a state public health department. Thank you for highlighting the magnitude of the longstanding 40-year HIV pandemic in May 27. As you mentioned, at least three people in the U.S. acquire HIV every hour. We've made progress in transmission reduction, but not everyone and everywhere. I'm hoping you can expand a bit more on the comment Vincent made about lack of HIV prevention.

"Although we don't have a vaccine, we do have other tools, namely PrEP, pre-exposure prophylaxis. There are daily oral medications, and when taken as directed, PrEP can reduce the risk of acquiring HIV through sex by over 99% and can reduce the risk by injecting drugs up to 74%. Now, these drugs can have side effects, and that's where provider-patient relationships are so important. The goal is to become undetectable if you're living with HIV or prevent it altogether." A little bit of info there.

DG: That's actually great. I'll just echo everything that was mentioned here. I think that it's important to realize that that is ongoing. We're seeing tens of thousands of new cases. I like the number there. Every hour, three new people here in the U.S. are infected. There are ways to combat this. Education, letting people know that the risk is out there, letting people know that there's several options. The pre-exposure prophylaxis, we do quite a bit of that in my practice, where people are taking a medication, really dramatic reduction in the risk of getting HIV. We meet with them on a regular basis, discuss behaviors.

There are things you can do, but the first thing is to know that you might need to do something. Thanks for bringing this up.

VR: Of course, Daniel, PrEP is not available everywhere, right?

DG: That is a problem. Also, there's not always a lot of providers that are there to provide this. There's also not a lot of providers that are having the conversation, so patients are aware that they might benefit.

VR: Joe writes, "After hearing your episode last week, I advised my elderly patients/parents with comorbidities to request Paxlovid from their healthcare provider ahead of a three-week trip to Mexico. We think neither have had COVID yet. They were told no by their primary care provider because it can only be prescribed when someone has COVID symptoms or tests positive. I researched it myself and found an FDA fact about the full authorization, which says you follow the EUA guidance for prescribing and specifically calls out the question about travel. Can only be prescribed when symptoms are there or a positive test.

My question is, will this ever change? As a prescriber, is it off-label to prescribe it for travel? Please advise.

DG: You probably remember this conversation, Vincent. Do you remember Jamie Cedric Rutland? He's one of these TikTok digital opinion leaders. I like that more than SMI or social media influencers. We talked about the fact that even under the EUA, certain economic, you're wealthy, white person, you are getting Paxlovid, where Cedric Jamie is a person of color and he's like, "Listen, in my group, people aren't getting it, people are sticking to the EUA." What we have here is now Paxlovid is licensed, providers can actually use their discretion. We do a lot of prescribing off-label. We are allowed to use our judgment. Pharmaceutical companies are not allowed to market, or push, or endorse beyond the FDA indications. They are required to do the studies to show what is and isn't safe and it needs to be studied. We often do a lot of things.

I remember atrial fibrillation when I first started to train, we had no FDA-approved medications to actually re-control that rapid atrial fibrillation, so we didn't sit there with our hands in our pockets. We actually use medications that we knew would work. We've talked a lot about Paxlovid and how critical it is for a person to get started on that medication in the right window if they test positive. This is not a medication that people are abusing. This is a medication with care, you can look at the medication list, you can look at kidney function. I certainly don't want this to continue to be an inequity issue, which it has been for the last year.

VR: Do you need a positive test or symptom to get it, to get the prescription?

DG: To prescribe it off label? You do not. That is since it's licensed, that is now something that can be done.

VR: Yes, we have a few emails from other people who the pharmacists won't fill the prescription for them because they don't have COVID.

DG: I think that pharmacists need to step back and realize that, "Boy, a lot of those medications that we're prescribing, we do have the ability under our license. That's the responsibility we have to make these decisions."

VR: All right, good. Finally, Joyce writes, as a longtime listener, had a plan for taking Paxlovid while on Eliquis for Afib, should I come down with COVID. That plan is no longer viable after having been prescribed Flecainide and Metoprolol for 90 days.

DG: Metoprolol.

VR: Post-cardiac ablation. My doctor does not want me to worry about that unless/until I were to come down with COVID, but I worry about not being able to reach him quickly or if he wouldn't want me to take an antiviral at that time. I would very much like to know your thoughts on what my plan for dealing with this situation should be.

DG: Yes, particularly the Flecainide, I had a patient - Actually, it was a Tuesday night, and I probably spent half an hour looking through every single medication to figure out what would be the interaction? What would I do in this case as an older, high-risk individual. This becomes a challenge. You have to look at Flecainide, you have to look at Metoprolol. I understand the doctor not wanting to put in that effort right now before the problem is before them. You really got to make sure that you're going to have access to them because we do have a window. We've this three-to-five days. It would be ideal in my mind to have that discussion ahead of time, have the plan in place. As I keep saying, have a plan.

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

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

[music]