This Week in Virology

TWiV 1138 Clinical Update

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Guest: Daniel Griffin

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

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VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1138, recorded on August 8, 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: Daniel, today I know exactly what is on your bow tie.

DG: What is it, Vincent?

VR: It's the logo for Parasites Without Borders, and it's a hookworm, right?

DG: Ascaris.

VR: Ascaris.

DG: Yes. It's the globe, and then you've got Ascaris wrapped around it with all the fine details that it took us so many back-and-forths with Dickson to make sure it was just right.

VR: I remember he wanted the tip to be sharp, because that's correct, right?

DG: Yes. "Can't be rounded. The tip's got to be sharp."

VR: It's a very nice design. I like it very much.

DG: It was worth the back and forth. Sometimes, to be honest, Dickson drives me a little crazy, but it's worth it.

[laughter]

VR: OK.

DG: All right. I don't even know if Dickson listens to these, but it's a shame. Anyway, let's jump right in. We've got a quotation. We've got a lot to talk about. Actually, this first quotation is

from the article that we're going to talk about right afterwards. I really thought it was an important quotation. "Science is humanity's best insurance against threats from nature, but it is a fragile enterprise that must be nourished and protected."

VR: I like this concept of fragility because it really is. So many people think science is a robust enterprise that can survive anything, but it's run by humans, therefore, by definition, it's fragile.

DG: It really is. We'll circle back to this. We learn in history about the times of Galileo and, oh my gosh, dare he talk about this model we have of the universe where the sun was the center and planets circulating around that, and how important some of those things are to our understanding of the world and what we do today. As we're going to see, we're under siege. We continue to be under siege.

This is the article, “The Harms of Promoting the Lab Leak Hypothesis for SARS-CoV-2 Origins without Evidence.” This was the editor's pick in the journal, *Virology*, and actually was shared with me by one of our listeners. This is where my quote comes from, "Science is humanity's best insurance against threats from nature, but it is a fragile enterprise that must be nourished and protected."

As has been discussed repeatedly on, really the *TWiV* deep dives, and a lot from this article, the preponderance of scientific evidence indicates a natural origin for SARS-CoV-2. Here the authors point out that the theory that SARS-CoV-2 was engineered in and escaped from a lab, it dominates media attention, even in the absence of really - They say strong evidence. I'm going to say, really, in the absence of much evidence at all.

Now, the authors point out that there is currently no verified scientific evidence to support the lab-leak hypothesis. Moreover, the assertions of a particular *New York Times* guest arguing for the lab leak have been challenged by a growing body of scientific data supporting the zoonosis. Now, the article's five key points, that was *The New York Times* guest piece, the article's five key points are well refuted by the data as discussed, and, you ready for this, publicly accessible platforms by Dr. Paul Offit in the science-based podcast *This Week in Virology* and in the scientific literature.

I thought that was nice that they're actually quoting Paul Offit. They're quoting *This Week in Virology*, they're quoting the scientific literature.

VR: Good.

DG: Yes. In this article, the authors discuss how the resulting anti-science movement puts the research community, scientific research, and pandemic preparedness at risk. I should actually mention that it's actually putting individual scientists at risk. We'll share a little bit about that as we go on. Here's the critical part of this discussion, and much of this I'll just read from the article. I'm going to put my reading glasses on.

Despite the absence of evidence for the escape of the virus from the lab, the lab leak hypothesis receives persistent attention in the media, often without acknowledgment of the more solid evidence supporting zoonotic emergence. These unfounded assertations are dangerous. They place unfounded blame and responsibility on individual scientists, which

drive threats and attacks on virologists. It also stokes the flames of an anti-science conspiracy-driven agenda, which targets science and scientists, even beyond those investigating the origins of SARS-CoV-2.

The inevitable outcome is an undermining of the broader missions of science and public health, and the misdirecting of resources and effort. The consequence is to leave the world more vulnerable to future pandemics, as well as current infectious disease threats. The lab leak theory, in all its forms, casts unsupported blame on scientists, many of whom had warned of the potential threat of and need for effective countermeasures to prevent zoonotic transfer of viruses into humans.

Scientists who studied coronavirus or led the response to the pandemic have been accused of engineering SARS-CoV-2 or allowing to escape from the lab due to inadequate biosafety. Some have been unfairly accused of being part of an international cover-up or accused of taking bribes from the NIH. Yet more scientists have been attacked for using objectively gathered data to conclude that zoonosis is the most likely origin of the pandemic, or for simply engaging in communication of the evidence with the media and the general public. The unsubstantiated claims of the lab leak theory have provoked harassment, intimidation, threats, and violence towards scientists, were often vile in the online space.

An article in *Science* reported that of 510 researchers who had published on SARS-CoV-2 or COVID-19, 38% acknowledged harassment ranging from personal insults to threats of violence, doxing, and personal contact. A second survey, which included 1,281 scientists in a wide range of fields, found that 51% experienced at least one form of harassment, sometimes repeatedly for years.

Now, as they go on to write, intimidation and threats have significant and long-term consequences, as scientists have withdrawn from social media platforms, rejected opportunities to speak in public, and taken increased safety measures to protect themselves and their families. Some have even diverted their work to less controversial and less timely topics. We now see a long-term risk of having fewer experts engaged in work that may help thwart future pandemics and of fewer scientists willing to communicate the findings of sophisticated, fast-moving research topics that are important for global health.

Research that could prepare us for future pandemics has been deferred, diverted, or abandoned. Most worrisome for future preparedness, the next generation of scientists has well-founded fears about entering fields related to emerging viruses and pandemic science.

VR: I like that the focus here is not on just trying to refute a lab leak but to talk about the impact on science and scientists. I think it's really important to bring that because, as you've read, many scientists have been attacked, including myself. I have been called a deceiver by one of the pro-lab-leakers who will not be named. That's the way. When you don't have any ammunition, when you don't have any evidence behind your ideas, you resort to attacking people, ad hominem comments. It's very common in science and other fields as well. We see it in politics all the time, people calling each other names.

This is horrible in science. I like that this article points it out. Unfortunately, it's not going to get a wide reading because it is in a science journal, but we'll talk about it here, we'll talk about it on *TWiV*. Hopefully, we can promote this view. I like it very much.

DG: I'm hoping people share this. What really throws me the most is when physicians they're sort of having fun with the idea of the lab leak hypothesis. I don't they realize the danger. You want to ask, "What are you doing? You're undermining your ability to take care of your patients." You're undermining your profession. You're undermining the integrity of our profession because what are physicians but people who actually use science and evidence to inform the recommendations? If we don't do that, if we're just random and we just resort to opinion and anecdote, then really what is that MD or that DO or what does that credential actually mean?

We tell our patient, "Oh, I'm going to recommend this particular antibiotic," or this particular medicine for heart failure, or this intervention. The patient asks us, "What do you base that on? Just randomness? You read about it in the mainstream media or is this actually something that we've tested?" That's all really a lot of science, is just looking at the facts, saying, "Hey, half the people got this, half the people didn't. Who did better?" As opposed to, "Well, we don't even need to look because I can just tell you what's true." That's not the case.

I would love if a lot of physicians could read this article and really just think about, it's not fun, it's not silly to promote the lab leak. It's an attack on the foundations of the knowledge that we use to take care of folks and the knowledge that we use to keep ourselves safe. Why do we even bother trying to predict the weather and use any science there? Why not just flip a coin? It's, "I think there'll be a hurricane tomorrow," or "I'm not even going to watch the radar because no need to evacuate until after the fact." Let's hope -

VR: Unfortunately, Daniel, two-thirds of Americans believe in the lab leak idea. Unfortunately, they get their information from mass media, which loves that kind of story because coming from a lab would be an amazing story, so they go with that. They can't really distinguish the science. They hear someone say, "Oh, the science is all wrong," so they say, "Ah, that paper saying that the market was the epicenter must be wrong," but it's not.

They can't figure that out. That's the problem with getting nuanced science from mass media. Mass media cannot handle it. With a few exceptions of a few writers, mass media cannot handle it. People get their opinions from that and they're misled essentially.

DG: Yes. I worry about that. The data was really compelling for this being a zoonosis. The data is really compelling for this being a zoonosis. We've been warning about this forever. Yes, this is not great for politicians. It's not great for the spies and the CIA, who want us to give them all the money and resources. We continue to suffer with lots of zoonosis.

Where did tuberculosis come from? Where did some of the other coronaviruses come from? Where did so many of the maladies come from? Where'd the plague come from, et cetera? Zoonoses are the reality. We need to continue to do the research to keep ourselves safe. I'll step off the soapbox at this point. Let's not undermine what's going to allow us to stay safe, what's going to allow our children and our grandchildren to stay safe.

All right. RSV. We've got an update. August 6, we got the CDC *MMWR*: “Use of Respiratory Syncytial Virus Vaccines in Adults Aged Greater than or Equal to 60 Years: Updated Recommendations of the Advisory Committee on Immunization Practices, United States, 2024.” Our regular listeners may be aware of this. It might be a repeat for them, but that's OK. Let's be sure everyone's up to date on what's going on with RSV vaccines.

The 2023-2024 RSV season was the first during which RSV vaccination was recommended for U.S. adults aged 60 or over, using - at that point, it was shared clinical decision-making. Go in, talk with your provider, come up with a shared decision here. That did not go great. It was an OK idea, but now we realize in retrospect, maybe not as OK an idea as we had hoped.

On June 26, now with a bit more data, 2024, the Advisory Committee on Immunization Practices voted to update this recommendation to as follows: Recommending a single dose of any FDA-approved RSV vaccine. We're going to have three here. We're going to have Arexvy by GSK, Abrysvo by Pfizer, or mResvia by Moderna. This is now recommended across the board, all adults 75 and older, and then for folks 60 to 74 who are at increased risk for severe RSV disease.

The interesting thing, and we'll talk about the nuance here, adults who have previously received an RSV vaccine should not receive another dose. All the folks that got the RSV vaccine this last year, you're good for the moment. Let's just do a couple of comments. What is this based on? It's a move forward, it's a move back, depending on how you look at it. We've got these choices we've talked about. One of the drivers here was a safety issue. That safety issue was Guillain-Barré. We're going to talk a little bit about Guillain-Barré.

I mentioned the three choices. One of the choices is an mRNA vaccine. That's the Moderna mResvia. I want to say no cases of Guillain-Barré or other neurological events, myocarditis, or pericarditis were recorded within 42 days after the Moderna RSV vaccine. All right. No safety issues there. It didn't come from that. We have talked about the durability potentially of that vaccine relative to the others, but not head-to-head. Just standing on its own.

Now, what about the other vaccines? That was the mRNA vaccine. What about the protein-based Abrysvo by Pfizer, the protein-based Arexvy by GSK? Now, among the beneficiaries vaccinated, the GBS adjusted incident was 2.3 and 4.48 for the two different vaccines. 2.3 for GSK's Arexvy, 4.4 for Pfizer's Abrysvo. Now, what does that number actually mean? We're going to leave a link into the article, but I'm actually going to go to this table and we're going to talk about what are we really talking about.

For the Arexvy, that's GSK, they're saying somewhere between zero and 10 GBS cases per million recipients. We're talking about a reduction. We're going to reduce, in the over 75, the hospitalizations by over 4,000, the ICU admissions by over 600, the deaths by over 600. There may be somewhere between 0 to 10, they're estimating maybe three per 1 million vaccine doses GBS. You see less benefit as you get into younger ages, which is why it's conditional. In folks 60 to 74 with risk factors, we're going to see 2,839 reduced hospitalizations, 647 reduced ICU admissions, 246 reduced deaths. Then we get less benefit when you're in the lower risk folks.

Now, Pfizer's Abrysvo, and this is where a lot of the signal came from, in the folks 75 years and over, we're going to see similar, almost a 4,000 person, so 3,817 reductions in hospitalizations per million folks that got vaccinated, 561 reduced ICU, 539 reduced deaths. Then as we drop down into the other, we're going to see similar protection that we saw with GSK. Here we're actually going to see a number of estimated vaccine-attributable GBS cases at 16 and a range of three to 29.

A couple of things to think about, is it really the same for all the vaccines when you're thinking? The other, what are those risk factors? Straightforward, 75 and older, very clearly risk benefit favors vaccination, but what about 60 to 74? What are those risk factors? They actually have this box, which is nice. Cardiovascular disease, that would be heart failure, coronary disease, congenital heart disease. This does not include isolated hypertension. Chronic lung or respiratory disease, end-stage renal disease, diabetes type 2, but diabetes type 2 complicated by certain things, such as kidney disease, neuropathy, retinopathy.

If you're requiring insulin, some neurological conditions, liver disease, some hematological conditions, obesity with a BMI of 40 or older, immune compromise, residence in a nursing home is enough alone. Then there's also a list of some other chronic medical conditions.

VR: Daniel, with respect to the side effects, do we have enough people to be able to pick up a rare event like myocarditis?

DG: At this point, we do. That was why things were updated. As we start to get more doses out there, I'm going to say with the mRNA, the RSV vaccine, Moderna mResvia, not as many numbers, but GSK's Arexvy, Pfizer's Abrysvo, we actually have a really large number. These are pretty robust and we're still getting a bit of a range. We're only going to get more as we go forward, more information.

VR: Is myocarditis associated with respiratory syncytial virus disease?

DG: Not often with the actual disease.

VR: Maybe we won't see it in vaccine, because with COVID, obviously, myocarditis can occur at a low rate, right?

DG: It can. I think it's really interesting to sort of apples to oranges. There was a couple of recent articles. One was a lot of the anti-science people equate that 24-hour, mild, self-resolving post-vaccine myocarditis to the debilitating, going on to death and hospitalization myocarditis that we get with COVID. It's two different things. If you're just, "Oh, I got a little bit of inflammation. It resolved with no sequelae after less than a day," that is a completely different myocarditis than these patients I take care of for months, who go on to get fibrosis and all the other issues from the disease because they didn't get that vaccine protection.

VR: Yes.

DG: All right. Now an update on COVID. Not a good update. Things are not going in the right direction. Start with our map. Things are still troubling in Puerto Rico, where 6-to-8% of all the people who died, died due to COVID. A couple of other places, we're seeing 2-to-4% of

the deaths in Colorado and New York are due to COVID. Somewhere between one in 25, one in 50 deaths, those are due to COVID. We're really -

VR: Have you seen it in your practice, Daniel?

DG: Unfortunately, yes. Unfortunately, we're really seeing an uptick in the number of hospitalization and deaths due to COVID.

VR: What's the population here? Elderly individuals mostly?

DG: Yes. Mostly it's older individuals. I was talking about this in the ICU the other day, is that it's very different and it's not in our face. Back in the day, let's say you had 10 or 20 people that would progress, and we would end up putting them on a ventilator, they'd stay in a ventilator for a month or two, so they would fill the unit. Every time you would walk in it was all full of COVID.

A lot of times what we're doing now is we're having those conversations, did that really make a difference? We had single-digit survival during certain phases with that ventilation approach. Do you even do that or do you just say, "Listen, grandma, granddad, it's progressed. You're requiring a lot of oxygen." I have a really pleasant woman at the moment who's going down this road. It's just a question of, they're on high-flow nasal cannula, are we really doing anyone any benefit putting them in an ICU for a month or two and then having them die?

We're making them comfortable and they're exiting the world that way. Sometimes they're staying in the nursing home, being made comfortable in that setting. The deaths are still there, the hundreds of deaths. We're trying to do it in a less, I'll say more humane approach.

VR: No point being in an ICU the last month of your life, right?

DG: Yes. Be with your family and friends. This one woman who - She always wants to shake my hand. She claims she's going to run for president in the fall. Her family is around. They're with her. She's always got a joke, but she's on the high flow and I'm not expecting her to survive.

Now, we also have the tracking of the wastewater. This is something that we keep talking about, is this huge surge that we're seeing now in wastewater. A lot of parts of the country, I'll say in the South, in some of these other areas, let's see, is that the West looking at the color? Yes. The West and then the South. We're actually seeing levels that are up where they were during last winter's surge.

VR: Yes. They're still rising, it looks.

DG: Yes, there's still - A lot of these places there - Actually, all the way across the country, it's all still on the way up, so not going in the right direction. All right. What are the things you could do? As we keep talking about, we've got vaccination. We should have some updated formulations here in the coming weeks, so it should be later this month. We have the Pemgarda. That's the prophylactic monoclonal antibody. Seeing better and better access. We're getting some folks at Columbia on this. Some upstate New York folks up by Buffalo. I had a woman this week who we're arranging for her to get it.

Sometimes this doesn't all work. People test positive. We still have access to the NIH COVID-19 treatment guidelines and the ID Society of America guidelines. Number one, early treatment with Paxlovid. You do not delay. Each day you're losing efficacy. Paxlovid, remdesivir-molnupiravir, convalescent plasma in certain situations. Unfortunately, yes, Virginia, you are contagious when you get this virus. That's how you got it. Yes, we continue to have the isolation guidance. I know it's inconvenient, but the biology is the biology.

The second week, that is not the rebound week. Let's stop using that word. That is the early inflammatory phase. That's when steroids at the right time, anticoagulation guidelines, pulmonary support, maybe remdesivir if we're still in the first 10 days, in some cases, immune modulation. Then we're going to wrap up things today. We're going to talk a little bit about Long COVID. This week, we have the article, “Long Covid Defined,” published in *The New England Journal of Medicine*.

We read that "In recognition of the shortcomings of the existing definitions, the Administration for Strategic Preparedness and Response and the Office of the Assistant Secretary of Health in the Department of Health and Human Services tasked the National Academies of Sciences, Engineering, and Medicine (NASEM) with developing an improved definition for Long COVID that would take into account the needs of patients as well as the views and understanding of a range of experts." Here, this article, we get the process and rationale for the resulting 2024 NASEM Long COVID definition.

What's really nice is these are the committee members and lead staff who produced the definition, and they're sharing with us the experience and process of producing this definition. They share that the committee used a multiphase process of systematic engagement and information gathering. This process, are you ready for this? Included the use of focus groups, a questionnaire, a public comment portal, and several public meetings, including a two-day symposium. More than 1,300 people participated in these activities. This was some serious work.

They included patients, caregivers, public health and healthcare professionals, researchers, policy and advocacy professionals, payers, healthcare business professionals, and members of the public. What did we get? In box one, we get the Long COVID definition: Long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

What's nice is they actually include some case vignettes. They acknowledge the limitations and they point out that not only do many suffer from Long COVID, but thousands have already died from Long COVID. I think that's important to point out. This isn't just suffering. People have actually gone on and this is a disease that can progress, actually lead to death. There's a nice figure where they actually have - You've got your acute SARS-CoV-2 infection. It could be recognized or unrecognized. It could be asymptomatic. It could be mild. It could be severe.

They talk about some of the common symptoms going through, mention the post-exertional malaise, the persistent fatigue, cognitive impairment, the cardiovascular impacts on heart rate. I have to say, it's a really nice read. The authors conclude by writing, "A standard definition should enable better tracking of the burden of Long COVID and facilitate the design

and conduct of robust clinical trials that produce better treatments for this and other infection-associated chronic conditions. Above all," the authors, "we hope that this definition contributes to compassionate and effective care for all patients in whom Long COVID is diagnosed."

VR: Daniel, are we not using PASC anymore as long COVID did?

DG: No. Actually, I think it's good that we have the two because post-acute sequelae of COVID is a larger umbrella. We'll have people get COVID, and then let's say they go on and they develop pulmonary fibrosis, that may not be recognized as a Long COVID syndrome, but it definitely is a post-acute sequelae. They might have a new diagnosis of diabetes, for instance. We see increased diagnosis of a number of cardiovascular maladies, heart failure, et cetera.

I think it's great to still have that overarching umbrella of PASC, but then to understand that there's this Long COVID syndrome as well with the various phenotypes. I should, this we'll share on a future episode, but my Long COVID paper just got accepted to the open-access journal of the ID Society. It's going to be the - What is it? “Featured Editors Pick.” When we actually get that up and accessible, I'll make sure to share that with folks as well.

VR: Great.

DG: All right. Yes, that was a lot of work. All right. Long and middle, no one is safe until everyone is safe. We've been saying that for a while. I want people to continue to participate, continue to be part of this effort. I'd love everyone to pause right here, go to parasiteswithoutborders.com, click on that Donate button. We can't do this without your support. Every little bit helps us continue to do our work, continue to do our work, as well as support our partners. Right now we're doing our Floating Doctors fundraiser.

A buddy of mine and his son are down there in Panama volunteering at the moment, so shout out to everyone. August, September, October, we'll double your donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Here's a hint, shorter letters are more likely to get read.

DG: [laughs] I love that.

VR: If you write pages, it's very hard to read. We want to get as many in as possible, so try to be brief. Patricia writes, "I'm a nurse in DC and I've gotten COVID twice less than six months apart. Both times I received Paxlovid and both times it helped shorten my illness. However, it was a struggle to secure the prescriptions and added to a very stressful time. I was recently told by my doctor there is no guarantee that the next time I get COVID I will receive Paxlovid. As a nurse, that feels like a slap in the face.

Getting COVID on a Friday after work is not that unusual for nurses whose immune systems are finally taking off adrenal ‘hijack’ as they exhale for the first time all week and the virus says, 'Aha, here's my opportunity.' When you get COVID on a Friday, in addition to scrambling to find a doc to prescribe it after hours, scrambling to find a pharmacy to fill it, I now have to

make sure the charge is not too much more than $1,500 and circle back to the pharmacy to make sure they will honor my PAXCESS coupon. I'm just not sure this is tenable.

Yes, there are coupons. The one offered by Pfizer covers up to $1,500. That's helpful until they move the next goalpost. I know there's a limited amount of what you can do. Perhaps you can tell us what to do. Thanks for all you do for patients, doctors, and nurses."

DG: Patricia, this is- Thank you for bringing up PAXCESS. P-A-X-C-E-S-S. Folks, go check that out. This is something you want to go and get yourself set up ahead of time because this is - If you're going to have issues with costs being dropped on you, even with insurance, then this is a great way to actually access it, either for free or to get this up to $1,500 to really make it more affordable. It is a challenge.

When you get that diagnosis of COVID, time matters. This whole idea that you might have to be jumping through hoops and how do you go and who gets it from the pharmacy? I love that model where our high-risk people, much like this flu model we had where people were accessing the medicines or maybe they even had it there to access right away. That's an ideal thing, is that you've got your Paxlovid. As soon as you test positive, you can get started right away. Then when you feel a little bit better, you get your next script, because it's really - At this point, it's a question of when you're going to get COVID. Very few of us are going to continue and not have repeated infections over time.

This is really tough, that comment. I'm not sure why someone would make no guarantee that next time you get COVID, you'll receive Paxlovid. Again, this is an issue where we really have to support the science. EPIC-HR, the EPIC-High risk trial, really demonstrated this close to 90% reduction in progression. Nobody who got treatment actually died as opposed to people who didn't get treatment who did go on to die.

I like the fact that you pointed out, shorten my illness. There was a study that was, does Paxlovid basically shorten the period to being completely symptom-free? Which is really a high bar, because if you look a little more closely at that data, yes, people feel better, quicker on Paxlovid, but they don't necessarily have 100% resolution of all symptoms. The fever might go away. The cough might get less. You might feel half as crummy, but it really is associated with a reduction in how long you feel crummy.

The science is out there, hundreds and hundreds of articles, vaccinated people, unvaccinated people across the board. When we look at the people who are still dying - At this point, people have been vaccinated, people have had prior infection. Who's dying? It's the people that are not offered antivirals in the first five days.

VR: Charles writes, "Hello, doctors. As part of the clinical update, would you please go over lenacapavir?" Charles sends a link to a really interesting *New England Journal* article showing that twice yearly lenacapavir for HIV prevention in cisgender women, and they did this study in South Africa and Uganda, nobody on lenacapavir got HIV. What is lenacapavir, Daniel? What do you think of that?

DG: We talked about this on *ID Puscast*, and maybe we can get people to listen to that as well. It's in the name, lenacapavir. It's an antiviral, and what is it working on? Why is “cap” in the name, Vincent? What are they talking about?

VR: Must be the capsid, right, Daniel?

DG: Yes. Yes, it's catchy, lenacapavir. This is a long-acting antiviral that in this study, folks that got an injection twice a year, it's subcutaneous, you get a subcutaneous injection twice a year, zero HIV. That was better than taking a pill every day, than any of the other approaches out there. This is a pre-exposure prophylactic twice a year. It's not a vaccine. I know it's been covered even in some of the medical. They say, "This vaccine." I'm like, "It's not a vaccine." This is a biological, this is a medicine.

It's actually a wonderful model if you think about it. I'd love if there was some sort of Paxlovid that I can inject twice a year on top of my vaccine and never even actually get sick. Yes, this was amazing. This is really game-changing. Now, it's not approved yet. This data that was published in *The England Journal of Medicine* is just incredibly impressive.

VR: All right. We'll put a link to the *Puscast* in the show notes so everyone could go listen to that. Ellen writes, "Last year when I tried to get Novavax vaccine, I was told by one local pharmacist that it was only distributed in 10-dose vials that had to be used the same day. It would have cost him $1,000. If he made 10 appointments and one didn't show up, he would be out $100, so he chose not to carry it. In the end, after searching the Novavax website, I did find it in one nearby supermarket.

I'm wondering if that pharmacist was misinformed or whether, if he was correct, whether the same problem in vial size will inhibit availability of the new vaccine. Additionally, it's my understanding that the larger drug chains like CVS contract with only one manufacturer, which would further limit Novavax's availability. Not enough words to thank you for all you do."

DG: Yes, Ellen, there's a lot of truth here in what you bring up. That was an issue last year, these 10-dose vials. It was this idea, "Am I going to open a vial, and then who knows if the other folks show up for this?" A lot of times what companies like Novavax, the others will do is they'll have some sort of a deal where, "Hey, if you open the vial, you're going to somehow get compensated." They're not going to make you eat that $100 or $200 or how many doses you don't need.

That is one issue. There's usually a way to address this potential concern. The other you bring up, which is actually - This was an issue with the RSV vaccines. Some of those large chains will pick a brand. They'll say, we're only doing GSK. We're only doing Pfizer. That can sometimes limit. A lot of times that Novavax website can be the way to figure this out. The others get a whole bunch of people. We'll have to have some social networking so you can get those 10 people to all show up together. No, this is a little bit of a challenge.

The other thing, I was talking to my wife about this while we were walking the dogs the other night, is, in some ways, I feel like we did put a lot of our eggs in the mRNA basket and we didn't really provide the support to Novavax. We as a populace, we as the government, maybe we as some of the other companies out there stepping in as now people have stepped in to help Novavax move forward because I think it's great to have this other option, and we're all very curious to know about durability and what about Novavax versus the other?

We see data, we share data on Moderna versus the Pfizer-BioNTech, durability, number needed to treat, et cetera. I'd love to have more data on Novavax, and I certainly would love for this to continue to be an option.

VR: All right. Andrew writes - This is about metformin. He says, "There's started to be some literature that metformin may be useful for decreasing viral loads. There's a study out of the University of Minnesota that suggests that. We don't know what the interplay with Paxlovid and metformin might be." His wife is taking metformin for polycystic ovary syndrome and he has some questions about that. Let's take them one at a time. One, "For people in my wife's situation, I was curious about what your opinion would be whether she should continue to take metformin in addition to Paxlovid if she developed COVID."

DG: This was actually a study that UnitedHealth Group, some of my colleagues participated, David Boulware. I think Ken Cohen was involved in this study. This was a study where there were a number of interventions looked at. Part of the idea is that metformin may have some mild antiviral property. Maybe metformin, because of that, like other early antivirals, might have a protective role with regard to Long COVID. I think David Boulware was the one who commented about the "poor man's Paxlovid." If you can't get Paxlovid, you can do this very complicated ramp-up of metformin.

I'm like, "Let's not have poor people who can't get effective antivirals such as Paxlovid or even molnupiravir." That's one thing. Now, folks that are on metformin, I think it's fine to continue. I should mention, it's not you just start taking metformin. It's very challenging ramp-up because in some of the preliminary stuff, the idea of just giving people metformin, too much vomiting, too much intolerance, so a difficult load. I would say, people who are on metformin, go ahead and add the Paxlovid. I don't think that there's a problem. Now, is there a synergy? Again, you need to do the science to figure that out.

VR: His next question is saying, "If you google on the internet, many people are going to do this. They're going to do metformin and Paxlovid. Do you think this is unsafe and not beneficial, safe but probably not beneficial, or safe and possibly beneficial?"

DG: It is safe. Lots of my patients - There's a lot of folks out there on metformin. They get COVID, they take Paxlovid. I don't really see there being a safety issue. Again, it's one of those things. You're doing stuff and you haven't studied it. Is there a downside? We don't know that either. Safe but probably not beneficial. We don't know. I think that we have to be willing to say that we don't know. If this is something a lot of people are interested in, we've got to do the science. We've got to ask the question in a way where we can actually generate that knowledge.

VR: I think that answers his third question, which is, "Do you think it will turn out that the combination will be useful?" I have to do the experiments, right?

DG: Yes.

VR: All right. The last one is from Scott. "My question relates to an antiviral medication that is currently prescribed for COVID in Europe and not recommended in the U.S.. In June, I joined several family members on a European vacation. All six of us came down with COVID. I wound

up with the worst symptoms, perhaps because of my IgA deficiency, and was the only one to see a doctor while we were in Prague.

When I inquired about Paxlovid, the doctor said it wasn't available in the Czech Republic and was very expensive and another medication was better. The doctor prescribed a 12-day course of Isoprinosine along with azithromycin. Have studies shown that Isoprinosine is effective against COVID-19 infection? If so, why is it not prescribed in the U.S.? I believe it's known as immunovir in some countries."

DG: One is I hate when they just throw stuff out like this and they say, "Oh, it's more effective." There he is giving you azithromycin as well. There's no data that I'm aware of with any head-to-head trial of Isoprinosine showing that it's more effective than Paxlovid. There also is not the degree of robust data that we have on nirmatrelvir or ritonavir, so the Paxlovid. Doctors can say stuff, but I'm not really sure that he's -

VR: This is an immune booster supposedly, right?

DG: Immunomodulator is the whole idea.

VR: As far as you know, it hasn't been subject to clinical trials anywhere.

DG: Exactly, yes. Not that I'm aware of.

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

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

[music]

[00:44:16] [END OF AUDIO]