This Week in Virology

TWiV 1142 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 1142, recorded on August 22, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from not New York -

Daniel Griffin: Singapore.

VR: Singapore, Daniel Griffin. I was wondering if I should let you say it. Welcome, Daniel.

DG: No, that works. Hello, everyone. Yes, I'm off here in Singapore, and I'm going to put my glasses on. Hopefully, David's going to get our audio up to the high quality that our listeners are used to because I'm doing the Apple AirPod thing. We'll see. Let's jump in. We got a lot to talk about, actually. Today is an exciting day. I'm going to start with the quotation. This is from Clarissa Goenawan from the book, *The Perfect World of Miwako Sumida*. "People reveal themselves in the small moments, not the big ones."

I just really like that. One of the big reasons that got me interested in medicine is I actually like people. I joke about it, I don't like huge crowds, but I do like individuals and I like the chance to connect and get to know people, and as negative people get at times. When you really get to know people, everyone has their small moment, their charm.

As Vincent pointed out, I'm recording from Singapore. I'm going to be doing a few lectures here and then off to Taiwan for about a week to figure out timing on how we do the next one. It was nice, when I got here, I was actually met by a *TWiV* fan, Vincent.

VR: Nice.

DG: Julie Huang. Yes, she's involved in communication. She's originally from Taipei, Taiwan. It was interesting. She was in the Netherlands during the early days of the pandemic. Interesting to - I'm always curious, like, where were you? What was it like? You can imagine a Taiwanese young professional woman living in the Netherlands. Yes, it could be isolated. Your family's half a world away. Then last night, I had a chance to have dinner in a restaurant with really a spectacular view of Singapore, so I have some sense of where I am.

Both of them were born and raised in Singapore. They lived through the pandemic here. It was interesting to compare their experiences. They're both married, they have kids. One of them didn't at the time, one of them has a seven-year=old. They had a child through the pandemic, young child. Just really interesting, the different experiences. I expect people are going to write all kinds of PhD theses on how different countries-- and then even, I think, the human experience of the pandemic. Now, Vincent, you've traveled more than I have lately. You've probably got a lot of accounts of different experiences around the world.

VR: Oh, yes. It was a life-changing event. I don't think we appreciated it at the beginning, even going through it, but now in hindsight, wherever I go, I ask people, "What were you doing? What happened? How did your country deal with it?" I think it's interesting to see how different places dealt with it in their own ways. You hear it different from what we heard in the press. The U.S. press tends to not always give the right account, let's put it that way.

DG: All right. Let's move into our next section. This is a little bit of a change. I know people had wished this hadn't been a change, but mpox. A number of us have been following this closely, but things seem to be escalating. We have the risk assessment for the EU/EEA of the mpox epidemic caused by monkeypox virus. It's disease mpox, viruses monkeypox. Monkeypox virus clade 1 in affected African countries.

At a high level, we read that the mpox virus, MPXV clade 1 epidemic, has been affecting the Democratic Republic of the Congo, the DRC, since November 2023, and recently spread to several other African countries, including Burundi, Rwanda, Uganda and Kenya. The size of these outbreaks could be larger than reported due to under-ascertainment and under-reporting. I think we're sort of expecting that to be true.

On the 15th of August 2024, one case of mpox clade 1b was reported in the EU, and more importantly, they're expecting more imported cases. In this report, they're actually giving a heads up. A couple of things here. They say in countries reporting clade 1 cases, human-to-human transmission through close physical contact and through both sexual and non-sexual transmission has been documented. Although age groups are represented among cases infected with clade 1, preliminary data show that infections by the clade 1b, so it's clade 1a and b, we'll go more into that, concern mostly the adult population, so 1b adults, but 1a is mostly impacting children.

Unfortunately, there still are some uncertainties about the main transmission routes, transmissibility, severity, natural disease history. Now, just an update on what to be looking for. Maybe this is for clinicians, but hey, it's also for everyone else, see something, say something. Mpox symptoms usually appear six to 13 days, up to 21 days after the infection. The clinical manifestation of disease includes general febrile symptoms. This distinct rash, these papules, sores on the mucosa, back pain, muscle aches, and the rash can spread quickly throughout the body within about three days of the initial symptoms.

A couple of other updates here. OK. I think we mentioned last week Sweden. Now we heard that mpox virus was detected in Pakistan. At least I was looking at this. We're not really sure yet about the Pakistan detection. Is that the West African clade 2 or the Central African clade 1? I'm keeping up on that. A report of four cases of mpox in Taiwan. I want to point out that is clade 2B. That's West African.

I got an email from Amy. Actually, we did get the report from Thailand. Yes, this is clade 1. This is from *The New York Times*. Thai confirms its first case of new deadlier mpox version written by Sui-Lee Wee. Here we read that health officials in Thailand say that they had confirmed a case of the version of mpox that prompted the WHO to declare the global health emergency. Second time we've seen this newer and deadlier. It's newer. It's newer for us. Clade 1 Version identified outside of Africa.

Just a little primer. What is clade 2 versus clade 1? Earlier outbreak, this is the one that we had the last few years, that was driven by clade 2, specifically clade 2B. This is really a sexual contact. It was really men who had sex with men proved to be the most at risk, the most number of cases. We did see some in children. We saw some in women. Behavioral change and vaccinations really curbed that spread.

Clade 1 has two subtypes. We've got a clade 1a and a clade 1b. While b may be predominantly through MSM and having sex with men sex, clade 1a appears to have spread mainly through heterosexual sex, household contact, exposure to animals. So far, it appears that it's young children who are most vulnerable to this subtype. A different story here.

What about this case in Thailand? What's the story? Thai officials said that the infected person was a 66-year-old European man who worked in an African country with an ongoing outbreak. They don't tell us which country. The man has a home in Thailand.

According to health officials, the man flew to Thailand from Africa, transiting in the Middle East, arrived on the evening of August 14, and the next morning, he started to develop a fever, found small bumps on the skin. Now, we hear from the general director of Thailand's disease control department, people should be washing their hands with soap and water, alcohol, gel sanitizer. I love these next ones. Avoid close contact with strangers, avoid going to places where there were outbreaks, and avoid rodents such as rats and squirrels from those places.

Here is, in my mind, a little bit of a game-changer. We have the news release from the NIH, “The Antiviral Tecovirimat is Safe, but Did Not Improve Clade 1 Mpox Resolution in the DRC.” It's just like, "Hey, we've got this drug. It's safe, but ineffective." This has me thinking of that reassuring message that our listeners, Rich Condit and I are always like, "It's OK. We have vaccines. We have an effective antiviral." Unfortunately, that gets cut short here to, we've only got vaccines.

The antiviral drug TPOXX, tecovirimat, did not reduce the duration of lesions. It's looking at children and adults. This is clade 1 mpox in the DRC. Now, this is a randomized placebo-controlled trial. In the study, these are people in a study getting a higher level of care. There was a 1.7% overall mortality. About one in 50, one in 60 people were dying among the enrollees. This is a little bit better than just the background mortality of 3.6 that we're seeing in the DRC; 3.6 is quite a bit, one in 25, one in 30 folks not surviving. They're not really attributing much here to this tecovirimat. As they say, these findings are disappointing. They give us essential information. We've really got to continue research and come up with something else.

VR: Daniel, can I ask you?

DG: Yes, jump on in.

VR: Clade 1b is the current one spreading out of Uganda into other countries. The idea that it's more virulent, I think we have to be careful because the kind of medical care you get in the country can determine how the outcome of an infection is. It could be very different in Uganda versus the U.S. or Europe, for example. I think headlines saying more virulent strain are just not useful. What do you think about that?

DG: Yes, I have to say, Vincent, this reminds me so much of all the reports of the different variants, like, more contagious, more virulent. We're not really sure. A lot of people, and we've talked about this before, they're concerned about what's going on, and should this get to their country, what will the mortality be? Are they going to really see 3% to 4% mortality in Sweden, in Thailand, the United States? I'm going to suggest probably not.

VR: I wanted to ask you one more question. People here in the U.S. are saying, "What should I do?" What do you answer? Not everyone needs to be vaccinated, right?

DG: Yes, and I think that's going to be a little bit of the challenge. If you're going to go - For instance, I go to Uganda, people go to Kenya, is there going to be a recommendation for travelers? With clade 2, there really was a high-risk population. You could really target that high-risk population.

I think we should have done it in a better way, where people didn't necessarily have to be stigmatized. They could just be like, "Hey, I'd like to get that mpox vaccine." You didn't have to be like, "Hey, why do you want it? What makes you qualify?" Not everyone necessarily wants to tell you. Ideally, it would be just more open. Do we start extending this? Who really needs to get vaccinated, Vincent? It's the people in the DRC. It's the people in these areas.

You think about the number of people in the United States, hundreds of millions of people. Do we really need to vaccinate everyone in the U.S.? Do we need to vaccinate everyone in Western Europe and in Thailand? Not really. The best response to this, actually, is to help the people there in these countries. If they can get vaccinated, the problem ends right there. Actually, a nice thing here is people are going down that road.

The U.S. actually announced, USAID actually said, "Hey, we're going to give an extra $35 million to really help with this response in Africa." That's going to bump us up to about $55 million from the U.S. to help. Yes, what's this going to go? This is going to go towards the vaccines. What are those vaccines? The main workhorse is actually the modified vaccinia Ankara. That's the JYNNEOS. We call it JYNNEOS in the U.S., Imvanex in the European Union, Imvamune in Canada. I don't think you need to remember all these names. This is this attenuated, non-replicating vaccinia virus. It's probably a two-dose. You get one dose, another dose. Four weeks apart. In the U.S., this is approved for prevention of smallpox and mpox.

Now, unfortunately, or how you look at this, the vaccine is made by this small Danish company, Bavarian Nordic. They've got this - It's very nice looking. They've got their ownKvistgård, commercial-scale manufacturing facility just northeast of Copenhagen in Denmark. People know I'm a huge fan of Denmark. I've already got this on my next list of places to visit. That's really going to be the workhorse. I think, as you point out, who needs to be vaccinated? People in the DRC need to be vaccinated.

VR: Daniel, is there any evidence for respiratory transmission of this virus?

DG: Very minimal. I was listening to our last episode, where I kept saying, generally, "generally," sort of qualifying the transmission. There were cases of clade 2 West African. They'd end up in the hospital, severe disease. We'd put them in, basically, isolation, negative pressure room, much like we would tuberculosis or anything else. I think part of it is you do this calculation of, "Oh my gosh, what a horrible disease if that gets to anyone," versus the likelihood, is it really going to spread? Is it really respiratory spread? Very minimal evidence for respiratory transfer. Really contact. That contact can be fomites. It can be bedsheets. It can be things that a person touched.

VR: OK. Not having a respiratory component is really going to limit the extent of spread compared to, say, SARS-CoV-2.

DG: It's a game changer. If this was respiratory, yes, it means COVID-19 with this just horrible, disfiguring - Yes, what a change.

VR: Yes, I think people are very nervous about mpox. I think you should not worry as much because it's not a respiratory, it's not community spread and so forth.

DG: Yes, I have to say that some of the cases I saw, it's a fate worse than death. Some of them, just disfiguring. A woman that we had there at Columbia, she had it down through her throat and her mouth. We've seen some young men basically have to go through reconstructive surgery because of just the devastation and scarring. Yes, it can be pretty horrible. Fortunately, yes, we do have some understanding of the transmission. We have vaccines. We really have the tools.

Yes, a nice segue into COVID. We've got a lot to talk about COVID. We've got a number of more states in that 2% to 4% when we look at the map. People told me I was confusing Mississippi and Alabama last week, because I think it's Mississippi that's in the 2% to 4% and Alabama sitting right between the two, between Mississippi and Georgia. I have my states right this time maybe. New York, Iowa, Texas, Tennessee, Florida, New Jersey, Connecticut, Massachusetts, really a number of states that are up in that 2% to 4% percentage of deaths due to COVID.

The wastewater is, some of these levels still rising almost everywhere. You get this hint maybe in the South, maybe in the Midwest. You might be getting a little bit of an early peak, but still really high levels across the country. I brought this up in a while, but I bring this up because we're going to be talking about the new vaccines here in a moment, spoiler alert, and what is going on with the variants. For a while, there was a lot of talk about the JN.1, and now we're seeing lots of KP variants.

Again, to vaccines, again, a little bit of a primer there on what's going on and what we're thinking about. That brings us into hot off the press: "FDA Approves and Authorizes Updated mRNA COVID-19 Vaccines to Better Protect against Currently Circulating Variants." The U.S. Food and Drug Administration approved and granted emergency use authorization for updated mRNA COVID-19 vaccines. This is the 2024-2025 formula, to include a monovalent single component that corresponds to the Omicron variant KP.2. They say strain, but all right.

I saw this hot off the press. I was trying to figure out, because I'm a day ahead, Vincent, did I get this news ahead of you? No, it drops when it drops.

Here's the story. Early June, the FDA advised manufacturers of licensed and authorized COVID-19 vaccines that the COVID-19 vaccines should be monovalent JN.1, but based on further evolution, the agency updated this and said, "If you could do KP.2, that'd be great if feasible." I just want to point out, this is updated mRNA vaccines by Moderna and Pfizer-BioNTech. This really raises two questions. One is, where's Novavax? The second is the variant issue.

Novavax, for starters, Novavax filed for U.S. EUA for their 2024-2025 formula in June. They're working productively with the U.S. FDA as they complete their review, giving them whatever extra information they need. It is interesting, their COVID-19 vaccine is going to target JN.1. We're going to talk a little bit about what does that actually mean. They say they're going to target JN.1, the parent strain of currently circulating variants. They report that this will provide coverage cross-reactivity against all the JN.1 lineage viruses, including KP.2.3, KP.3, KP.3.1.1, and LB.1.1. That'll be our protein-based vaccine option.

What is KP.2? Fortunately, there was a nice primer that was actually just put out the last day or two by the ID Society of America. For context here, this is all Omicron. Then several emerging variants have been given these specific names according to the amino acid changes at key sites in the spike protein. See how I changed mutations from what they had to say there? Everyone's forgotten how to use those words, Vincent.

We had those FLip variants, which have an L for F change at amino acid site 455 and an F for L at site 456 in the backbone of the XBB.1.5. Then we have the FLiRT variants, right? These are JN1 lineage. The FLiRT variants are so named because they exhibit the amino acid changes and F for L at position 456 and R for T at position 346. The emerging KP1, KP3, and LB1 are all considered to be in this family of FLiRT variants. This also includes all the other descendants, KP.2.3, KP3.1.1.

This KP.2 variant is also called JN.1.11.1.2, maybe to make people feel better. It's a descendant of the JN1 variant, contains several amino acid changes that are associated with escape from the vaccine-needed immune protection from our last year's monovalent vaccine. There's this whole question, Vincent, about, is it going to really matter JN1 versus the KP.2? [crosstalk]

VR: I was going to ask you that. I wanted to ask you, Daniel, is there any evidence that KP1, KP2, or JN1 makes a difference? Because if Novavax can make JN1, why do we need KP2?

DG: Yes, it's interesting. Here in Singapore, they're going to actually use the mRNA, for instance, I think the Pfizer is supplying a JN.1 mRNA vaccine for the fall here in Singapore. We don't, honestly, know. I think that's the challenge. There's this idea, let's get as close to the starting line as we can, because we expect things to continue to change. A lot of what drives the changes are antibodies in people, and then people get exposed, and then there's this selective pressure. It's not like the virus is happier with all these changes, it's just these are fitness-within-a-context changes. Yes, so I don't know.

What I would love to see, in all honesty, and we're going to get on this because we've got some other articles coming up, but a really nice comparison of Novavax efficacy, for

hospitalization, disease, compared to the different mRNAs. I would love to also see at a place like Singapore, where you actually have the JN1 mRNA, so you can see how much is it head-to-head difference with mRNA versus the protein platform versus which variant you chose to target in your vaccine. Imagine that, asking for science. [laughs[

Should we get our vaccines? Here we have the article, "What is the Economic Benefit of Annual COVID-19 Vaccination from the Adult Individual Perspective?" published in *JID*. This is, does getting that COVID-19, does it benefit you financially? Here, these researchers developed a model, a Markov model, representing the potential clinical and economic outcomes from an individual perspective in the United States of getting versus not getting an annual COVID-19 vaccine.

What is a Markov model? Very simplified, don't yell at me, statisticians. This Markov model is a model used to predict certain types of changing systems. Things are changed, but you assume that you have a current state. You just forget about where things were going before, you say, here we are today, if I make one change, what's going to happen? That's our Markov model.

Now, using their modeling, they suggest for an 18-to-49-year-old getting vaccinated at its current price, they say $60. If you had to pay that yourself, it can save the individual on average $30 to $603 if the patient is uninsured, and $4 to $437 if the patient has private insurance. Apparently, depends on how good that insurance is. As long as the starting vaccine efficacy, are you ready for this, against infection is greater than 50%.

The weekly risk of getting infected is 0.2%, corresponding to an individual interacting with nine other people per day. You get to calculate how gregarious are you, how much do you spend. Then if you've got 50-to-64-year-olds, the cost saving increases to $111 to over $1,000. It's up to $1,706. This is for people without insurance. This is not about are you going to die, this is looking at the whole issue. Are you even going to get infected? Are you going to end up going to see a doctor? Are you going to end up in the hospital? The risk threshold, of course, changes by how gregarious.

An interesting, I think they're trying to make this argument that it's in your best interest financially to go ahead and get that vaccination. Now, how good, I guess, were the current vaccines when we followed them out? The XBB vaccines. We have the article, Early COVID-19 XBB, 1.5 Vaccine Effectiveness Against Hospitalization Among Adults Targeted for Vaccination." This is the VEBIS hospital network Europe, October 2023 through January 2024, published in the journal *Influenza and Other Respiratory Viruses* as a short communication.

Here we get the results of a multi-center test negative case control study covering the period from October 2023 to January 2024 among adult patients aged 18 or older hospitalized with severe acute respiratory infection in Europe. They provide early estimates of the effectiveness of the XBB COVID vaccines against PCR-confirmed SARS-CoV-2 hospitalization. That's disease. I like this as an endpoint. Vaccine effectiveness was, let's say, only 49% overall, ranging between 69% at 14 to 29 days and 40% at 60 to 105 days post-vaccination.

The XBB vaccines conferred protection against COVID-19 hospitalization in the first 3.5 months post-vaccination with a vaccine efficacy of greater than 70% in older adults. I think

we're just seeing a replay here. These current boosters - Remember, you're comparing this against a background of immunity. This is not the same metric we had in the early days when you said, "Oh, but this is at 95%." This is 49% and 70% compared to a background, getting the booster or not. We're also seeing that efficacy drop as time goes by.

VR: Daniel, is the drop due to waning immunity or a new variant or lack of good memory induced by these vaccines? We really don't know. We're just assuming that neutralization assays tell us everything and we make a new vaccine every six months, which seems to me is not driven by any science.

DG: The big challenge is also the uptake. We keep going down this road. We've got a lot of focus on these neutralizing antibodies and, yes, do we get as much focus on the T-cells? I guess here we're seeing, yes, over time, are we losing this because of a mismatch with the variant or are we losing this just because that's what happens over time with these vaccines?

The second study to look at this issue is COVID-19 in pregnancy, a retrospective cohort study, and these are the results of a retrospective cohort study looking at pregnancies in Northwest London general practice. This is a nested case control analysis. The study included 47,000 pregnancies among 39,218 women, 57% of the pregnancies women had at least one dose. Here's a comparison. Women admitted to the hospital were much less likely to be vaccinated, only 22% of those, versus the ones that stayed out of the hospital with majority, 57%.

Novavax. The article, “The Novavax Heterologous Coronavirus Disease 2019 Booster Demonstrates Lower Reactogenicity Than Messenger RNA: A Targeted Review,” published in *JID.* This is really this question we keep talking about. People are like, "I really want to get another one of those vaccines. I was down for a day or two. Is there something I can get that's not going to do this?"

I think this is pretty timely. They're going to look at reactogenicity, the occurrence of any local systemic side effects, because this really plays a part, particularly now. Early on, people are like, "Just give me that vaccine. Whatever happens, I want to have that protection." After the second, then people are like, "Yes, I don't know anymore if it's going to be a cost to me. We talked earlier about a financial cost, maybe that's $60. Here's that impact on your life, like hey, I get this on a Friday afternoon, and then Saturday, it's just a wash.

Here, the researchers conducted a targeted review of the reactogenicity of authorized approved mRNA and protein-based vaccines, Novavax. They found that the mRNA-based boosters showed a higher incidence and an increased severity of reactogenicity compared to the Novavax protein-based. They actually talk about - remember, this is an analysis putting stuff together. They're looking at a number of studies.

One of the studies was from the National Institute of Allergy and Infectious Disease. We hear the incidence of pain, tenderness, swelling, erythema, fatigue, malaise, headache, muscle pain, or fever was higher in the BNT group or the Moderna group compared to the Novavax. Really evidence suggesting that the Novavax as a heterologous boost is just a little easier to take. They've got a nice graphical abstract where you can see a little bit of this.

VR: Daniel, I think that many people still do not trust the mRNA vaccines. Having a protein-based vaccine, a more traditional vaccine is a good option. I think that's the strength here,

and why you and I are bullish on Novavax, for that reason. What I would like to know, though, is whether you get more durable immunity with protein compared to mRNA. That's something we don't know.

DG: Yes, I think that's correct. There's a lot of ideas, but we always want the science. Is one really better than the other? What's great is choices. You are right. There's a lot of people that still have concerns about mRNA. Oh, it's gene therapy. It's great to have this other option. Yes, I'm a little worried about the delay and when Novavax is going to get to market, because the message is very clear from all the public health resources. We're encouraging everyone, as much as possible, to go ahead and get the updated shot, whether it's important that it's updated or not, whether it's just important that people get the shot because you get this rise in protection.

As we talked about with measles, is there some sort of population benefit maybe we're hoping we'll get from that? Is there some sort of decrease as far as impact on the health care system? Across the board. Particularly, we're in the middle right now of a rise, so that normal idea, oh, wait till like early November of protecting against the Christmas, December holiday, January holidays, the Jewish holidays, Hanukkah, I guess. What are we forgetting? What other holidays are going on in December? Kwanzaa. I think my youngest brother celebrates Kwanzaa.

Right now, for the oldest among us, we're just, hey, go ahead. We're in the middle of a wave. Get a shot now. You probably recommend to get another shot after New Year's. For folks that just had it, this is important. If you just had it three to four months, you should wait and then consider getting it. For a lot of folks, they want to give Novavax a few extra weeks. People starting school, people about to travel, things like that that might impact the timing and choice.

Passive vaccination. We have Pemgarda, with the changing variants. We had said 70% risk of reduction. There's a preprint out there from David Ho's lab, sort of questioning with neutralization antibodies. Is it still as effective with the KP2? Let's move right into the early viral phase. We keep hitting on this, NIH treatment guidelines, ID society guidelines. You got to understand this disease. The first week is the viral replication phase. That's when we can do the most good.

Number one recommendation is Paxlovid for five days. I know people say five versus 10. Remdesivir, we say five versus 10. Five was as good or better. We have yet to prove that any further than five days is worth it with the Paxlovid. There are drug-drug interactions. People complain about that metallic taste. I shouldn't say complain. They report, they share. Number two is remdesivir. That's the three-day infusion. Molnupiravir, convalescent plasma in certain cases, and isolation because you can spread it to others. Remember, 85% during the first five days, but we still see spread day six, seven, eight, maybe a little past there.

Then two, the early inflammatory week. I think people keep needing a reminder here. COVID has not turned into a five-day illness. You got that five-day viral replication phase, crummy, fever, and then boom, it's that second week. This is what I worry about, this early inflammatory week. This is when people can feel rotten, this is when they get hypoxemia, this

is when people can end up in the hospital and not survive because of these things. What do you do during that second week? There really isn't a lot. You've missed your window.

It's that first week we can do the most. Steroids at the right time, in the right patient. People can take Afrin, they can take Mucinex, they can take Tylenol. If they're going to take an ibuprofen or something like that, then, let's be careful that they're not on a drug that interacts. Anticoagulation guidelines for those in the hospital, pulmonary support, remdesivir, maybe some immunomodulation.

All right, and now we have a little bit here in our late COVID section, the late-phase PASC/Long COVID. This trying to decide, does it go here, does it go in children? We have the article, "Characterizing Long COVID in Children and Adolescents," published in *JAMA*. Here, the objective was to identify the most common prolonged symptoms experienced by children, 6 to 17. We're going to break them down into school age, 6 to 11, and adolescents, 12 to 17. Hoping that some of those 12-to-17-year-olds are still in school, and looking at how they might cluster into different phenotypes.

These results come from a multicenter longitudinal observational cohort study, the RECOVER Pediatric Observational Cohort Study, RECOVER-Pediatrics. Participants were recruited from more than 60 U.S. healthcare and community settings. Now, ultimately, in this analysis, we've got 898 school-age children, 751 with previous SARS-CoV-2 infection, and 147 without, mean age 8.6, 49% female, 11% Black or African American, 34% Hispanic, Latino, or Spanish, 60% were white. The median time between the first infection and symptom survey was 506 days. This is really far, 506 for the school age children, 556 for adolescents.

In models adjusted for sex and race and ethnicity, 14 symptoms in both school-age children and adolescents were more common in those with the SARS-CoV-2 infection than those without. Amazed they keep finding folks that have never been infected. These symptoms affected almost every organ system. They're working on creating this index. This index, if you go through it, it emphasizes neurocognitive impacts, pain, gastrointestinal symptoms in school-age children, change or loss of smell, taste, pain, fatigue, malaise in adolescents. They end up defining these four PASC symptom phenotypes.

What are the big takeaways here? This is an article we're spending some time on. The big takeaways are that we see Long COVID in kids. There was a recent retraction, an article suggesting that we did it, which was flawed in so many ways. We see Long COVID in kids. It's different from what we see in adults. It's even different between the adolescents and the younger children.

I'm going to wrap up before we get to emails with, no one is safe until everyone is safe. I'm hoping we would pause the recording right here. Go to parasiteswithoutborders.com and click Donate. Even a small amount helps. We're doing our Floating Doctors fundraiser, where 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. Edward writes, "I've been a long-time listener to *TWiV* and Daniel's clinical updates. I applaud the evidence-based approach you have promoted. Your insights have been of great value to my

clinical practice, also personally. However, I have to take issue with Daniel's interpretation of Paxlovid rebound. Daniel has repetitively stated that the Paxlovid rebound is a manifestation of the T-cell inflammatory response to the infection.

While this teleologically makes sense, I cannot find literature to support this position. Rather, when searching PubMed for Paxlovid rebound, I find only one article theorizing that viral dynamic models explain the rebound phenomenon based on the idea that five-day Paxlovid treatment started near the time of symptom onset reduces the depletion of target cells but does not fully eliminate virus, thus allowing the virus to rebound once treatment is stopped.

According to an article published in the *Annals of Internal Medicine* November 2023, viral rebound occurs in one in five patients receiving Paxlovid. The accompanying editorial goes on to speculate that the most compelling explanation for the relationship between N-R treatment and COVID-19 rebound is that five days of treatment at the current dosage is inadequate.

The editorialists refer to the mathematical model mentioned above and state that early treatment with NR leaves too many target cells susceptible to infection, and complete suppression of replication-competent virus would be expected to lead to rebound. I would appreciate your comments." Edward Gold is Chairman of Medicine at Pascack Valley Medical Center.

DG: We got to keep having this discussion, and I think this is fine. The first thing you want to ask is, when people got on the news and they said, "Oh, I had Paxlovid rebound, my patients have Paxlovid rebound," now, what were they talking about? Were they doing quantitative PCRs every day on their patients? Were patients just saying, "I started to feel better, and then, boom, that second week, I really felt crummy"? As a clinician, you're talking about the latter. You're saying, "I've got a patient, and they said, 'Hey, I was starting to feel better, and then, oh, my gosh, that second week, I just got hit like a truck and I feel crummy."

One is just to point out, we've been seeing that dynamic to this illness since the early days. A week one with viral replication, a week two with the cytokine storm, the inflammatory phase. That, I have to say, is completely different. The week two, the return of symptoms, that we see with and without Paxlovid, and actually, the severity of those symptoms during week two is actually reduced in people that get Paxlovid.

Now, the second question is, oh, what about the viral genetics? What about those PCRs that I check in the nose? Yes, what is the goal of Paxlovid? Is the goal to completely get rid of viral replication? That seems great from a science standpoint, but as a clinician, we're taking care of patients, so our goal is not necessarily to get that PCR down, but it's to make our patients feel better. It's to make our patients stay out of the hospital. It's to reduce mortality. It's to reduce the chance you end up in the ICU, the chance you end up on a ventilator.

Five days of Paxlovid does that. Five days of Paxlovid, when we started with the EPIC-HR, close to a 90% reduction in people progressing to end up in the hospital. One of the people got Paxlovid, the people who didn't, people get Paxlovid, zero folks ended up on ventilators, zero folks died. You actually had a number of people in the control group that ended up on ventilators and ended up dying. That's a big thing.

The second is, have we actually looked at this? By we, I mean Pfizer. Has Pfizer compared five days to 10 days as far as anything that matters as far as patient outcomes? They presented this data at CROI, where what they did is they took-- They went, which I thought was low-hanging fruit, I was surprised they didn't show it, they said, "Let's take immunocompromised people and let's compare five to 10 days and look at outcomes."

You know what? No difference. No benefit to the 10 days. We've looked at this, and I think what ends up happening is when people talk about Paxlovid rebound, they're confusing what they might see when they chart out a bunch of PCRs. Yes, it starts up in the millions and you might get a little bit of a bump into 100,000, and oh my gosh, that's failure. Is it really failure? The failure would be as if our patients had issues, and Paxlovid in the unvaccinated and now we see data in vaccinated has a really tremendous job of reducing the risk of progression to hospitalization.

As we're seeing with the vaccines, 50% reduction in progression to hospitalization. You still have a lot of folks out there that are going to end up in the hospital. They're going to end up not surviving. The data for this last year, we saw over a thousand people a week still dying of COVID in the U.S. Paxlovid is going to reduce that number even further down.

VR: I would suggest that searching PubMed for Paxlovid rebound is the wrong search term.

DG: I was like, are there UFOs? I looked, and oh my gosh, look what came up.

[laughter]

VR: All right, DJ writes, "I'm a retired band director who does a lot of substitute teaching in schools with lots of newcomers to North America. In the run up to COVID, I was out buying hand sanitizer and cold medicine already in February. What precautions should I be taking regarding mpox? It's not spread respirally," is that a word? "In the band room, there's plenty of spit around. Hand sanitizer, gloves, I would appreciate your thoughts. Incidentally, I'm triple-vaxxed and a NOVID, at least as far as tests can confirm, which I laughingly chalk up to having been exposed to every possible germ during 40 years of teaching little spit factories."

DG: All right, I like that, d.j, and G-A-Y as far as his last name. This is reasonable. You're concerned about it, you're hearing about it. "I'm in a school. There's all these kids." As the band teacher, you're going to be in and out. I see lice and stuff in some of our musical teachers. Right next to someone and they're teaching them piano, or you're describing a lot of these brass instruments and all this saliva flying everywhere.

Yes, as Vincent and I talked a little, no evidence that you're going to see respiratory spread of the mpox disease, of the monkeypox virus. Wash your hands. That's what we're recommending. People really start to spread this disease when they have lesions. I don't think you need to go overboard with hand sanitizer or gloves. Yes, this would be a situation where you probably have someone nervous like this and like, "Hey, can I just get the vaccine and worry less?" Reasonable consideration.

VR: Ellen writes, "Twice now I've heard that doctors are telling their patients that Paxlovid is not that effective against the current strains of COVID for people over 65 with or without underlying conditions. Is this true? If not, where are doctors getting this information? These

are reputable doctors in progressive cities who I wouldn't think are susceptible to misinformation."

DG: Yes. Ellen, let me answer this. Unfortunately, yes, reputable doctors in progressive cities are still susceptible to misinformation. Here's the way to look at it. Early on when we do the EPIC-HR, the epic-high-risk study, so let's say you've got an individual who's 65 years of age and older, got a 20% chance of ending up in the hospital. You give Paxlovid and that 20% goes down to 2%. That's huge. No one dies. No one ends up on a ventilator. That's huge.

Now you've got vaccines and we're seeing with the vaccines that 20% is now maybe down to 10 or even less. We'll use 10 because the math's a little bit easier. 10%, most of your patients, 90% of your patients are going to be fine. They're not going to end up in the hospital. There's a big psychological difference there. Now you give them Paxlovid and that 10% goes to 5%, let's say. Now it's not like your anecdotes are going to give you the feedback, but Paxlovid still works.

We have now hundreds of real-world studies on efficacy of Paxlovid. The big thing here is that people have immunity. People are vaccinated. They have prior infection. What can we do to address that over a thousand deaths per week in the U.S. from COVID-19? The big common denominator here is they're not being offered Paxlovid. Then when they die, the doctors seem to shrug and say, "Oh, well, this or that," but come on, we can save hundreds and hundreds of lives each week if we do a better job prescribing Paxlovid.

As far as changes in the virus, the changes we keep talking about are changes in the spike protein. The Mpro, the target of Paxlovid, has not changed and this drug continues to be effective.

VR: Rich wants to know, is there any indication that Long COVID can occur after an asymptomatic infection?

DG: Rich, unfortunately, yes, a number of folks with Long COVID had asymptomatic infections. Sometimes we trace back in history, oh, everyone else was sick, everyone else tested positive. You felt fine. Here we are three, four months later and you've got the classic historical, biochemical, physiological abnormalities that we see in Long COVID.

VR: Finally, Carrie writes, I may need to travel to urban and rural Kenya for work. I'm a middle-aged female, mostly healthy, except for a type of autoimmune arthritis, so any infection can cause a flare which can be debilitating. I'm looking forward to getting the updated Novavax vaccine when it's available, given the latest mpox outbreak, and potentially staying in hotels with questionable housekeeping, being on planes, crowded locations, having limited access to quality health care, getting an mpox vaccine, and traveling with Paxlovid seem to make sense. What is the optimal sequence of getting Novavax and mpox vaccine to ensure an effective immune response? So far, I'm not on biologics, so I think I would generate an immune response to both vaccines.

DG: Yes. With you, there's a few subtleties here. One is we have not done any studies where we give people Novavax and mpox at the same time, but we do have a lot of studies where we go ahead and give people multiple vaccines at the same time, and they get the flu, and they get the COVID shots. We don't know exactly, but I would not think our understanding of

vaccines that there would be a problem getting the Novavax and the mpox vaccine at the same time.

Logistically, there may be a little difference in when it happens. I'm not sure there really is much that we know about the optimal sequence of the Novavax and the mpox. There might be a priority, much more likely to get COVID than you are to get mpox, so prioritizing the Novavax vaccine, seeing how you do. The other twist for you is you have some immune issues, the autoimmune arthritis, potentially could get a flare. For you, it may help to space them two weeks apart, just so if there is any a reaction, you have some sense of what was responsible for that.

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

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

[music]

[00:52:09] [END OF AUDIO]