This Week in Virology

TWiV 1144 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 31 August 2024

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

[music]

From *MicrobeTV*, this is *TWiV, This Week in Virology*, Episode 1144, recorded on August 30, 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. I am just back, as Vincent knows, from Taiwan. In Taiwanese [foreign language], or in Mandarin [foreign language].

VR: Can you fluently speak on the street, Daniel, in those countries?

DG: The problem was, I think that they overestimated my ability to understand Mandarin. They honestly did. I can pick up some, but I was presenting for the Taiwanese Medical Association, it was like 1,000 people. They were back and forth between Mandarin and English and I was beyond struggling. Twenty years ago, I could speak and read and write and I did translations, but my Mandarin is just -

[laughter]

VR: Before you go on, Daniel, what's on your tie? Is there anything?

DG: It is Friday. This is sexually transmitted infection day. There is hands clapping. This is the clap.

VR: Clap.

DG: It's one of my favorite Friday bow ties. Let's start off with a quotation. Actually, we have a lot to talk about today. This is, "Everything must be taken into account. If the fact will not fit the theory, let the theory go." That's Agatha Christie, one of my favorite authors. We're going to mention a lot of things. I don't think we can mention everything. There's so much going on.

West Nile virus. Perhaps our listeners have heard or read, "Fauci recovering at home following hospitalization for West Nile virus infection." This is a quotation, "I really felt like I'd been hit

by a truck," he said in an interview, "I have to tell you, I've never been as sick in my life ever. By far, this is the worst I've ever been with an illness."

VR: I guess it was worse than his case of COVID. Right?

DG: Apparently, much worse, actually. I was putting in a link here.

VR: Do you take care of West Nile patients ever, Daniel?

DG: Actually, yes. Right before I left for Singapore, we had a lady. She came in, and it was one of those she had a fever, a headache. This woman in her 30s, I believe, sick enough that she ended up in the hospital with West Nile. The way we test for it is we'll do serology testing. Sometimes we can do viral PCRs as well. She did not have the encephalitis. There's a neurological - Long history with West Nile, actually.

Back when I was in Colorado in Fort Collins, I diagnosed the first case of West Nile in the state of Colorado. It was before you could actually order any testing. I actually had to reach out to the CDC and do the testing. We were sending testing to Atlanta to be done, so it's interesting. Then a couple of years later, we were the epicenter of West Nile virus out there in Colorado.

VR: People of Fauci's his age, he's over 80, he's more likely to have severe outcomes of West Nile, right?

DG: You can die, actually. We have a number of deaths every year from West Nile. If anything, I feel like it's underdiagnosed. A lot of cases we end up seeing at Columbia, where they've been sent from the "outside hospital" and have a CSF West Nile virus PCR that's positive. Older individuals can actually not survive this infection. Supportive care, there's no specific antivirals that we use.

The next one, polio in Gaza. Actually, we're going to also say polio in India. Vincent, you can explain why that's such a big deal. Just between each of us, Vincent, you, and I are recording three podcasts each today, and not all the same. I did an *ID Puscast* [crosstalk] this morning. You just did a *This Week in Virology* deep dive. We just both did *This Week in Parasitism* together. Between the recording, I got this message, which we'll talk about. Polio vaccines are coming to children in Gaza. Sewage samples taken in Gaza have tested positive for poliovirus.

The warning was, it was just a matter of time, but there's already been cases of acute flaccid paralysis reported in Gaza. We got a couple of update, I could actually see it. "Supported by a US $5 million commitment, this polio vaccine campaign is going to inoculate 640,000 Gazan children." This is going to be WHO, UNICEF, and UNRWA.

VR: Israel has agreed to a ceasefire so that this can be done, which is great.

DG: Apparently, there's strips. There's these three days during which they're going to have these pauses, and they're going to allow the vaccines in. What vaccine are they using, Vincent?

VR: Unfortunately, they're using nOPV2, which is the infectious attenuated Sabin vaccine derivative. This is being used because it's easy. You just have it in a vial and the kid drinks it,

but it reintroduces Sabin. The case of polio in Gaza is caused by vaccine-derived poliovirus type 2. The more you put OPV2 into the population, the more such cases you have. What should be done is to use an activated injected polio vaccine, but they've decided to use nOPV2. It will just perpetuate this endless cycle of vaccine-derived viruses causing paralysis because there always are people who are not immunized everywhere.

DG: Yes. This was an interesting thing I came across. I think this was in Singapore or Taiwan. I forget where I ran to. I think I was actually at WONCA, this world primary care conference in Singapore recently. It was about a week ago. There was a woman there from the Philippines. The whole issue of antibody-dependent enhancement came up with the Dengue vaccine, which I have to say, was not actually true.

Some politicians all got behind this, and at the end of the day they're like, "Oh, 12 children died because of the Dengue vaccine." It turns out it actually wasn't even true, but by the time the truth comes to light, everyone's lost interest, but because of that, it really triggered a lot of vaccine fear. What she was saying as a primary care physician in the Philippines, that the people were still absolutely fine with people getting oral vaccines, but they did not want the needles.

Really interesting. There's this perception. The needle vaccine is much safer than this oral vaccine approach, but because of this growing distrust, for whatever reason, it was really political in the Philippines, the babies were ready, the moms were totally fine with the oral vaccine, but no to those injectable vaccines.

VR: This case in Gaza, the paralytic case is caused by OPV-derived polio. You'll keep getting those as long as you use it because it will not eliminate itself. That's why IPV is preferable because IPV will not cause paralysis.

DG: Yes. They give us this number, 645,000. How many doses of the OPV do you need to vaccinate 645,000?

VR: Let's get out our big-button calculator.

DG: [laughs] OK.

VR: [chuckles] 1.8 million, if I got the right number, divided by 640,000. Two doses, you need 640,000.

DG: 640,000 children thereafter, you need two doses.

VR: 1.28 million, they need two doses.

DG: What happens if you just give them one, Vincent? What's the problem?

VR: You get sub-effective immunity and it doesn't help. It gets worse. They say in the article, more than 1.2 million doses have arrived for 640,000 children. It's over, so that gives them a little leeway in their estimates. That's fine. There's also a case in India, as you've mentioned, and India has been free of polio since 2014. Now there's a case of - It's again, vaccine-derived,

which tells you, again, the virus is circulating in India, they didn't pick it up, and there are enough unimmunized people to have a kid get paralysis.

Remember, for every kid who's paralyzed, there are about 100 cases of infection without paralysis, so the virus is circulating. It's vaccine-derived. The disturbing aspect of the India story is that they're downplaying it. They're saying, "It's just vaccine-derived poliovirus, we're not worried."

DG: Just.

VR: It's not just. It's poliovirus, which can paralyze you and transmit. There's no difference. This is a big problem.

DG: We will keep letting people know. I have to say, Vincent, apparently there are a lot of *TWiV* fans in Singapore and Taiwan, so people are listening.

VR: Great to hear.

DG: We'll keep spreading the good science. What a week. There are 21 people with sloth fever. We cover this in a little depth on the *ID Puscast*. Sloth fever, what to know about the deadly virus. This is Oropouche virus disease. In general, this is a viral disease. We see cases in Brazil, Bolivia, Peru, Colombia, Cuba. We have a CDC, “Oropouche Virus Disease among U.S. Travelers, United States.” I guess, apparently we start carrying when it comes to our shores.

This is actually a good *MMWR* worth reading. They describe these 21 U.S. residents returning from travel, apparently to Cuba, 20 Florida, one here right in New York. An interesting thing about this viral disease is there tend to be these recurrences. People get better and then they relapse. They actually go ahead and they - They don't talk about pregnancy status in this report when they describe the people because pregnancy status was felt to be a confidentiality issue.

What did they see: 95% of people have fever. Most people have muscle aches, headache, significant fatigue, joint pain. One of the interesting things, about a quarter of the people have these Dengue retro-orbital pain presentations. Number of people, three of them were hospitalized. No one actually died from this, but there have been deaths reported recently in Brazil. One of the biggest concerns, which has actually triggered a Pan American Health Organization alert, is vertical transmission of this virus associated with adverse pregnancy outcomes, actually including fetal deaths and congenital malformations.

Now checking before people go to these areas. Mpox, oh my gosh, are we ever going to get to COVID? The monkeypox virus, can we get them to update that name, has now spread to Gabon and Gabon's health ministry announced the nation's first mpox case. This was a resident who had recently spent two weeks in Uganda. We learned that this 30-year-old man arrived back from Uganda with fever, fatigue, and a rash, hospitalized, placed in isolation, and they're doing some contact tracing.

What are our options here? I've talked about a couple of the vaccines in the past, and we're going to talk a little bit about this again. We've got the old traditional smallpox ACAM2000. That's a replication-competent smallpox vaccine. We've got the JYNNEOS by the small Danish

company, Bavarian Nordic. There's also a Japanese company, KM Biologics. They've got a vaccine called LC16, which is also a replicating smallpox vaccine derived from the Lister strain of vaccinia licensed in Japan.

Let's talk a little bit about a couple of papers that came out. The first paper looked at historical smallpox vaccine. This is this paper, "Effectiveness of Historical Smallpox Vaccination against Mpox Clade II in Men in Denmark, France, the Netherlands, and Spain." This was published in *Eurosurveillance*. Really what they're looking at here is individuals that at some point in the past had gotten the smallpox vaccine, and then they're going to calculate this efficacy.

It's interesting, the comment, "Is it vaccination or scarification?" because this is an interesting way this is delivered. You see quite a bit of variability here as far as the estimated vaccine efficacy. In the Netherlands, they're giving us about 42%. Spain is suggesting up to 84%. Pooled effect, maybe 70%, but really a broad confidence interval, somewhere between maybe 23% to 89%. Interesting enough that this vaccine made by Emergent BioSolutions, this is the ACAM2000, it just got FDA approval today, the day we're recording this.

I'm almost glad we're a little delayed in our recording. The FDA clearance announced late on Thursday, so I guess just yesterday, late in the day. Makes this the second FDA-approved shot against mpox in the U.S. after Bavarian Nordic's JYNNEOS. I tell you, given the choice, which one I'm going to choose.

VR: Which one?

DG: I would choose JYNNEOS. Much safer. I think, as we're going to see, we have in *Emerging Infectious Diseases*, "Mpox Epidemiology, Vaccine Effectiveness, England 2023." Here we read that based on the UK data, estimated effectiveness of the two-dose, and this is Bavarian Nordic's JYNNEOS vaccine, was about 80% and no vaccinated mpox patients required hospitalization. It's really interesting. You seem to have that efficacy right after the first dose.

VR: It's interesting that two doses didn't make much of an improvement. One is plenty.

DG: One is probably plenty. I guess the issue will be durability.

VR: Exactly.

DG: We should actually follow that. Do you need to keep giving everyone two doses? You're already at over 80% with just that first dose, so that'll be interesting. The next, and I think this is a response. I also listen to the *TWiV* deep dives. Listen to Rich Condit's comments. He is our mpox virologist. It's really interesting because we still have questions about how much benefit we get from the TPOXX or the Tecovirimat for clade II.

We heard that, hey, it didn't seem like it was doing much in the DRC, Democratic Republic of the Congo, when it was used for clade I. I was emailing with my colleague, Jason Zucker. He's an adult pediatric ID physician at Columbia. He's really, I would say the U.S. mpox expert. There is a trial. It's still ongoing, still enrolling, called the STOMP trial. They're studying Tecovirimat for mpox. I'm going to leave in a link for the stomptpoxx.org trial.

Really, we don't even really know how well this works for the West African clade II. There's great animal data, and our clinical experience was that it seems that about day three, people start to get better when you start them on the TPOXX. We're not sure how that compares to natural history. Certainly described that poor woman that we took care of at Columbia who just really just progressed with the horrible esophageal disease despite being on the Tecovirimat.

VR: Daniel, this STOMP trial was initiated during the clade II outbreak last year.

DG: It's still ongoing. They still have not completed enrollment. We need to keep sending people that way. We'll leave in a link, clinicians, patients as well. We need to do the science because we don't actually really know how well this stuff works. We also have some good news. The WHO announced the, “Global Strategic Preparedness and Response Plan Launched by WHO to Contain Mpox Outbreaks.” This followed the declaration of public health emergency of international concern.

This plan is going to cover a six-month period, September 2024 through February 2025, envisioning a U.S. $135 million funding response, and hopefully strategic vaccination. Here, they're going to not only vaccinate individuals at high risk, but they're also going to vaccinate healthcare workers, recent contacts, try to interrupt the transmission chains. Actually, it seems like it would make sense for us to start considering healthcare worker vaccination in the U.S. because, unfortunately, a lot of providers are just not really familiar. It's actually not always so obvious who has or doesn't have this disease.

We'll talk a little about transmission coming up, but cases in the DRC, the main hotspot, have topped 18,000 this year. Just astounding. We're waiting for the emergency-use listing, which could happen. I think, September 16 is the day for the WHO. Tedros said the WHO has said, "In the meantime, I've given the green light to Gavi and UNICEF to go ahead and procure those vaccines pending this EUL decision."

I think the data is very good, actually, for at least the Bavarian Nordic one since we have the ACAM one as well. Here's an interesting, I'll say, news article, “Mpox Strain is Changing Fast; African Scientists are ‘Working Blind’ to Respond, published in Reuters. Basically, there's a lot of concern here that we just don't have all the information that we would like. I'll leave a link for that. I did want to end this section with some comments on transmission. I keep qualifying transmission with terms like “in general.”

I wanted to share some links to both the U.S. CDC and the African CDC, where we read in the posting, we'll start with the U.S. CDC, "Prior studies of monkeypox outbreaks show that spread of monkeypox virus by respiratory secretions appears uncommon. Most cases of monkeypox report close contact with an infectious person. While we do not know with certainty what role direct physical contact has versus the role of respiratory secretions, in instances where people who have monkeypox have travelled on airplanes, no known cases of monkeypox occurred in people seated around them, even on long international flights."

Under examples where monkeypox can spread, "Yes: Respiratory secretions through face-to-face interactions (the type that mainly happen when living with someone or caring for someone who has monkeypox)." The African CDC, "Transmission: Transmission between

animals and humans occurs from direct contact with infected blood, bodily fluids, lesions or infected fomites. Person to person transmission mostly is through close contact with respiratory droplets (amplified by sustained face-to-face contact, skin lesions, and infected fomites as well as mother to child transmission via the placenta or at birth through close contact)."

What's the science? We have these recommendations, but we're sticklers here. We have the article, “Mpox Respiratory Transmission: The State of the Evidence,” published last spring in *The Lancet Microbe*. Here we read that laboratory experiments have initiated MPXV. That's the mpox virus infection in animals via respiratory routes. Some animal-to-animal respiratory transmission has been shown in controlled studies and environmental samples studies have detected - they say airborne mpox virus.

Now reports from real-life outbreaks demonstrate that transmission is associated with close contact. We know that it's difficult to infer the root of mpox virus acquisition in individual cases. So far, respiratory transmission has not been specifically implicated. They go on to say, "Based on the available evidence, the likelihood of human-to-human mpox virus respiratory transmission appears to be low. However, studies should continue to assess this possibility."

VR: I think we should emphasize this is not SARS-CoV-2 where if your mucosal cells are infected, in every breath you're exhaling virus. I would guess, Daniel, if you have lesions in your mouth, you would be exhaling some virus and droplets. You do see lesions in the mouth sometimes.

DG: Yes, we definitely see lesions in the mouth. I think that's the distinction here is you don't want to get caught in this binary. I think we described when we had that woman with really bad mpox in the mouth and she was in a negative pressure room. We wore N95s. We also wore the yellow gowns because clearly a big part here is contact.

VR: Yes.

DG: COVID. We made it to COVID and we're not done. As I like to say, we might be done with COVID, but COVID is not done with us. We've got a lot of states here in that 2% to 4% of deaths are due to COVID currently, including New York. Nationwide, though, we might be peaking on our wastewater tracking. At least it seems like in some areas, really, we got as high as last winter in some of these areas, particularly out there in the West, and the South.

It looks like maybe in some areas we're on the way down, not in the Northeast, we're still on our way up. SARS-CoV variants, I'm going to start leaving in a link here again. Just updated COVID-19 vaccines, this might be an issue. I just wanted to talk, I think we mentioned a little bit last time about the days of Omicron. I remember people like, "Oh, now it's going to be so much easier to keep track." I'm like, "Oh my gosh, in what way?"

Is it easier for me to remember KP.3.1.1 as opposed to Omicron or PFI? "I want my PFI," would have been a lot easier. This is going to be a discussion, and I'm going to circle back to this in a few minutes with regard to JN.1 versus KP.2 when it comes to the updated vaccines. Also, I'm going to talk about this when it comes to PEMGARDA. Pre-exposure period transmission testing, more tests in the mail.

Dawn O'Connell, J.D., probably related, assistant secretary for preparedness and response at the Department of Health and Human Services, said that starting in the end of September, people can order four free COVID tests to be delivered through the mail. This is the seventh round of free tests since 2021. I'll leave a link in there to where people can go. They've so far delivered 1.8 million tests.

Hot off the press, “FDA Authorizes Updated Novavax COVID-19 Vaccine to,” as they say, “Better Protect against Currently Circulating Variants.” They say variants up there but don't worry, they're going to say strains pretty soon anyway. Hot off the press, August 30, 2024, the U.S. FDA granted emergency use authorization for an updated version of the Novavax COVID-19 vaccine that more closely targets current circulating variants to provide better protection against serious consequences of COVID-19, including hospitalization and death. The updated vaccine is authorized for use in individuals 12 years of age and older. It includes a monovalent single component that corresponds to Omicron variant, JN.1.

VR: Daniel, why does Novavax get away with JN.1, but mRNA is KP.3?

DG: It depends where in the world you are, which is interesting. The history here, and it's really funny to look at the variant tracker over time, back in - it's about April, you see JN.1 and there's this whole, "Hey, we're going down the JN.1 path," and our immunization experts get together and they say, "We would like the next vaccine to be JN.." Then a couple of months go by and they say, "By the way, if you could make that a KP.2 nudge, nudge, we'd prefer that." [chuckles]

It's interesting. In Singapore and Taiwan, they're getting mRNA JN.1 vaccines. Taiwan's all Moderna, Singapore has some Pfizer. Here in the U.S., we're going to get JN.1 from Novavax, but we're going to get KP.2 from Moderna and Pfizer. It looks like Moderna is having some supply issues. It's probably start off with Pfizer and then Moderna will get here and Novavax. Maybe we're going to learn something because I think there's two choices here.

One is we've talked about, is there any difference in the durability between the protein? Now I think they're going to get here in time for the market. The other is it'll be interesting to see in places where it's JN.1 and you have a choice of mRNA and protein, head-to-head there versus also just the durability.

VR: In Taiwan, is that because JN is predominant?

DG: Apparently, there was just a decision made in both places. This was made a little while ago that they're just going to go ahead and do the JN.1. They don't perceive - and I think I should point out, the KP that we're going down, these are JN.1 lineage. It's not like suddenly it switched, because that really - if you look at the variant mapping, XBB was like one offshoot, but then we went up this other JN.1 variant direction.

VR: Daniel, the problem is, these decisions are based on neutralization titers, which are probably not very different and most likely clinically irrelevant. I think JN.1 is sufficient.

DG I suspect it's going to be fine. I think we talked at one point, I think it was the UK where there was both access to the XBB, but also the bivalent, and it didn't look like there was any difference. Sometimes I wonder, I don't know if we'll ever do the science, but it would be

interesting. What if we just had never changed? What if we just kept giving the same vaccine? Would it really matter? How important, honestly, are the neutralizing antibodies to -

VR: According to the helminth paper we just did, it doesn't matter.

DG: It's really the T-cells that are protecting you against severe disease. Maybe the antibodies help against that temporary reduction in infection. This changing in variants does impact our pemivibart. Maybe. We have an update on pemivibart. This is Pemgarda. This is the updated pre-exposure monoclonal antibody. Actually, interesting, they use Evusheld in Taiwan as treatment.

VR: It still is effective?

DG: We don't know. It's talked about. It's going to expire in the end of December. They're like, "Use it up. We bought it already." They're giving it to folks. It still may work because it still may have not neutralizing antibody impact, but the Fc-mediated impact on the virus. Here we have updated IDSA guidelines suggesting the use of P to prevent severe COVID-19 in immunocompromised patients.

They go through the whole thing and they've got a bunch of remarks. I'm going to leave a link into it. This is a 4,500 milligram IV every three months. This is going to be for - Who are the candidates? People who are in active treatment for malignancies. Actually, MSK is one of the bigger utilizers of this therapy. Then they go through other folks that have impacts on their immune system.

I'll also leave in a link to the infusion center locator. That's pemgarda.com. This is prophylactic monoclonal treatment. Their data would suggest approximately a 70% risk reduction of developing symptomatic COVID-19 compared to placebo. Does it still work? We have a preprint out of the David Ho Lab. That's up there at Columbia.

VR: Yes. It sure is.

DG: It sure is. “Pemivibart is Less Active against Recent SARS-CoV-2 JN.1 sub-lineages.” That's the title. This data is generated by looking at pseudovirus neutralization assays. There's also some interesting structural analysis to try to understand how the amino acid changes in spike protein will impact the virus neutralization by this monoclonal antibody. They have some pretty good figures where you can actually see the BA.2.86 going into the JN.1.

Then you see the different JN.1 lineages that they're going to test. They're actually going to show you the different amino acid substitutions in the protein. Then they're going to give us the pseudovirus neutralization changes. It's really the 3.1.1 that has this most significant fold increase when it comes to the IC50.

VR: Yes. These are in vitro neutralization assays with cells and culture and pseudovirus. The clinical impact is unknown, unfortunately.

DG: Let's not make that same mistake again and throw this out just because we have pseudovirus neutralization. Let's see how are our patients doing and are we seeing any drop in actual efficacy.

VR: On top of that, Daniel, you may remember from a recent *TWiV*, we know that pseudoviruses are different from authentic virus. We did a paper where, instead of making a pseudovirus, which could be a lenti or VSV, they used a common cold coronavirus to put the spike of SARS-CoV-2 and makes a big difference in neutralization. The pseudoviruses are tenfold off.

DG: Yes. That could be a problem because they say, "Oh, 32, but if it's just three," and then you're not looking at Fc-mediated. COVID, early viral phase. NIH treatment guidelines, IDSA guidelines, number one recommendation. This is true throughout the world, wherever evidence-based recommendations rule the roost.

Now we have the article, "US Real-World Effectiveness Study of Nirmatrelvir/Ritonavir in Preventing Hospitalization of High-Risk COVID-19 Patients," recently published in the journal *Current Therapeutic Research*. This is data from an ongoing U.S. population-based observational cohort study with retrospective and prospective collection of national electronic healthcare data collected from the US Optum, the identified COVID-19 electronic health record data set.

During December 22, 2021 through July 20, 2022, hospitalization rates within 30 days from COVID-19 diagnosis were evaluated. Overall, they've got 12,440 and 234,123 patients included in the, say, Paxlovid and non-Paxlovid groups, respectively. Pretty well-balanced group. The incidence of hospitalization within 30 days was 0.90 for the nirmatrelvir group.

Less than 1% of the folks that got Paxlovid ended up in the hospital, but about 6% of the folks that did not get Paxlovid ended up in the hospital. We're seeing an 85% risk reduction.

VR: That's darn good.

DG: It's really good. The interesting thing here - a couple of things here. One is, I always have mixed feelings about Optum because that's where I work. Can't enjoy our - the thing I have to say is, there's a lot of people out there and they're like, "Oh, I remember the EPIC-HR and you had a 90% reduction, but those were unvaccinated. That was before Omicron." I have to point out, we are still seeing - we saw 75,000 people die of COVID in the last 12 months. That's a big deal.

This is not the flu. The flu is about 20,000 deaths. This is four times as many deaths. Here, we're seeing in real-world data, this 85% risk reduction. If you break down the data even more, overall, you look at White and Black, you look at under or over 65, you look at vaccinated or unvaccinated. This is overall 85% risk reduction. The other thing I really like about the study that I think it's important, is this study looked at patients that met the criteria for Paxlovid.

We're seeing about 6% of them actually progressing and ending up in the hospital. You're going to reduce that 5%. Really a number needed to treat is about 20 people. About 20 scripts for the Paxlovid and you keep someone out of the hospital. That's good stuff. All the naysayers. I think the interesting thing too, is that the sooner you get them on the Paxlovid.

A lot of studies show about a 50% reduction independent of when you get them on, but if you get them on the day of that positive test, it's about a 90% risk reduction. Even a little bit higher

than what we're seeing here. That's in the world of Omicron, and remember, we're still seeing these deaths. Number two, remdesivir. Three, molnupiravir convalescent plasma in certain options.

Remember, if you've got COVID-19, you are contagious, so isolation recommendations. Second week, early inflammatory week. Just to remind people that this is the bad week. This is when people really feel rotten. About 20% of our high-risk folks will experience the second week. If we do what we're supposed to do during the first week, we can reduce the risk of ending up in the hospital by about 90%, 85% we just saw.

Steroids at the right time, in the right patient, right dose. This is after that first week. This is in patients with oxygen saturations less than 94. This is not in the first week when steroids can actually increase the risk of death, hospitalization, and Long COVID. Anticoagulation guidelines, pulmonary support, Remdesivir if we're still in the first 10 days, and immune modulation.

We're going to wrap it up with just a couple of articles here in late phase/Long COVID. The article, “COVID-19 and Mental Illnesses in Vaccinated and Unvaccinated People,” was published in *JAMA Psychiatry*. This study was conducted with three cohorts. We had one before vaccine availability during the, they say, wild-type Alpha variant eras. That's January 2020 through June 2021. Then two, we've got a vaccinated and unvaccinated during the Delta variant era. That's June through December 2021.

This is data from the OpenSAFELY-TPP, which has linked data from 24 million people registered with general practices in England. People registered with a GP in England for at least six months and alive with known age, sex, say, deprivation index information, and region of baseline were included. They're going to give us adjusted hazard ratios, comparing the incidence of mental illness after diagnosis of COVID-19 with the incidence before and without COVID-19 for depression, serious mental illness, general anxiety, post-traumatic stress disorder, eating disorders, addiction, self-harm, and suicide.

I think the design is really important because I don't want people to walk away with the idea that this all could be explained by suggesting that people that decided to not get vaccinated just had more mental illness to begin with. Listeners might feel that way, but that's not the way the study was designed. Now, the largest cohort, the pre-vaccine availability cohort, had over 18 million people, equally split, male, female.

The vaccinated cohort had over 14 million, again, fairly equally split. The unvaccinated cohort included 3,242,215 individuals. The incidence of mental illness was lower in the vaccinated cohort compared with the pre-vaccine availability and unvaccinated cohorts. Then we get basically about a two-fold increase with a number of these outcomes. The elevation incidence was higher and persisted longer after hospitalization for COVID-19.

They pull it all together and say, "In this study, incidence of mental illness was elevated for up to a year following severe COVID-19 in unvaccinated people. These findings suggest that vaccination may mitigate the adverse effects of COVID-19 on mental health."

Just a couple here to close this out. An important question is whether what we do during acute COVID impacts our risk of getting Long COVID.

We have the article, “Post-acute COVID-19 Outcomes Including Participant-reported Long COVID: Amubarvimab/romlusevimab versus Placebo in the ACTIV-2 Trial.” This is different monoclonal antibody cocktail. Are we going to get the same results we saw in our study? Here, non-hospitalized high-risk adults within 10 days of COVID-19 enroll in this trial. Late symptoms assessed using a participant-completed symptom diary were assessed.

Really, the primary outcome for this was the composite of Long COVID. They're also going to look at hospitalization or death. Yes, monoclonals were highly effective in keeping folks out of the hospital, preventing deaths, but just like our study, we did not see a reduction in the risk of Long COVID with early monoclonal antibody treatment. As promised, Vincent, the article, “Postacute Sequelae of COVID (PASC or Long COVID): An Evidenced-Based Approach*,”* my paper, was published in *Open Forum Infectious Diseases.* This is open access. My plan is to devote next week's *TWiV* to a deep dive into this paper.

I'm actually going to be presenting this up in Maine next week. Next week will be all about Long COVID. I'll be the keynote speaker up at the Maine Medical Association. Also, I will cover in deeper depth an article that just came out, “Fibrin Drives Thromboinflammation and Neuropathology in COVID-19,” published in *Nature*. I'll wrap it up there by saying, no one is safe until everyone is safe. Pause the recording right here, go to parasiteswithoutborders.com, and click Donate. Even a small amount helps.

You've noticed I've modified that, Vincent. I say that, if you enjoy the work that we're doing, or you just want us to keep doing it. We are doing our Floating Doctors fundraiser. August, September, October, we'll double your donations up to a potential maximum of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. A lot of people send them to twiv@microbe.tv, but I'm nice and I'll forward them here, but you should send them to daniel@microbe.tv. Sue has questions about the new COVID boosters that we've just talked about. Three questions. One, will a protein-based vaccine based on JN.1 provide better protection against severe COVID than an mRNA vaccine? I understand from *TWiV* that these vaccines are not intended to prevent infection.

DG: The first one is, as we discussed, we don't know. We're going to find out. Most of the thought is that JN.1 versus KP.2, the KP's are all JN.1 lineage variants. We don't expect there to be a huge difference, but it's going to be interesting. I think we keep learning, and I think that's the whole point. The quotation I started with, is that we have our theory, we have our ideas, we have our hypothesis, and then we go ahead and we see what the data has to show. We will find out.

VR: Number two, how much more effective/durable is one compared to another? Is there a measurable difference between a protein-based vaccine that targets the parent strain or an mRNA vaccine targeting variants evolved from the parent strain?

DG: This is a great question because the mRNA platforms are a little quicker to respond. They say, "Give us a new request, and within 60, 90 days, we've got you a new vaccine." The protein-based, so Novavax, they want their 90 or more days to respond. This will be interesting. Is speed more important? Is being closest to the starting line more important?

This is an area where we're going to keep learning. Now, thankfully, that Novavax is out in time for the fall, we're going to get, hopefully, some of that data.

VR: Three, what data are there about these distinctions, durability, and efficacy, from earlier vaccines that target parent strains compared to evolved and circulating variants from the parent?

DG: We just talked about that one paper where it was data from the UK, where both the monovalent and the bivalent were available. It really was not particularly different. We're going to learn more, but I'm just not sure that the data really - we keep rushing to update these things. For instance, JN.1, KP.2, XBB, it'll be interesting to see going forward.

VR: Yeida writes, "I recently visited my PCP for my physical. I asked them if they could prescribe Paxlovid." He's going to be traveling. He's an asthma patient. "The physician said the healthcare system she works for requires filing and submitting a form after testing positive that can only be completed and submitted while the person is in state, and this is Florida, they will not prescribe Paxlovid."

"She also mentioned they are not prescribing the drug much and mostly treating COVID like flu due to decreased Paxlovid effectiveness. I feel somewhat skeptical about their claims, and I'm concerned about the difficulty in obtaining a prescription. Could you please clarify about prescription guidelines as they refer to prescribing for people with asthma and potentially leaving the country? Also, are there any guidelines for healthcare systems regarding their policies that affect clinician prescription practice? I'm concerned that the procedure she explained makes getting Paxlovid more difficult and can cause delays in starting treatment."

DG: This is very troubling. We just shared more real-world data. In a high-risk population, 6% are ending up in the hospital. How is that better than giving people Paxlovid and dropping that to less than 1%? Unfortunately, the majority of physicians in the U.S. now actually work for large organizations, either healthcare systems or large conglomerates. Then you have a lot of these administrators who maybe at one point were clinicians or some other area, and then involved in these guidelines.

I use the same line, Vincent, that you use when I see a patient and they ask, "Oh, who do you work for?" I say, "I work for you." It's completely different who may or may not sign my paycheck. This is troubling. We keep sharing the data that Paxlovid continues to be effective. The only discussion is number needed to treat and the issue of cost-effectiveness. When I was in Taiwan, you have to be 65 for access under their public health.

In Singapore, it was 60. Here in the U.S., being above 50, which is a fourfold increase in your risk of a bad outcome, is when we start looking at doing this. I think the data really supports Paxlovid. It's really troubling that there's all these barriers being put in the way. The other is, when you travel, let's say you're going to go traveling somewhere and you say, "Oh, in case I get diarrhea," and you get a script for azithromycin, in what way is it different to have Paxlovid in pocket?

VR: Amy writes, "I'm 50 and I'm in the ELEVATE clinical trial. I'm in the ribociclib arm, taking 400 mgs daily for three weeks, then a week off. I'm also taking 300 mgs elacestrant daily. So far, my WBC count has been low but stable. I've asked my oncologist if she has a

recommendation for timing vaccines this fall for best immune response, and she has had no opinion aside from after scheduled scans and in my left arm. Should I time my vaccines during the one-week break? Am I overthinking this? I'm looking to get shingles, COVID, and flu when they become available."

DG: No, you're not overthinking it. These are good questions. Part of it is you want those white blood cells around so that you can respond to the vaccine. This is going to be a little bit of a challenge. You're certainly someone, it sounds like you would be a Pemgarda candidate. Then you've got to ask which vaccines do you want to get, when. There's really no problem getting the shingles, the COVID, and the flu at the same time. I know some people say, "Oh my gosh," but no, that's absolutely fine. Try to time it so you're going to be getting these vaccines when that Y count comes up.

VR: Finally, Richard writes, "I got Long COVID, early December '20, little information then. My primary care physician was fantastic. He acted as quarterback as I got all manner of testing and treatments as that first 12-to-18 months felt I would not survive. It had seemed all organs and systems were malfunctioning. With extreme PTSD, I was very fearful of reinfection, which happened two years later, still suffering Long COVID, although improved. "

"I asked my doc for Paxlovid, which he called in immediately. My goal was to cut viral load ASAP to limit damage. I'm happy to report, pretty severe flu symptoms dissipated within 24-to-36 hours. Fast forward, post-infection, my doctor wrote me another script for Paxlovid to keep on hand. I have not had COVID since, but is it true that Paxlovid can expire out? Another doctor client of mine told me it's just not true, to keep it on hand."

DG: The interesting thing with Paxlovid is, it had these expiration dates and then as we would reach them, you'd get new stickers and just put them over the old one. I'm not sure that any of the Paxlovid has actually expired out there, but, if we hear it differently, we'll let you know.

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

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

[music].

[00:52:06] [END OF AUDIO]