This Week in Virology

TWiV 1038 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 1038, recorded on August 24, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from somewhere, Daniel Griffin.

Daniel Griffin: Hello, everyone. Yes, I am joining you from the mountains of Switzerland, a little town called, well, I'm going to pronounce it wrong, of course, but Mörel. It's got the M and it's got the U with the two dots, the umlaut stuff going on, so I am certain I'm mispronouncing it.

VR: What are you doing there?

DG: I'm visiting my sister-in-law, my brother-in-law, their three kids.

VR: Cool.

DG: It's a bit of a family vacation, and I am not wearing a bow tie.

VR: Yes, you're chilling. Very good.

DG: Let me jump in with my William Shakespeare quotation. Hopefully, this will set the tone. "Since brevity is the soul of wit, and tediousness the limbs and outward flourishes, I will be brief." Hopefully, this will be one of our shorter episodes. Definitely shorter when it comes to the COVID section, but I actually have quite a bit to talk about with regard to a few other diseases.

Polio, let me start with the *MMWR*, "Progress Toward Polio Myelitis Eradication, Pakistan, January 2022-June 2023." Start with a little bit of background.

Since the establishment of the Global Polio Eradication Initiative in 1988, Pakistan remains one of only two countries, along with Afghanistan, with continued endemic transmission of wild poliovirus. This report describes Pakistan's progress toward polio eradication during this

period, January 2022 through June 2023. What we read is that during 2022, Pakistan reported 20 wild poliovirus type 1 cases, all of which occurred within a small geographic area encompassing three districts in South Khyber Pakhtunkhwa. As of June 22, only a single WPV1 case from Banu district in Khyber Pakhtunkhwa province has been reported in 2023, compared with 13 cases during the same period in 2022.

Now, in addition, 11 wild poliovirus 1 detections, they say isolates, have been reported from various environmental surveillance sewage sampling sites to date in 2023, including in Karachi, the capital of the southern province of Sindh. Now, the authors point out that substantial gaps remain in the quality of supplemental immunization activities, SIAs, especially in poliovirus reservoir areas. I share the concern about the isolation of WPV1 from an environmental surveillance site in Karachi. People may have in their head these ideas about, oh, Karachi, Pakistan, but Karachi is a large city. It's reportedly the 12th largest city in the world with a population of greater than 20 million individuals.

VR: Yes. Daniel, if there's one, there's many more because their surveillance isn't perfect, right?

DG: Yes. I think they make a point. There's substantial gaps, not only in the supplementary immunization activities, but I think we're also aware in surveillance. Also when you go to parts of the world where not everyone really has proper access to a sewage system, where some of this, particularly the more affected populations. The other side of the coin, so to speak, are the cases of vaccine-derived polio.

Just looking at the polio cases reported the same day that are at this *MMWR*. This is in polioeradication.org this week. Afghanistan, we saw one WPV1-positive environmental sample. We saw detections in Algeria, Benin, Botswana, Burundi, Cameroon, Chad, DR Congo, and Guinea, all vaccine-derived environmental samples.

VR: That's the biggest problem, the vaccine-derived viruses that have been circulating a long time, because polio, when immunization is not sufficient. It's really, they go in with this new OPV2, but it's not clear to me if that's going to get rid of it.

DG: I also share, we're a little bit heavy on polio this time, but I think appropriate. The article, "Modeling Poliovirus Transmission and Responses in New York State," published in *JID.* Here are the authors adapted an established poliovirus transmission and oral poliovirus vaccine evolution model to characterize dynamics of poliovirus transmission in New York State, including consideration of the immunization activities performed as part of the declared state of emergency. We've discussed those.

They found that despite sustained transmission of imported VDPV2 in New York State involving potentially, I think it's really important, thousands of individuals depending on seasonality, population structure, and mixing assumptions in 2022, the expected number of additional paralytic polio cases in 2023 and beyond, they say, is small. I think the big thing they really point here is that the risk is in areas where they do not maintain high immunization coverage. This continues to be a risk for the unvaccinated, the non-immune population.

All right. Moving on, can you believe this? Malaria, Texas, Florida, and now Maryland. It's right at our - knocking at our door. The Maryland Department of Health has confirmed, reported a

positive case of locally acquired malaria in a Maryland resident living in the national capital region. The individual is hospitalized. Hopefully at this point has recovered. They did not travel outside of the U.S. or to other U.S. states. They do point out that malaria was once common in the United States, including in Maryland. We've discussed this, but we have not seen a case in Maryland unrelated to travel in over 40 years.

VR: What's going on, Daniel?

DG: I'm getting a little worried. RSV and now let's - some good news here. OK. Again, talk a little bit of RSV influence. RSV, the exciting announcement, "FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in Infants." We've talked about the data on this whole concept that during that last trimester of pregnancy, individual gets vaccinated and then they can protect the newborn child. August 21, 2023, the U.S. FDA approved Abrysvo, the RSV virus vaccine. This might be familiar. The first vaccine approved for use in pregnant individuals to prevent lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through six months of age.

This is approved for use at 32 through 36 weeks gestational age of pregnancy. This is administered as a single dose injection into the muscle. Yes, this is the same vaccine that the FDA approved in May for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

VR: Daniel, how does this go with the monoclonal that you give to infants?

DG: The nirsevimab.

VR: Yes. nirsevimab, right.

DG: I wouldn't see any reason why, one is approved here, right? We've got the individual getting it and then protecting the newborn birth through six months of age. Remember, you're going to get even more protection and a more durability looking at, let's say a child is born in, we'll say August, that's a fine time. Then by the time you start getting to February, it would be nice to have jumped in early, beginning with the nirsevimab, the monoclonal. I don't see any issue with co-administration during pregnancy, this, and then the newborn getting the monoclonal antibody. Listen to the Paul Offit special episode on that, which I admit I recommend people listen to. That was a great coverage.

Flu, we have the *MMWR*. What about the flu? "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023-2024 Influenza Season." Not too early to be thinking about the flu shot, but is it too early to be getting one? Routine annual influenza vaccination is recommended for all persons aged 6 months or older who do not have contraindications, right? Pretty broad. Everyone 6 months and up.

All seasonal influenza vaccines expected to be available in the United States for 2023-2024 season are going to be quadrivalent. They're going to contain the hemagglutinin derived from one influenza, H1N1, one H3N2, sorry about that. Then a couple of the influenza B, we've got the Victoria lineages and the Yamagata lineage virus. We're going to have inactivated

influenza vaccines. We're going to have recombinant influenza vaccine, live attenuated influenza vaccine, all expected to be available.

Here's what I want to point out. This is in the *MMWR*, something we've talked a bit about. Timing matters. For most people who need only one dose of influenza vaccine for the season, vaccination should ideally be offered during September or October.

Vaccination, are you ready for this, during July and August should be avoided unless there's concern that vaccination later in the season might not be possible. For pregnant persons who are in the third trimester during these three months because if vaccination, if you get your vaccination during that last trimester, this is associated with reduced risk for influenza illness in infants during the first months after birth, when they are too young, less than 6 months, to receive their own influenza vaccine.

Another exception to think about is travelers, right? Let's say a traveler is going to be heading out of the country July, August, right about now. You might want to think about doing this two weeks before departure. Then remember, this is another new as of last year, and I bemoan the fact they waited until everyone had put in their orders and then we had to scramble, but we now have specific product recommendations for those age 65 and over.

The ACIP recommends that for adults age 65 and older, preferentially receive one of the high dose or adjuvanted influenza vaccines. The quadrivalent high dose inactivated influenza vaccine, that's the HD-IIV4, the quadrivalent recombinant influenza vaccine, the RIV4, or the quadrivalent adjuvanted inactivated influenza vaccine, aIIV4. In none of these three vaccines is available an opportunity for vaccine administration than any other age appropriate, right? If you can't get these, then go ahead. This is just an encouragement, a preference, but get that influenza vaccine.

All right. I should look at the timestamp. We're about 12 minutes in for Jolene. Those people who are only here for COVID, hopefully people are here for more. This is a question I've been getting a lot. I told a lot of people, just listen Saturday, I'll answer it. What about boosters? A lot of people are hearing the number of cases are going up, the number of hospitalizations are going up. "Dr. Griffin, should I run out and get my booster right now?" The answer is no.

Now we are starting to hear that Novavax, Moderna, and Pfizer-BioNTech will have updated boosters. We hear that they have preliminary data that these will work against the newest variants. When the data is actually shared, we will certainly take a look and share how compelling it is. Currently, what is the advice for COVID-19 vaccination boosters? Two things. First, I'm going to say timing matters for two reasons. Number one, a number of studies we have shared suggest that the current formulation does not do much to boost against the current variants. Even though you may be hearing that lots of your friends are getting COVID, wait for the new shots.

Two, just like we discussed with influenza, getting a shot in October makes the most sense, as we are only anticipating that four-month boost due to generation of neutralizing antibodies that will contract. Due to the nature of transmission of this respiratory pathogen, we anticipate the highest numbers in December and January. Maybe avoid that end of September rush and wait for the end of October to get your flu shot, your COVID shot. Get

those RSV shots as soon as they're available. Those are probably going to be durable out to two years.

Then the last important consideration, I know Vincent will want to have a comment on this, the booster may not be something that every single person on the planet needs to get. Everyone may have a different strength of recommendation. Yes, from a public health perspective, in an ideal world, everyone gets in line. This boost might decrease our risk of even getting infected for a few months, might then prevent us from spreading it to our coworkers, our friends, our family, our children. Really the biggest target population will be people who are over the age of 50, those with medical problems, those who might be at risk of severe disease.

Will booster lower one's risk of Long COVID? It would seem that if one doesn't get infected, well then how can you get post-acute sequelae? I think we need to wait for that data. Any comments there, Vincent?

VR: Do we know which Omicron subvariant is going to be in the booster yet?

DG: We know what it was based upon, right? It was based upon the XBB. Now we're starting to see what has been termed the Eris by our buddy up in Canada. We're also seeing some other - That's what we're hearing, the preliminary data. We've got some companies giving us data from my studies, Novavax claims they've got some human data. When we see it, we'll actually -

VR: All right, so basically the XBB that's going to be in this booster seems to be active against the Eris, et cetera, right?

DG: Yes, that's what we're hearing. When I see the data, we'll definitely share it. All right. Now, unfortunately, like too many people, you test positive. Number one, as we've talked about for a while, Paxlovid, now licensed. I just wanted to share this article, give it some perspective. It's the article, “Nirmatrelvir resistance - de Novo E166V/L50V Mutations in an Immunocompromised Patient Treated with Prolonged Nirmatrelvir/ritonavir Monotherapy Leading to Clinical and Biological Treatment Failure - A Case Report,” published in *CID*. Really in the title. Here, the authors describe an immunocompromised patient who was treated with repeated and prolonged courses of nirmatrelvir and developed these mutations in the Mpro region. These mutations, they report, were associated with clinical and biological treatment failure.

Just to give you a sense of how much exposure, I suggest people take a look at figure one. They basically got this following out for hundreds of days. You can see standard dose of nirmatrelvir actually at day 22. Another course of nirmatrelvir day in the 60s. Then day 85, more nirmatrelvir. Then more nirmatrelvir. Then starting at day 127, nirmatrelvir goes out to day 239. There's actually a co-treatment with molnupiravir. They're tracking the CT values over time for us. Lots of exposure.

VR: Eventually the infection seems to be cleared, right?

DG: Yes. I think that's the interesting thing about this isn't so much doom and gloom. They end up actually treating for a prolonged period of time with nirmatrelvir and molnupiravir. Actually, CT values really drop all the way down to 45, really limit of detection.

VR: I would guess, and I don't know because I don't see the data, that this resistant variant is not very fit. It doesn't really pose a threat to the general population.

DG: So far, we have not found a fit variant that is really undermining Paxlovid as our first-line therapy. I don't consider this to be worrisome. Number one, Paxlovid. Number two, remdesivir approved for down to 28 days of age. It's that early three-day. Number three, molnupiravir, Thor's hammer. Number four, convalescent plasma. Remember, this is restricted to the treatment of immunocompromised COVID-19 patients at high risk for progression, no other treatment options. Then let's avoid doing those harmful things.

A person progresses that second week, if they actually have a lower respiratory hypoxic phase where the oxygen drops less than 94, remember dexamethasone, six milligrams a day times six days. We have anticoagulation guidelines, pulmonary support. Remdesivir may still make a difference if still in the first 10 days, immune modulation. Again, avoiding those unnecessary and unproven therapies.

I'm going to wrap us up with COVID, the late phase. I've got a couple articles here. One is the "Incidence of New-onset Hypertension Post-COVID-19: Comparison with Influenza," recently published in the journal, *Hypertension*. Really a good reason for the expanded concept of PASC rather than just a focus on the syndrome of Long COVID. These are the results of a retrospective observational study conducted in a major academic health system in New York City. Participants included 45,398 patients with COVID-19 and 13,864 influenza patients without a history of hypertension.

They report that hospitalized patients with COVID-19 were more than twice, 2.23 times, and non-hospitalized patients with COVID-19 were 1.5 times more likely to develop persistent hypertension compared to their influenza counterparts.

The article, "Postacute Sequelae of COVID-19 at 2 Years," was recently published in *Nature Medicine*. I have seen so many spins on this, so let me just mention a little bit about it.

These results come from a cohort of 138,818 individuals with SARS-CoV-2 infection and 5,985,227 non-infected control groups from the U.S. Department of Veterans Affairs. Followed them for two years to estimate the risks of death, and 80 pre-specified post-acute sequelae of COVID-19 (PASC) according to care setting during the acute phase of infection. There is a lot here to go through. A couple high things to point out. The increased risk of death remained significantly elevated through the two years in individuals that required hospitalization.

Now, something that maybe our listeners are not familiar with, but disability-adjusted life years, DALYs. They point out that cumulatively at two years, post-acute sequelae contributed 80 disability-adjusted life years per 1,000 persons among non-hospitalized and over 642.8 disability-adjusted life years per 1,000 persons among those that were hospitalized. Pretty impressive. They found that while risks of many sequelae declined two years after infection, there was a substantial cumulative burden of health loss due to PASC.

All right, so I will finish as I've been finishing for several years now. No one is safe until everyone is safe. Hoping everyone pause the recording right here. This was brief, just hitting the high points. Help us support Floating Doctors. We are doing our Floating Doctors fundraiser, August, September, and October. I'll be down there in December doing a CME with them. We are hoping to get up to a number of donations where we can give them a maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Marsha writes, "I live in Toronto, Canada. October 2022, I tested positive in an outpatient clinic at Michael Garron Hospital. The doctor on call did not recommend antivirals because I am on Eliquis for atrial fib. I'm 68 years old. I recovered. As far as I know, I don't have Long COVID, although with aging, it's sometimes hard to know what's what, and our health system in Ontario isn't what it used to be.

"I'm wondering if you can tell me what your recommendation is around blood thinners and antivirals. I'm concerned in case I get COVID again. I'm up to four COVID vaccines. I get sick for a week every time I get a shot, so I space them out a bit. Love this show, particularly your updates. I find it difficult to find the real dope on matters of science, and it's a comfort to me to hear you all speak of research."

DG: All right. Thank you for writing in, and you do, you present a challenge. A lot of the blood thinners, the direct oral anticoagulants, the DOACs as we call them, medicines like Eliquis can be metabolized through the cytochrome P450, so there can be an issue with Paxlovid. All of the listeners, I would say talk to your clinician or if you're a clinician, I'll just say this straight, the Liverpool Drug Interaction Checker can help you manage some of these.

Now, you may want to look at the risk and benefit of pausing the Eliquis in certain standpoint. You want to talk to your doctor. "I've got atrial fibrillation. Do I have heart failure? Do I have valvular disease? What is the risk benefit of pausing for five or six days or reducing my dose or what is my dose of Eliquis? Would it be OK?" Have these discussions. Don't just say, oh, it's on the list. A little subtlety here. We also talked a little bit about the boosters. Higher risk individual. You may be looking at getting that booster this October, as we've discussed.

VR: All right. We have an email from Bill Muller, who's a professor of pediatrics in Chicago and a physician at Ann &. Robert Lurie Children's Hospital. He writes, "Thank you to you and the *TWiV* team for all you do for science communication. In response to a question from Portia in *TWiV* 1036 regarding Paxlovid for her 2-year-old grandson, you accurately noted that we need to learn more about using this drug in certain populations. To put a finer point on your response, nirmatrelvir-ritonavir is only authorized for use in people over age 12 years and over 40 kilograms. The EPIC-Peds trial for high-risk children that do not meet these criteria is ongoing.

"As you've noted before, trials in children are in several ways more challenging than those in adults, not only because of the often smaller number of eligible participants, but also because new formulations may need to be studied since younger children cannot typically swallow pills. It may not be as simple as dissolving a pill in water; ritonavir is actually an example. When we need to use it in children, it's often an alcohol-based formulation, which is not palatable and can be very difficult to convince a child to take.

"You've done this before on your podcast, but I'm hoping you can remind your listeners who may have children that fulfill the enrollment criteria listed at the clinicaltrials.gov site to consider whether they would try to enroll their child in this study should they live near one of the participating centers and have their high-risk child get infected. Thanks for all you do."

DG: Thanks for writing in. I'm glad to give some air to that great email. Thank you.

VR: This one I believe we have answered in this program, but I'll read it. This is from Danielle. "Over 65 here. With a new BA.2.86 variant around am I better off getting the old booster with the ancestral strain included or waiting for the new XBB-derived booster later in the fall?"

DG: I think we've answered this, and I would say wait until the fall. It'll be after September 15th. Probably October is good timing for you.

VR: Michele writes, "I was told by my nephrologist that if I should get COVID, which I've not had yet, I should take the renal dose of Paxlovid. I'm 64 years old and have mild, stable kidney disease. Are there any studies that compare the effectiveness of the renal dose of Paxlovid with a regular dose in terms of severity of disease in keeping people out of the hospital? Based on any research you know, might remdesivir, I live in New York, be a better option than the renal dose of Paxlovid?"

DG: I think you bring up some good points. One is Paxlovid has been studied, and fortunately, we've learned more and more about the pharmacokinetics of Paxlovid. If you're looking at the FDA approval, you're looking at the ability to give this to people with a GFR greater than 60, normal dose, 30 to 60, you're actually seeing equivalent outcomes. Remember, people with kidney disease, self-included, are at higher risk.

Now comparison. What about remdesivir versus Paxlovid? We've even talked about how Paxlovid can be used below 30. Now this is off-label based upon a study we talked about. Remdesivir, there's no issues. Fully licensed and fully licensed all the way down with no renal issues at all. Very similar reduction and progression, right? We're talking about 88% versus 87%. I think in consultation with your provider, both would be very reasonable options and probably pretty similar as far as efficacy.

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

DG: Thank you. Everyone, be safe.

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