This Week in Virology

TWiV 1040 Clinical Update

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

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From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1040, recorded on August 31, 2023. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Last day of August, Daniel.

DG: Summer is wrapping up, so I'm going to start us with a quotation, a summer-ending quotation. "What good is the warmth of summer, without the cold of winter to give it sweetness?" That's by John Steinbeck. Does that make you feel any better about summer ending, Vincent?

VR: It doesn't bother me because as soon as it ends, it'll be back. That's how I look at it.

DG: [laughs] I was listening to the Neil Diamond song, *America*, today, give people some insight into my musical listening. He was talking about coming to America and the warmth, and I was like, "I'm just hot. I don't want any more warmth, Neil." [laughs] All right. A little bit of a theme seems to be emerging over the last year. Leprosy, malaria, dengue, West Nile virus, polio, all here in the U.S., and now the article, “The Public Health Significance of Finding Autochthonous Melioidosis Cases in the Continental United States,” published in *PLOS Neglected Diseases*.

Just some background. People are familiar with this. Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, a bacterial pathogen that can infect humans and other animals. Human case disease has been thought to be restricted to Southeast Asia and Northern Australia, where the pathogen is endemic, found in the soil and water. In recent years, the presence of *Burkholderia pseudomallei* has been demonstrated in the African and American continents, in the Caribbean islands, as well as the rest of Asia.

Now, recently the pathogen that causes melioidosis was found in the Gulf Coast region of Mississippi, United States of America, associated with human cases. I think we're actually up to three cases now here in the U.S. The CDC&P has declared the pathogen as endemic in the continental United States for the first time. Specifically, the Gulf Coast region of Mississippi has been declared by the CDC as an endemic area.

VR: I just noticed, Daniel, you said CDC&P, right?

DG: Yes. I'm one of the few people that adds that "and Prevention." People say the CDC. I'm like, "It's the CDC and Prevention."

[laughter]

VR: Well, here in Europe, I happen to be in Italy, it's called the European CDC. That's it.

DG: OK. In China, it's the China CDC. Most of these organizations have dropped the Centers for Disease Control and Prevention part. We always talk about the ASTM&H, where the H is hygiene. People seem to be forgetting about hygiene and prevention and just waiting to mop up after the fact.

VR: Well, Daniel, control can imply prevention, right? I don't have a problem with that.

DG: OK. Let's just do that. Let's decide that control is the new prevention.

[laughter]

VR: OK.

DG: All right. Let's move on. Now, this one is just a fun - Well, fun up front. Fun from interesting, not fun from the human cost here, but lots and lots of texts and questions about this one. I think you even sent something my way, Vincent, about this.

VR: That's right.

DG: This is the dispatch, "Human Neural Larva Migrans Caused by *Ophidascaris,"* I'm pronouncing it that way specifically*, "Ophidascaris robertsi* Ascarid," published in *Emerging Infectious Diseases*. *Ophidascaris* species are nematodes with this indirect life cycle. They infect various snakes across the old and new worlds as their definitive hosts. These nematodes are native to Australia where the definitive hosts are carpet pythons.

The adult nematode inhabits the python's esophagus and stomach. They shed their eggs into its feces, and then the eggs are ingested by various small mammals in which the larvae establish. Those are the intermediate hosts. Somehow those small mammals end up inside a python. In this case, a 64-year-old woman from southeastern Australia was admitted to the hospital with abdominal pain, diarrhea, dry cough. They see some stuff going on in her lungs. They see elevated eosinophils, some stuff also in the liver and spleen. They diagnosed her with an eosinophilic pneumonia, and what do they do? They put her on steroids.

She gets a little better, which steroids will always do, and then three weeks later, recurrent fever, cough, more issues, goes on to develop neurological symptoms. They scan her brain.

They see this lesion, and when they do an open biopsy, out comes a live worm. They have some great pictures. This was a live and motile worm that was living in this woman's brain. Actually, in the front right side of the brain. They treat her with ivermectin. This is a situation where that actually is helpful, by the way. Four weeks of albendazole. They gradually decrease down the steroids. She does have improvement, but there are some symptoms that persist.

VR: Daniel, how did this get there in the first place?

DG: The idea is just like the intermediate hosts, she probably ingests one of these embryonated infectious eggs. She's taking the place of the small mammal, and so the larvae basically is in her, waiting for her to be eaten by the python.

VR: It crossed her blood and got into her brain and developed further there.

DG: One of the challenges here is, did it end up in her brain because of all the steroids?

VR: Ah, interesting.

DG: Yes. Which she just ended up with this eosinophilia and ended up with some pulmonary issues and eventually cleared it. How much of this was us taking our hands out of our pockets when they were best left there?

VR: Daniel, do you think her neuropsychiatric problems are a consequence of finding out she had a worm in her brain?

DG: How traumatic, right? Can you imagine-

VR: Yes.

DG: Moving forward, forget about the damage done, just the whole concept that for months you had this worm, which now, everyone can see that this worm was inside her brain.

VR: She's going to have nightmares for some time, I think.

DG: I'm going to have nightmares for some time after this.

VR: [laughs] OK.

DG: All right. Moving into COVID, I had an interesting conversation with one of my colleagues in the hospital this week. Now, he's a cardiologist, but that's OK. I could share what we are seeing. I could share what the CDC COVID tracker has to say. Let me start there, and then I'll get back to this conversation. As everyone probably is aware, this is now mainstream news, is we are seeing an increasing number of COVID hospitalizations, not just people admitted with COVID, but people admitted for COVID.

We're also seeing about a 20% increase in the COVID-19 deaths, just over the last week. Maybe numbers help. We're sitting here about 500 to 600 deaths per week from COVID. This is certainly regional. Actually, at the hospital where I was earlier today, I actually calculated the numbers, how many patient beds, how many patients positive for COVID? Twenty percent

of the patients in that hospital have COVID. This is pretty significant. Yes, we're seeing hundreds of deaths each week.

Let's put this in context, and I think it's important that we're honest here. When I say 20%, it's a 20% increase from a relatively low number. We're still at about half of what we were last year, the same time last year, and we're still about one-fifth of the level where we were in 2021. What are the predictions? What happens next week on Tuesday? My son and many other children head back to school. My daughter, Eloise, is already headed back to university. My daughter, Daisy, a week later, will start nursing school.

Summer is ending. We're going to have a lot of people in these close quarters. What are the predictions? We are expecting there to be a continued rise over the next few weeks here. New York, we have the Jewish holidays, which actually we have a large Jewish population That's probably going to have some impact as well, so we are expecting something of a rise. Then we're still expecting the big rise to be December-January. As we talk about boosters, that'll continue to be relevant. Now back to my cardiologist colleague.

The interesting thing about the conversation is people don't want to hear that it's vaccines that are making this mild. They still want to hear that the virus has gotten milder. I'm not sure I understand exactly that. There also is this continued, maybe people - Actually, there's an epidemiologist who's referred to it as “we're entering the revisionist phase of the pandemic,” and he brought up again, "Oh, but we don't really have to worry about the children. It was never a problem in children." I basically said, "Are you one of the people who wants to put the word only in front of 1,000 deaths in children?" Continues to be a challenge as we move forward.

Let me move forward. Something I will say is positive, is interesting. We heard that, “Project NextGen Awards Over $1.4 Billion to Develop the Future of COVID-19 Vaccines and Therapeutics.” What is Project NextGen? It's a $5 billion initiative led by the Biomedical Advanced Research and Development Authority, BARDA, in partnership with the National Institute of Allergy and Infectious Diseases, coordinated across the federal government, private sector. There's a lot of coordination here.

What were the awards that were announced? $1 billion to four BARDA clinical trial partners to support vaccine trials, $326 million to Regeneron for development of next-generation monoclonal antibodies, $100 million to the Global Health Investment Corp that is going to manage the BARDA Ventures investment portfolio. That was interesting. [laughs] Ten million dollars to BLUE KNIGHT, a joint initiative between BARDA and J&J Innovation to distribute to the awardees of BLUE KNIGHT Resident QuickFire Challenge: Accelerating Project NextGen. Not sure I quite get what's going on with these last two.

Let's talk about what happened in China when the zero-COVID policy ended. It takes time. You've got to wait. You've got to gather the data. Here we have the article, “Excess All-cause Mortality in China After Ending the Zero COVID Policy,” published in *JAMA Network Open*. These are the results of a cohort study that analyzed published obituary data from three universities in China. They did search engine data in each region of China over this period of time. Basically what they're trying to estimate is how many people died in those two months after the end of zero COVID.

They actually came up with an estimate of somewhere between 0.7 and 4.43 million excess deaths among individuals 30 and older, just in those two months after the end of COVID. Kind of shocking. I don't know. I guess, are we becoming numb to statistics? The idea that millions of people, maybe two to three million people died in two months.

VR: That's a lot of people, Daniel, but if they had had a lot of Paxlovid, they could have prevented a lot of them, right?

DG: That is the challenge, right? They knew this was coming, they knew they were going, they knew, "OK, we are going to decide to just stop this approach." Ninety percent reduction. Instead of 2 million, maybe 200,000. Could have saved almost two million lives. [crosstalk] That's something I think will -

VR: Paxlovid alone. You could add remdesivir and molnupiravir and maybe get it even lower. The same with the deaths that you just noted in the U.S. All of those or many of those are preventable. If people would just stop worrying about Paxlovid, we could get over this.

DG: Yes. I've got another story. We're going to get to that again.

VR: [laughs]

DG: What about children? Remember, only 1,000 children died. I'm not one of the people who finds the word “only” to properly fit in front of 1,000 children dying. The article, “International Pediatric COVID-19 Severity Over the Course of the Pandemic,” was published in *JAMA Pediatrics*. The objective of the study was interesting. These investigators set out to determine whether the dominant circulating SARS-CoV-2 variants were associated with differences in COVID-19 severity among hospitalized children. Thousands and thousands of children ended up in the hospital due to COVID.

Clinical data from hospitalized children and adolescents. These are all younger than 18 years of age. These are SARS-CoV-2 positive. They looked at nine countries, Australia, Brazil, Italy, Portugal, South Africa, Switzerland, Thailand, UK, and the U.S. They looked at these three different timeframes. The timeframe for the ancestral, we have our pre-Omicron, and then we have our Omicron, respectively.

The age groups for analysis were those younger than 6 months, the 6 to 5 years of age, and the 5 to 18. If the children just had an incidental test, if they didn't have COVID-19, just an incidental SARS-CoV-2 positive, they're excluded. We're not looking at people who had a positive test. We're looking at people that had the disease. Among 31,785 hospitalized children - I just want to repeat that number - 31,785, tens of thousands of hospitalized children and adolescents, the average age, median age was 4 years old. I want people to picture a 4-year-old in their head. 16,639 were male. About half, 52%.

In children younger than 5 years across successive SARS-CoV-2 waves, the only reduction they saw was in the percent of the kids that ended up in the ICU, but not ventilatory support, not oxygen therapy. Now, if they start looking in contrast, ICU admission, ventilatory support, oxygen therapy decreased in the different waves in children 5 years to younger than 18. Now, this was interesting. The results were consistent when data was restricted to unvaccinated children. What's the big difference here between the really young kids, new to this world, and

the other kids who are out there who are actually seeing perhaps repeat infections? Very interesting to speculate what's going on here.

What do the authors have to say? They say it may be that the reduced rate of ICU admission over the course of COVID-19 pandemic in children younger than 6 months is reflective of maternal vaccination and or infection, which is interesting, but that's the only benefit they got. They just reduced the ICU admission. They also say it is possible that the same effect was not seen in terms of ventilatory support and oxygen support because maternal vaccination may be most efficacious in protecting against these most severe outcomes, but not against the moderate outcomes.

The authors also point out that a direct comparison of disease severity between the different age groups disease severity was elevated in all children in this first period. This data actually was consistent throughout the different parts of the world.

VR: I have to register a little dismay here, Daniel. I don't understand how you could do a study like this and not have all the data. For example, who was born to a mother that had been vaccinated or infected? Who got vaccinated? That data would help you know what is going on in terms of immunity, which is likely what is moderating pathogenesis in the long run. In the end, you don't come out of it with any real conclusions here, right?

DG: Yes. I hate to have speculation at the end because these are all questions that you can ask, and you can say, "OK, what if we looked at children whose mothers were vaccinated or got infected during the last trimester versus parents who decided not to get vaccinated?" You could ask that question in this cohort. Maybe you're not going to get the answer for all 31,785 kids, but if you could get 1,000 yes, 1,000 no, compare that. You could even ask the question, which I always do when I admit someone now, is this your first COVID infection? Your second, your third? Some of the speculation could actually be addressed. I think that would be helpful.

VR: There are so many confounding factors that could be addressed here like if a kid played in the dirt a lot as a young kid and the other one didn't. You've got to make a list of all these potential things that could influence the outcome. I get the impression that the authors just want to take the big numbers, crunch them a bit, and try and get an answer. That is not very useful.

DG: Yes. At least what we are seeing is that for the youngest kids, those under the age of 5, we really were seeing pretty similar severity. We're seeing same ventilatory support, same oxygen therapy. The only thing they found a statistically significant impact was what percent end up in the ICU.

VR: Daniel, I'm at this clinical virology meeting. I can't tell you how many times I hear somebody say the virus wants to be milder because it can -

DG: [chuckles]

VR: - spread better. They seem to ignore the fact that even if you die, if in the first five days, you shed virus and you transmit it, that's all that's needed. Being milder doesn't help with transmission, right? You get what I'm saying? [laughs]

DG: What you're saying is right on. Let's talk about it. Eighty-five percent of the transmission is in the first seven days. People don't die in the first seven days.

VR: Exactly.

DG: One-hundred percent of the transmission is in the first 10 days, so nobody dies in the first 10 days.

VR: No.

DG: Mortality does not impact transmission. Now, if people were dying on day two, if they were dying during the transmission period. There's no evolutionary, there's no selective pressure here on severity. What is it? There was some rabbit study once. Everyone quotes one study, rabbits in Australia or something. All right.

[laughter]

We're not [crosstalk] rabbits and we ain't living in Australia. Let's move on. This is a good one because this is this question. You go in, this happens all the time. I was vaccinating some individuals on Tuesday for all sorts of stuff, which arm do you like least is usually my question. Which arm do you like least? Does it matter? Should you be getting all your shots in the same arm, all your shots for the same thing in the same arm? What's the story?

Here we've got the article, “Differences in SARS-CoV-2 Specific Humoral and Cellular Immune Responses after Contralateral and Ipsilateral COVID-19 Vaccination,” published in *eBioMedicine*. We're going to compare getting all your shots in the same arm or getting your shots in different arms. Here they ask this question. Specifically, we're going to look at should you get the booster in the same arm or should we switch things around.

Now, these are the results of an observational study, so people weren't randomized. Maybe people are a little different. Actually, if you think about it, you might be a little different if maybe you got that first shot and you said, "Oh my, let's try the other arm this time." Here, 303 previously naive individuals, now they're no longer naive, were recruited who received the second dose of COVID-19 vaccine BNT162b2 on either the same side, we've got 147, or the opposite side, 156. Spike-specific IgG, IgG-avidity, and neutralizing antibodies were quantified using ELISA and a surrogate assay two weeks after dose two.

A subgroup of 143 individuals, we've got 64 ipsilateral, 79 contralateral, were analyzed for spike-specific CD4 and CD8 T-cells using flow cytometry. Unfortunately, I don't get to see the flow cytometry, just the data. The median spike IgG levels did not differ same side as opposed to opposite side. IgG-avidity was also similar. However, differences in neutralizing activities were statistically significantly different between the two groups, reaching a P value of 0.024. The spike-specific CD8 T-cells were statistically significantly impacted. Good P value there, less than 0.05. Spike-specific CD4 T-cell levels were similar but showed statistically significantly higher CTLA-4 expression after contralateral vaccination.

Looking at the actual data and degree of overlap, which I've got up here for you to see as well, Vincent, I'm not sure how impressed I am that the statisticians were able to find a difference.

VR: This is a case where, don't be taken by the statistics because those look pretty similar, and as you say, probably not clinically significant.

DG: It's one of those things where they looked at so many variables that you start to-- should you start to do some kind of a correction or are you going to just keep doing t-tests until you find one that works?

VR: That's right. Basically, Daniel, I don't think it matters what arm, if anything.

DG: [laughs] Unfortunately, I don't think it matters either. I just get all my shots in my left arm because I don't like my left arm.

[laughter]

All right. Boosters. We are actually starting to get some more information, or information is starting to be gotten. I'm not sure we are getting it, but we have the press release. Are you ready for that press release? “Pfizer and BioNTech Receive Positive Committee for Medicinal Products for Human Use Opinion for Omicron XBB.1.5-adapted COVID-19 Vaccine in the European Union.”

Just as people remember, we had our bivalent back in the fall. Oh, no. Spring, I guess. Now, for the fall, the plan is to get this monovalent XBB.1.5 vaccine. To get this committee opinion, they actually had to submit preclinical data showing that the Omicron XBB.1.5, basically, the new COVID booster, generates an immune response against multiple XBB-related sub-lineages, including, not surprising, XBB.1.5, XBB.1.6, XBB.2.3, and EG.5.1, the Eris variant. What about the other variants, which seem to be even outcompeting the Eris so quickly? They say that the doses are basically ready to ship as soon as they get approval. All right, Vincent takes a deep breath. [laughs] All right.

VR: Good thing these are not mandatory, Daniel.

[laughter]

DG: All right. Now, you are here, you are there, who knows where you are, but you test positive, you have symptoms, you've got COVID-19, what do you do? Number one, I'm going to say this, Paxlovid. Within the first five days, you call your doctor, check the kidney function, check the drug-drug interactions. I recently had a visit with one of my patients who, dare I say, made the mistake of going to visit Florida.

While in Florida, this high-risk individual tested positive and went into an urgent care clinic. They confirmed the test. Then my patient said, "Doctor, would you be willing to call in some Paxlovid for me?" What did the urgent care doctor say? "Oh, we don't prescribe that here. We are too concerned about the risk of rebound and death. If you really want that, I will only give it to you if you sign what we call the death waiver. You have to accept responsibility should you have rebound or die from the Paxlovid."

VR: Did he sign it?

DG: That's shocking.

VR: Did he sign it?

DG: No, he called me. [laughs] Just a little bit taken by this whole, "You need to sign a death waiver."

VR: It's ridiculous.

DG: It's troubling. It's ridiculous. What happens when this individual or an individual who isn't one of my patients ends up in the hospital, ends up dying? There should be responsibility here. Probably the same doctor is giving out Tamiflu on day three and four, which does nothing, and giving antibiotics for those other viral illnesses. Here we have an effective 90% reduction in progression medication and he's getting his information from, I don't know what source, but not from the literature.

VR: That's why all those people are still dying that you mentioned earlier because this happens over and over again.

DG: I don't know if I mentioned last week, but it was a little troubling. I was talking to the daughter of an older woman who recently died in a nursing home. She was a little bit beside herself because here in New York, her mom was in a nursing home. The roommate tested positive for COVID, her mom then tested positive, had symptoms, no treatment was offered. They told her it would all be fine, and then her mom died. Now she is basically realizing, "I should have asked," and was asking me, "Should she have gotten Paxlovid?" The answer is yes.

These 500 people who are dying every week, common denominator is they're not getting treatment, so preventable deaths. All right. Let's talk a little bit about the remdesivir. Paxlovid is one option. I had a patient today who was on atrial fibrillation medicine, so not able to get Paxlovid. Remdesivir is the thought there. What about this issue of early three-day remdesivir? We've talked about the impressive data from the PINETREE study.

If you're in the first seven days, only three days of remdesivir is going to get you that 87% reduction in progression. If you are in that eight to 10 days, that little window where you end up in the hospital, but still before day 10, and you're not in the ICU, that's when you're looking at that five days remdesivir. Now we have the article, “Clinical Antiviral Efficacy of Remdesivir in Coronavirus Disease 2019: An Open-Label, Randomized Controlled Adaptive Platform Trial (PLATCOV),” published in *JID*.

We've got some more data here. These are the results of an ongoing multicenter open-label, controlled, adaptive, pharmacometric platform trial, looking at low-risk adult patients with early symptomatic COVID-19, randomized to one of eight treatment arms, including intravenous remdesivir. It's five days here or no study drug. The primary outcome was the rate of severe acute SARS-CoV-2 clearance in this duplicate oropharyngeal swab eluates. This is a modified intent to treat.

The two study arms enrolled 131 patients. We've got, in these two study arms, remdesivir for 67, no drug in 64, and they're going to do a whole bunch of swabs. Actually, a total of 2,356 QPCR reactions. Not surprising, you actually have remdesivir accelerated the mean estimated

RNA copy number. The reduction in that RNA copy number. You can imagine that I changed that from viral load to RNA copy number reduction.

All right. Number three, Thor's hammer, molnupiravir. Number four, convalescent plasma for immunocompromised COVID-19 patients at high risk in that first week with no other options. Remember to email Arturo Casadevall if you're having access issues. Let's avoid doing those harmful, useless things. All right. Now this person progresses to week two. They get a significant early inflammatory lower respiratory hypoxic phase. This is week two. We see this in about 20% of folks, whether or not they get treatment at that first week, but if they get treatment in the first week, they are 90% less likely to require medical care during this period of time.

If they do require medical care, let's talk about, one, steroids at the right time in the right patient. Remember it's always hard. What is most important and the least reliable is the history of trying to get that symptom onset. If they're hypoxic, you're probably getting into week two. If the oxygen saturations are less than 94%, remember that's the dexamethasone, 6 milligrams a day times six days.

We get a lot of questions. When did it change from 10 to 16? We talked about the article, “Optimal Duration of Systemic Corticosteroids in Coronavirus Disease 2019 Treatment: A Systematic Review and Meta-analysis,” published in *OFID*. This was that analysis that looked at 13,404 hospitalized COVID patients, seven RCTs, two observational studies. Found no benefit extending that beyond six days. I'll leave a link in here so people can have that when they want to update those order sets and treatment recommendations.

Two, we have anticoagulation guidelines from American Society of Hematology. Pretty much across the board, we are recommending anticoagulation unless there's a risk-benefit that pushes against it. Three, pulmonary support. Now, this is, I think, a really important article. The article, “Clinical Outcomes Associated With Overestimation of Oxygen Saturation by Pulse Oximetry in Patients Hospitalized With COVID-19,” published in *JAMA Network Open*.

This is they put that little thing on your finger, your ear, they say, "Oh, your oxygen saturation is great. Doesn't seem to make sense." Maybe they do a blood gas, and they say, "Oh my gosh, your oxygen is actually much lower." Really glad to see this article because this is something we were seeing quite often. You'll realize which patient population we saw it in. In this cohort, we have 24,504 patients with pulse oximetry and that arterial oxygen saturation measurement done at the same time.

The pulse oximeters more commonly overestimated the oxygen saturations. In which patients? Those from minority, racial, and ethnic groups and led to delayed recognition of the need for COVID-19 therapy among black patients compared with white patients. In a subset of over 8,000 patients without immediate need for COVID-19 therapy on admission, overestimation of oxygen saturation was associated with delayed delivery of COVID-19 therapy.

Let's just go through a little bit of the details here because among 24,504 patients with both measurements done, 41.9 were female; 16% were black; 32.2% Hispanic; Asian, Native American, Alaska Native, Hawaiian Pacific Islander, or any other race or ethnicity 10.4%, and

white 41.4%. Now, this is interesting. We talked about the delay in treatment, we talked about this overestimation. They did not find, there was no association of unrecognized need for COVID-19 therapy within hospital mortality or length of stay. Pretty wide error bars on this study.

All right. Number four. We've talked about hospitalization. Remdesivir still in the first 10 days. Zero to seven, three days. Eight, nine, and 10, five days. Still, in some cases, immune modulation with tocilizumab or baricitinib, only using those antibiotics in the appropriate context.

Getting ready to wrap us up, the late phase, the "Risk of Autoimmune Diseases Following COVID-19 and the Potential Protective Effect from Vaccination: A Population-based Cohort Study." published in *eClinicalMedicine*.

Here's this question. Lots of people are worried about those vaccines, but can the vaccines not only protect you against hospitalization, death, ending up in the ICU, but can the vaccines maybe protect you against autoimmune disease? These are the results of a retrospective cohort study conducted in Hong Kong. The study included over a million COVID-19 and over three million non-COVID individuals.

Compared with non-COVID controls, patients with COVID presented an increased risk of developing pernicious anemia, adjusted hazard ratio 1.72; spondyloarthritis, adjusted hazard ratio 1.3; rheumatoid arthritis, adjusted hazard ratio 1.29; other autoimmune arthritis, adjusted hazard ratio 1.43; psoriasis, 1.42; pemphigoid, 2.39; Graves' disease, 1.3; anti-phospholipid antibody syndrome, 2.12; immune-mediated thrombocytopenia that's where the platelets drop, 2.1; multiple sclerosis, 2.66. Two to three times more likely to get multiple sclerosis. Then vasculitis.

Now, among COVID-19 patients, completion of two doses of the COVID-19 vaccine was associated with a decreased risk of pemphigoid, Graves' disease, anti-phospholipid antibody syndrome, immune-mediated thrombocytopenia, lupus and other autoimmune arthritis.

VR: How much of a decrease, Daniel, do you know?

DG: They were all different. They calculated for the different - I will recommend people to read this. It's worth reading because it's quite a lot of numbers here as far as the increased risk and then the potential benefit reduction with the vaccines. Remember, this is just two doses. This is not, as we would say, completing the three-dose series.

I will finish with no one is safe until everyone is safe. I was recently in Switzerland. People probably know that. It's in the Geneva Canton where air conditioning is not legal, and it was 104 degrees, so it was very hot. Maybe that's why I'm looking forward to winter a little bit. [chuckles] It was interesting because my brother-in-law is a part of the U.S. mission to the UN and there's still a lot of concern, as he was saying, about the therapeutic differences with regards to COVID-19 between the West and particularly a lot of parts of Sub-Saharan Africa. By therapeutic, he's talking about vaccines, medicines, a lot of these different things.

I want people just to remember this, that we're all in this together. No one is safe until everyone is safe. I'm hoping everyone would pause recording right now. Go to

parasiteswithoutborders.com and click on the ‘Donate’ button. We are trying to raise enough money to give a donation of $20,000 to Floating Doctors down there in Panama. I'll be down teaching there in December again. All donations, August, September, October, we will double up to this potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. We have a letter here from Kathy Spindler. One of the *TWiV* hosts.

DG: Oh, I know, Kathy. [chuckles] Hey, Kathy.

VR: It's all about Paxlovid prophylactic prescription. "I wrote to my University of Michigan doctor, who I talked to in person in May before the FDA approval. For my upcoming trip to Croatia, I was hoping to get a prescription to take along. Here's what he wrote back. Is this your experience too? 'I checked with our pharmacy and infectious disease teams. Unfortunately, even though Paxlovid is FDA-approved, it can still only be written for treatment of active COVID and can't be given for prophylaxis to bring abroad for travel. Seems silly to me, but unfortunately, our hands are still tied.'"

DG: Your hands are not tied. Actually, you probably remember this, Vincent. Vincent, you and I were on this group discussion. One of these social media influencers, Jamie from out in the LA area, was talking about how there were certain different economic groups that were even under the EUA getting Paxlovid for travel. Jamie is a man of color and he's like, "It surely isn't happening for people in my particular racial group." People were doing this even before you really could. Right now, Paxlovid, it is a licensed medication. Licensed medications, one of the deals is physicians are allowed to use it off-label, so yes, your doctor can go ahead and your doctor can actually use it off-label.

We talked about when I was training, we had at that point, no FDA-approved medications for rate controlling people's atrial fibrillation, so we used medicines that we knew worked. Someone is traveling, Kathy, your age alone is going to put you at high risk. I don't know the rest of your medical history. When you travel, you should have some rapid tests with you, but what's going to happen? You are in Croatia, you test positive, are you going to be able to get Paxlovid within the first five days? Are you going to be able to get a 90% reduction? It actually makes a lot of sense and it is definitely OK to use medicines off-label.

Kathy, give me an email. Should you put us in touch? Kathy has my email. [laughs] She can just call me too.

VR: All right. Marianne writes, "What is the bell curve perhaps, which you see for severe RSV infections in the 60-plus population? I'm generally wary of new vaccines for a few years until more data are collected about adverse events. Exception was that COVID vaccine boosters, I'm a bit concerned about the new RSV vaccines for adults because Pfizer without an emergency status had about 36K in their stage three clinical trial with about 2.4% severe reactions, with GSK having about 24,000 in their study, with about a 4% severe reaction. GSK used an adjuvant, which seemed to give them higher efficacy while Pfizer did not. This is just my brief summary without the benefit of a PhD or MD education.

I believe both studies were done over six months. I will continue with my flu and COVID booster vaccines, and I think I'll wait a bit longer to learn more about the RSV vaccines before getting an injection. I do wear an N95 mask indoors. I would appreciate your feedback."

DG: This is great, Marianne. Actually, I was just checking because the other day I got a text from one of my colleagues, David Wertheim, he's our head of allergy and immunology here at what's now Optum Tri-State. He had similar questions. He is like, "Are these true? Was it 36? Was it 24? What were the adverse reactions? What are the recommendations?" This is why for this first year it is being recommended as shared decision-making.

What is that? If a person is 61, completely healthy, no medical conditions, that may not be a person that you have jumped to the front of the line. Let's say you've got someone who's 86, they're overweight, they have hypertension, they have high cholesterol, they have some other issues, that's someone you're going to say, "Listen -" We are seeing probably 15,000 to 25,000 deaths every winter from RSV in the adult population. We're seeing lots of hospitalizations. Are they going to be around children? There's a lot that goes into this.

That's a person that you're going to say, "Hey, from a risk-benefit, even if these are the numbers that hold," you would make that recommendation. Next year, next fall, we anticipate probably millions of people vaccinated. We'll have much more data, and then we'll start being able to ask that 61-year-old, otherwise healthy person, what's the risk-benefit there? Then we'll see how it goes, but no, I think this is reasonable.

As Paul Offit always points out, and I think this is really important, is that we need the science, we need the data. This is the data that we have right now. We only have about 60,000 individuals in these studies. We will have data on a million people, probably more, by next year, and that will help with the decision-making.

VR: Janie writes, "I don't recall that you recommended Paxlovid for teenagers, the young adults, since they generally fare pretty well with COVID, especially having been vaccinated. My son received two doses, first-generation Pfizer vaccine when he was 12. He's now 14. My daughter has three doses of first-gen Pfizer. School just started, they're finally done with masks. Should I put them on Paxlovid if they get COVID? We have a family member with Long COVID and I'm concerned with Dr. Topol's finding."

DG: [laughs] All right. There's a lot to unpack here. I'll discuss Dr. Topol's findings last. Paxlovid is indicated down to about 12 years of age. There's also about 44- or 40-kilogram weight, so there's a weight and an age on the lower end there. The reason I say 40/44, they're more like 39 or 45. You wouldn't do this if there weren't any other reasons, so it's a risk-benefit here. I see we're going to talk about Long COVID in a second, but it's a risk-benefit.

If you said, "Oh, I have a 14-year-old child. They're morbidly obese. They have diabetes. They have congenital heart issues," OK, yes, that's someone that we want to talk about treatment. If you say, "My son is 14. He's vaccinated. He's otherwise healthy," then we're not recommending Paxlovid in that context. Not everybody gets Paxlovid. I see you bring up the issue of Long COVID.

That's one of the challenges. In a 14-year-old if they get COVID, do we have compelling evidence that Paxlovid is going to significantly decrease that risk? There's some suggestion.

That's not really an indication, we need more science, so that's not something we're currently recommending at this point. If you said, "Oh, that family member is me and my husband and one other sibling," OK, then you start asking questions.

Dr. Topol's substack. This is not actually Dr. Topol's findings. If you look at this, Dr. Topol is merely sticking in his substack the research findings of other folks who actually did the research. I know Dr. Topol's name was on one of these Long COVID review articles, and I know in this is actually a mention of the VA study where they talk about continued issues in certain individuals two years out.

We've talked a little bit about that. Certainly, Long COVID is an issue. In the study that Theodore Iwashyna and colleagues covered 208,000 veterans, they actually were looking at individuals continuing to have some risk at as late as two years, so yes, this continues to be a concern. I think as we've talked about many times, we're not just concerned about ending up in the urgent care, the ER, the hospital, the ICU, or not surviving. Probably, as far as numbers go, this is one of the biggest concerns, is Long COVID and what actually can we do to prevent that from happening.

VR: Remember, that VA study is not the same age group as Janie's kids.

DG: Yes. I don't think anyone in the VA study was 14.

VR: We would hope not.

DG: [laughs] I hope no 14-year-old veterans.

VR: Finally, Lesa writes, "I was positive for COVID August 30th, will begin PaxlovidD today," Today is the 31st, very good. "My mom lives with me, she's 88 years old, and has bronchiectasis. Of course, my fear is that I have passed this to her before I began feeling ill. Would you play it out for me if she tests positive? My husband, my mom, and I have all been vaccinated and boosted as many times as we could. She would go straight to the ER?" That's a question. "Once there, no steroids for at least a week, would I ask for monoclonals or Paxlovid for her? What else should I be asking for her if she tests positive?"

DG: This is great because it's always nice to do a real-world example of what happens, right? Your mother is 88 years old, so already high-risk. Bronchiectasis. This is a pulmonary abnormality where you actually have this fixed dilation of your bronchioles, the breathing tubes. Again, adding to the high risk. 88 years old, chronic lung disease. This will be an individual who has a non-zero risk of progression, even having been vaccinated and boosted. This is a person that would qualify for treatment.

Number one, as we were saying, Paxlovid. What you want to do is you want to reach out to her provider. What are her other medicines? Are there any drug-drug interactions that need to be addressed? What is her kidney function so that the Paxlovid can be adjusted? We've talked about the fact that there's now data showing that you can safely use Paxlovid all the way down to an individual on dialysis. It's really going to be only the drug-drug interactions that we're most concerned about. At this point, remdesivir is number two. Molnupiravir, number three. We do not have any current monoclonals that work, so just forget about the monoclonals. That's it.

VR: She does say here, Daniel, "Once there are no steroids for at least a week, should I ask for Paxlovid?" That's too late, right?

DG: You want to get treatment within the first five days. The first five days of symptom onset. That's one of the things you want to do, is watch your mom, see how she does, try not to give her, if you haven't given her it already. You're still in that transmission period. You want to keep mom safe. If she starts getting symptoms, if she gets COVID, which is symptoms and a positive test, then you would want to treat her within the first five days. Yes, no steroids in the first five days. You wait until the second week and only in the second week if the person has an oxygen saturation of less than 94%.

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

DG: Thank you. Everyone, be safe.

[music]

[00:51:04] [END OF AUDIO]