This Week in Virology

TWiV 1020 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 1 July 2023

pdf of this transcript available (link)

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

[music]

VR: From MicrobeTV, this is TWiV, *This Week in Virology*, Episode 1,020, recorded on June 29, 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: Daniel. I'm in Atlanta, Georgia, just finished up ASV, American Society for Virology, where we did a podcast with Trevor Bedford. Some of our listeners may know developed nextstrain.org the virus-tracking website. I just wanted to say one thing that he related to us, the U.S. is on track to accumulate 80,000 COVID deaths in 2023, and as I told him, Daniel says they're mostly preventable.

DG: Any comment from Trevor on that one?

VR: He agreed completely.

DG: I know Trevor. He's done some good stuff. Do I get to listen to some kind of recording? Is there a podcast where I get to listen to Trevor or -?

VR: Yes, it will be this week's episode 1,021. The one right after this one, which drops on Sunday, which I think is July 1st, right at midnight.

DG: I know what I'm doing on Sunday [laughs], so let's get right into it. This is my HIV bow tie today. I'm actually going to start with a quotation from someone who was on the show a while back. "You can't take a knife on a plane anymore, but you can get on carrying a virus." That's David Quammen.

VR: Daniel, where do you carry these viruses on?

DG: You can carry them anywhere you want. They can be in your GI tract. You can carry them in your lungs. They can be on your hands. All over the place.

VR: Do you think we ought to be testing for these, Daniel, before you can get on a plane?

DG: I'm not sure it makes sense at this point. You wonder at some point with the technology, if you could know that you are safe getting onto that plane or safe in these other environments, like those dogs we talk about. Maybe we've got all these dogs around. It'll be interesting to see what the future holds. What is the hardest thing to predict according to Yogi Berra? The future.

This would be something that I don't know how many people had predicted this, but malaria, we are up to five cases of, I love this word, autochthonous malaria acquired here in the U.S. These are people, they did not travel hanging out here in the U.S. "minding their own business." In Sarasota County, Florida, officials confirmed they had identified a case of locally transmitted malaria. In mid-June, they confirmed a second. On June 23rd, a third case of malaria was identified in Texas, and now we're up to four cases in Florida. That one case in Texas so a total of five cases. These are the first documented, locally acquired cases in 20 years. So far these have been Plasmodium vivax.

I think a lot of folks don't know the history of malaria in the U.S. They don't know that malaria was for a period of time endemic all the way as far north as the swampy Washington, DC, region. Out as far west as parts of Kansas. A *Little House in the Prairie*. There's actually a little bit of an episode there where the family gets sick with what we think was a description of malaria. We've got the Anopheles mosquito, so we do have a vulnerability to reintroduction here.

VR: Where did these parasites come from, Daniel?

DG: The parasites probably came from a region. They came - as we talked, you can't get on an airplane with a knife, but you can get on the airplane parasitemic, with parasites in your blood. You then end up getting bitten by a female Anopheles mosquito. Then about 1 in 100, about 1% of female anopheles mosquitoes are double-biters. You get bitten by one of those double-biters, and then the double-biter bites someone else and gives them malaria.

VR: It seems to me that if we did genomic surveillance, we could know where this came from.

DG: Actually, you could really explore this because it's Plasmodium vivax, and then you could look at the gene X and say, "Where is this coming in from? Is it coming in from Central America, Sub-Saharan Africa, somewhere in Asia?" Actually, I think that would be interesting. I'm not sure if we would act on it in an appropriate way. I'm going to have trouble with only five cases.

VR: That's a good point. I think we shouldn't identify because then it would just lead to discrimination against that country, right?

DG: Yes. That's actually what I would worry about more than us doing the right thing. Give human beings the opportunity and they will.

Measles, I thought this was -

VR: Oh, one more thing. Sorry. What do you do with these patients? Can you treat them?

DG: Very treatable. The big thing is you got to be thinking about it, got to make the diagnosis, again, can be treated and these people should do well if the diagnosis is made and they're treated. My understanding is these five cases have all been diagnosed, treated, fully recovered at this point. Remember though, it's vivax, so it has the ability to get the hypnozoites in the liver. You've got to make sure you clear those or these people can have a relapse.

VR: How do you make sure you clear those?

DG: There's certain medications that will use like primaquine. Our *TWiP* fans, *This Week in Parasitism* fans, are probably familiar with that, that next step you have to do in addition to just treating the acute.

VR: Got it.

DG: Measles, I just got the health advisory from the CDC guidance on measles during the summer travel season. The CDC recommends that all U.S. residents older than age 6 months, your parents might need to jump in if you're about 7 months there, who travel internationally without evidence of immunity, receive the MMR vaccine prior to departure. They go on, infants 6 through 11 months of age should receive one dose of MMR vaccine before departure. Infants who receive a dose of MMR vaccine before their first birthday should receive two more doses of MMR vaccine.

The first of which should be administered when the child is 12 through 15 months of age. The second, at least 28 days later. Children 12 months of age or older should receive two doses of MMR vaccines separated by at least 28 days. Teenagers and adults without evidence of measles immunity should have documentation of two doses of MMR vaccine separated by at least 28 days.

This is due to measles outbreaks occurring throughout the world. I'll leave a link to this. Just a reminder across the board, these are vaccine-preventable illnesses, so fortunately we're starting to see more measles out there. Keep yourself safe and you do not need to remember all those recommendations because hopefully, your physician will help you walk through it.

Influenza, now that I know Dr. Bob Krug might be listening, I feel obliged to make sure I keep everyone updated on flu therapeutics beyond Tamiflu. A company out of San Diego, Cidara Therapeutics, is developing a drug with the catchy name CD388 in collaboration with Janssen Pharmaceuticals. On June 22, this drug received FDA fast-track designation. Part of why I'm presenting this is it's an interesting class of therapeutics that get people thinking about, so this is something they're familiar with. CD388 is a long-acting drug-Fc conjugate, so a DFC. This is a type of therapeutic and a class referred to as antiviral conjugates or AVCs. Lots of three-letter acronyms here.

These have one portion that is a small molecule that targets a highly conserved part on the surface of the influenza virus and a second Fc portion that recruits the immune cells such as NK cells. If you think about this, we often think of trying to use an immunoglobulin, let's think of the Y and the parts at the tips of the Ys, the tips of the fingers that bind, but here they're actually making a small molecule that targets that highly conserved area. Then they're putting

an Fc portion so that the hand part of the slingshot on the end of this so that the immune cells can jump in there.

It's an interesting and creative twist on the antibody-drug conjugate or ADC approach. I'm going to leave a link with a short little explanatory video that I think is actually helpful for understanding this class.

VR: What does it mean to be fast-tracked, Daniel?

DG: Basically, instead of the normal process, we're hoping this is going to move quicker through the FDA. I'm also going to put in this week a link to more info on XOFLUZA, the flu medication that functions by targeting the influenza viruses cap-dependent and no nucleus activity, including the link to the IDSA guidelines for influenza that were released in 2018 and have not been updated since. I do want to point out if people remember from last week, 2018 was right when XOFLUZA was FDA approved.

I will also link to the CDC page which has been updated since where we can read that there are four FDA-approved antiviral drugs recommended by CDC, not just Tamiflu, and we have oseltamivir, we have zanamivir, we have peramivir, and we have XOFLUZA. I'll leave a bunch of links there. I just want people to be thinking about the fact that we have more options. People don't just have a knee-jerk to grab something that, as we have discussed, is not as impressive as we would like.

Mpox, Vincent. We have started to see some mpox cases. We just admitted a gentleman yesterday morning, a severe case to the local hospital. Local when you come back to New York. We're starting to see cases here in New York, and as mentioned, some severe or several severe enough to require hospitalization. This was not unexpected. When we see enough of these cases and understand more, I will share. Right now just an alert to our listeners, particularly the providers in our local area, we want this back on the radar. On the nyc.gov page, they report there were five cases. They say last week, June 18 to June 24, we've seen more since then.

The reminder, if you do not think of it or test for it, you will not diagnose it. For our folks out there, if you're at risk, consider getting vaccinated. That's going to be the biggest thing that reins us in, in the coming months.

VR: Daniel, there haven't been cases for a while. Why now?

DG: There's been a trickle. There's been about 50, 60 cases since the beginning of the year, so it's out there. This is a time when maybe there's a little more contact going on. Unfortunately, the individual that we were taking care of yesterday, was in what they thought was a monogamous relationship, but obviously, the partner had been out there, had the exposure.

VR: Daniel, when you have these cases, do you do a travel history to see if they've been elsewhere?

DG: We do. You know ID docs, right? We ask everything.

VR: Yes, I do.

DG: Where were you born? Where have you been your entire life? What pets do you have? What food do you like to eat? Where have you been recently? There'll be a thorough - this looks like the partner acquired it locally, and there is this low-level background going on.

I think this also brings us right into COVID, what's going on with COVID. COVID keeps trickling in, so we do have that background level. When you have that background level, you can potentially see a rise in cases once you change a few of the dynamic. As we get into the late fall, early winter, there is an anticipation that more than just the trickle, the several cases that we're seeing in the hospital and in the community that we'll start to see that increase again. We'll keep everyone up to date on what they need to know going forward.

One of the things, I thought this was interesting, I was talking to my cousin, sometimes I call my honorary cousin, but he's my cousin as my wife reminds me. My cousin Peter and I were talking about the fact that he was supposed to be having an in-person meeting with some of his clients and they actually had to cancel and switch over to Zoom because in the office a number of individuals had ended up developing COVID-19.

Let's talk a little bit about testing because he asked the question about what's going on with antigen testing, are they even available? The article, "The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Antigen Testing," was published in *CID*. We've talked a lot about the data. What did the IDSA recommend? The IDSA convened an expert panel to perform a systematic review of the literature and develop best-practice guidance related to SARS-CoV-2 antigen testing. This guideline is an update to the third in a series of frequently updated COVID-19 diagnostic guidelines developed by the IDSA.

There were 10 different recommendations, but I'll sum this up. I'm going to say this is consistent with the science so I think that this is a reasonable bit of guidance. Rapid RT-PCR, or laboratory-based Nucleic Acid Amplification Testing, so NAAT, remain the testing methods of choice, the most sensitive for diagnosing SARS-CoV-2 infection. However, when timely molecular testing is not readily available or is logistically infeasible, antigen testing helps identify individuals with SARS-CoV-2 infection.

As we've said several times, antigen test sensitivity is dependent on the presence or absence of symptoms, on the timing of testing after symptom onset, and in most cases, positive antigen tests can be acted upon without confirmation. The sensitivity is the issue. The specificity is great. Results of point-of-care testing are comparable to those of laboratory-based testing and observed or unobserved self-collection of specimens for testing yield similar results.

Now, they do comment that modeling suggests that repeat antigen testing increases sensitivity compared with testing once. We've talked a little bit about, wait till that second day, if you still have symptoms, test, if it's negative, test again. Remember, there's a sensitivity, not a specificity issue. Now, this was interesting, and we'll see how many people are still fired up.

Data were insufficient to make a recommendation about the utility of antigen testing to guide release of patients with COVID-19 from isolation. I leave that out there, because I know

there's recommendations out there. What we're talking about here in this guidance is what does the science give us?

VR: We still are isolating, you mean, after positive test, Daniel?

DG: I liked the way you asked that. Some people are, some people, they're like, "I'm not testing because I don't want to know." Some people test, they say, "I got COVID, but I'm not going to change the way I behave." Other folks, though, they will get a positive test, and then they may do the recommended five day. Like we talked about these office workers, they may do the five days of staying out of the office, and when they do return, they'll wear a mask for five days. It's a mixed landscape out there.

VR: If you tested negative, you could just, if you're isolating, release from isolation, since they don't have a recommendation, right?

DG: Here's the interesting thing that we see is, people as soon as they get a positive test, they're like, "I got to get a negative test." Sometimes it's like day three. Day three, and they've been sick for three days. They're still feeling crummy, who knows, maybe they're feeling better. They do an antigen test, it's negative, and they say, "I'm done," and then they go into a crowded situation. I just don't think that we have the science to say that that makes a lot of sense.

We will move into ventilation transmission. I recently had to retake my New York State infection control course. It's a regular thing we do. I found it easy because I had written the test so--

VR: Wait a minute, I should write a test for you.

DG: [laughs] You should do it. I was like, "Oh, I know this answer." Another, I'm going to say, great article, “SARS-CoV-2 Variants and Age-dependent Infection Rates among Household and Nonhousehold Contacts,” was published in *Emerging Infectious Diseases*. Here the investigators analyzed COVID-19 cases recorded in a city in the Toyama Prefecture, Japan, over four periods, dominated by each of the four main viral variants.

We've got July 1 through October 31, 2020, that's the pre-VOC period. Then we've got April 1 through 30, 2021, that's the Alpha period. We've moved from the pre-variant of concern period to the Alpha period. July 3, through April 15, 2021, the Delta period, that's when everything changed. January 3 through 23, 2022, Omicron period. I don't think anyone got that, that's when everything changed, joke about Delta, but pointing that out.

VR: You got it, changed.

DG: We got a Delta joke. All right, Vincent, you got it. I got a birthday card or a Father's Day card from my daughter and she said, "I just hope I can grow up and be as funny as you think you are daddy."

VR: Wonderful.

DG: They defined a close contact as someone who had contact with a COVID-19 case patient during the period from two days before symptom onset until diagnosis. Close contacts were divided into household contacts, those who reside in the same household, and non-household contacts others who had contact with a confirmed COVID-19 case patient for greater than 15 minutes within one-meter distance without wearing any personal protective equipment. All contacts received SARS-COV-2 PCR testing regardless of symptom status. If the PCR results for the first test were negative, contacts received PCR testing again, if they went ahead and got some COVID-19 consistent symptoms.

Now infection rates during the Omicron period were 35% for household contacts and 15% for non-household contacts. After they adjusted for age, symptoms, sex, contact history, interval from diagnosis of index case patient to PCR test, and household size, the odd ratios for infection were 6.22 times higher among household contacts and 3.55 times higher among non-household contacts during the Omicron period than during the pre-VOC period. The risk for infection among household contacts 0 to 19 years of age increased significantly from 3% in the pre-VOC period to 38% during the Omicron period.

VR: This makes perfect sense because Omicron is immuno-evasive. Even if you have antibodies, they won't prevent infection, although your T cells still prevent severe disease, right, Daniel?

DG: How many times do we have to say that, Vincent? Just keep saying that. Anytime you get an opportunity.

VR: Forever. Vaccines work, we can say that a lot too.

DG: Vaccines work, they prevent disease. Another article, the article "Effect of COVID-19 Vaccination on Household Transmission Vaccination on household transmission of SARS-COV-2 in the Omicron Era: The Vaccine Effectiveness, Networking, and Universal Safety, (VENUS) Study." Now we're going to have to pull this apart because I want to make sure people understand all the implications here and how important timing might be. This was recently published in the *International Journal of Infectious Diseases*. These results of a retrospective study that was conducted using vaccination records, COVID-19 infection data, and resident registry data from two Japanese municipalities.

A household that experienced their first COVID-19 case between January and April, 2022, were categorized into two groups, according to the presence or absence of children age less than or equal to 11. Oh my gosh. During the study period, the following three vaccines were approved for use in Japan. The Pfizer-BioNTech, the Moderna Takeda, and the Oxford AstraZeneca.

For this study, they defined fully vaccinated individuals as those whom seven days had passed after receiving a third COVID-19 vaccine dose, other individuals were considered unvaccinated or I guess incompletely vaccinated. Those included those who had received only one dose that was only about 1%, two doses, that was 44%, and three doses, but they hadn't gotten through that seven days and that was 22%.

Based on combinations of the vaccination status of each primary case and each household contact, they set up the following four categories. Neither the primary case nor the household

contact were fully vaccinated, only the household contact was fully vaccinated, only the primary case was fully contacted, and both the primary case and household contact were fully vaccinated. They went ahead then and analyzed 7,326 households with 17,586 contacts.

I'm going to give you four bullet points. Several, things really stood out, and I'll couch ahead of time. These things may vary from time. They're looking here, seven days and onwards, so relatively soon, potentially, after vaccination. This may be different if you look six to eight months out. I just want to acknowledge that right up front. Vaccination of household contacts reduce the odds of household transmission by approximately 60% in all households. Both vaccination of cases and vaccination of contacts, conferred protection. No infections were detected when both the index patient and the contact were vaccinated.

The secondary attack rate in households with children, these 11 year and younger, was approximately twice that of household members where everyone was 12 or older. The odds for household transmission for women aged 20-59 years as household contacts was 70% higher than men aged 20-59 in the same households.

VR: Daniel, the further out you get from vaccination, obviously these numbers are going to drop, right? Did they stratify it according to that distance?

DG: I wish they had. I mean, I was digging for that because I would love to see - because we really want to understand what's the durability of that when we say transient protection against infection. Here you're seeing at least for a period of time this effect. You're also seeing, "Oh my gosh, children can actually be involved in the spread." Also, they made a suggestion that maybe the women are at higher rate because they're taking care of the kids even though the kids are sick. At least the idea here was when the kids were sick, the men were just keeping their distance. I know that goes on in my house whenever the kids are sick, I flee. My wife does all the heavy lifting.

COVID active vaccination. This is an interesting one. People got a little bit fiery or should say - I'll just say fiery. The article, “Incidence of Myopericarditis after mRNA COVID-19 Vaccination: A Meta-analysis with Focus on Adolescents Age 12 through 17 Years,” was recently published in the journal *Vaccine.* Lots of discussion over the last couple years about safety of the COVID vaccines and the relative risk of myopericarditis with vaccines versus infection without the protection of vaccination. I want to point that out because I saw a couple comments, "Well, we're all going to get COVID anyway, so why add the risk of vaccine?" The reason we're talking about this is getting that low risk with vaccination is going to significantly reduce your risk if you get infected without that protection. That'll be an issue more going forward.

Here the authors did a meta-analysis by searching for electronic databases up until February 6, 2023, observational studies reporting on adolescents age 12-17 years who had myopericarditis in temporal relationship to receiving mRNA COVID-19 vaccines were included. The pooled incidence of myopericarditis and 95% confidence interval were calculated using a single group meta-analysis. Fifteen studies were included. The pooled incidents of myopericarditis after mRNA COVID-19 vaccination among adolescents aged 12-17, where we think we see a peak, was 43.5 cases per million vaccine doses. Pretty much for

both the Pfizer-BioNTech and the Moderna vaccine. Looking at 39,628,242 doses and 41.8 cases per million vaccine doses. If you just looked at the Pfizer-BioNTech alone.

Myopericarditis was more common among males. That was 66 cases per million vaccine doses. Females, it was 10 cases per million vaccine doses. As they noted among those receiving the second dose, that was 60.4 cases per million vaccine doses compared to those first dose where it was 16.6 per million. None of the incidence of myocarditis pooled in the current study were higher than those after non-COVID-19 vaccinations. All of them were significantly lower than those in adolescents aged 12-17 after COVID-19 infection. I think what they need to throw in is do the math of, get this incidence, and then look at the reduced incidence of the much higher issue post-infection without this protection.

VR: Any fatalities involved here, Daniel?

DG: Not that they reported here, no. We certainly have seen COVID-related mortalities in this age group, unfortunately. The article, "Intrinsic and Effective Severity of COVID-19 Cases Infected with the Ancestral Strain," I wish they wouldn't use that, and Omicron BA.2 Variant in Hong Kong," was published in *JID*. Here the authors use COVID-19 patient data from Hong Kong to characterize the severity profile of COVID-19.

I'm going to say, if people go out and read one article this week, this is it. Time-varying and age-specific effective severity measured by case hospitalization risk and hospitalization fatality risk were estimated with an all individual COVID-19 case data collected in Hong Kong from 23 January, 2020 through 26 October, 2022, over six epidemic waves.

The intrinsic severity of Omicron BA.2 was compared with the estimate for the ancestral with the data from unvaccinated patients without previous infections. This is pretty tough to do. We're really asking the question, was there an intrinsic difference in the severity of the virus, or was the milder disease of Omicron due to preexisting immunity?

You know what, I'm thinking they're probably going to find but with 32,222 COVID-19 hospitalizations and 9,669 deaths confirmed over the six epidemic waves, the age-specific fatality risk in unvaccinated hospitalized Omicron cases was comparable to the estimates for unvaccinated cases with the ancestral. This might surprise many but in this analysis they concluded that Omicron has comparable intrinsic severity to the ancestral Wuhan, although the effective severity is substantially lower in Omicron cases due to -?

VR: Immunity.

DG: Yes, due to immunity.

VR: Hey, it doesn't surprise me, Daniel.

DG: It's crazy though. I have to say, this is one of those things that people have, I'm believing this, and don't let science stand in the way of a good story.

VR: The problem is that, unless you're doing a careful analysis here with the right patient group, if you just look at hospitalization data, you're going to get misled. That's what people do. Many scientists who are otherwise good scientists say, "Oh, Omicron is milder. It's quite

clear." Even the wonderful Mohsan Saeed, who did that great study at BU, about what contributes to Omicron, even he said, "Well, there's evidence in patients that it's mild." This shows you that if you do the right study, it's not.

DG: That's what you really have to do. Let's take someone who's not immune. Let's take a population that's not immune, and let's see what happens when they get the ancestral. Let's see what happens when they get Omicron. Oh my gosh, they do just as poorly. What makes Omicron mild is immunity.

VR: Now, what about in an unvaccinated person? The age-specific fatality risk in unvaccinated was comparable to unvaccinated with ancestral. Even in an unvaccinated, it's still comparable to the ancestral, correct?

DG: Yes. If you're unvaccinated, if you have no prior infection, whether you get the ancestral, whether you get Omicron, the fatality rate is the same. The intrinsic severity of the virus has not changed. Immunity is what has changed things.

VR: Omicron is not mild, and Daniel has said that multiple times over the past year and a half. You can go back and count them all.

DG: The article, "Safety, Immunogenicity and Protection of Heterologous Boost with an Aerosolised Ad5-nCoV after Two-dose Inactivated COVID-19 Vaccines in Adults: A Multicenter, Open-label Phase 3 Trial," was recently published in *The Lancet Infectious Diseases*. Now, this is one of those articles where I advise caution and suggest people focus on the details. I have seen this tweeted out to provide confirmation bias for a lot of people's ideas. I just want to start with this question up front. Is this a mucosal vaccine to induce mucosal immunity, or is this just a mucosal delivery method of a general COVID vaccine?

I think people are going down this road of saying here it is. Here's the mucosal vaccine, but let's see what we see. These are the results of a multicenter open label Phase 3 trial, done in 15 centers in six provinces in China, aim to evaluate the safety and immunogenicity of aerosolized Ad5-nCoV-2 in healthy adults. This study contained a non-randomly assigned safety cohort, and a centrally randomly assigned one-to-one immunogenicity subcohort.

The patients in the immunogenicity subcohort received aerosolized Ad5-nCoV or inactivated vaccine. The primary endpoint was the incidence of adverse reactions within 28 days following the booster vaccination in the safety population. The geometric mean titer of neutralizing antibodies at day 28 after the booster dose in the immunogenicity subcohort, and these are measured with a pseudo virus neutralization test. For clarity, we're going to see IgG data, not mucosal IgA data. Thus we are really just talking about mucosal delivery and not a mucosal immunity vaccine. Participants in the aerosolized Ad5-nCoV-2 group, had a significantly higher level of neutralizing antibodies against Omicron BA.4/5, than those did in the matched in the inactivated vaccine group at day 28.

VR: It's not surprising, Daniel, that you could deliver a mucosal vaccine, you get higher antibodies, than a parenteral I guess, or this is comparing inactivated vaccine. The real question is the longevity. How long is this going to last?

DG: The other thing is people are tweeting this out, "Look, we're making advances on that mucosal vaccine." For instance, we talk about FluMist, I don't think having the option of getting your vaccine squirted up your nose is necessarily what people are really after. They're after the idea of some enhanced mucosal IgA level maybe that persists. Let's be honest when we tweet stuff out there, folks.

VR: Oh you're asking for honesty on Twitter. Oh my god.

DG: Oh, good god, yes. Should I just give up? Just don't.

VR: No, no, you can't give up. As Churchill said, never, ever, ever, ever give up, but it's just very frustrating.

DG: Yes, I will not give up. This is a recap, I want people to keep this on the radar. The person tests positive. You test positive, COVID early viral, upper respiratory, nonhypoxic phase, maybe you got your immunity, that's great, but now you've got that ongoing viral replication. We're in the first week. You've got symptoms, you've got COVID-19. You're an individual with a non-zero risk of progression and having some problems, number one Paxlovid. Number two, if you can get it, IV three-day remdesivir. Number three, molnupiravir. Number four, early treatment option for the immunosuppressed without any other options. The big thing we keep hammering on stop doing harmful things, stop giving out those Z-Paks. Definitely, don't do steroids in that first week unless you really are compelled.

Moving into the second week, and fortunately, we're still seeing some folks come into the hospital during the second week. The cytokine storm, things got a little bit better, but now we have that early inflammatory, lower respiratory hypoxic phase. In the right patient at the right time, steroids. Anticoagulation guidelines from a number of societies, including American Society of Hematology. Pulmonary support, something new here. I'll say confirming, I'll say, some of our ideas.

The article, “Awake Prone Positioning for Non-intubated Patients with COVID-19-related Acute Hypoxic Respiratory Failure: A Systematic Review Based on Eight High-quality Randomized Controlled Trials,” was published in *BMC Infectious Diseases*. Eight randomized controlled trials, RCTs, involving 2,657 patients were included in this meta-analysis.

They reported that this intervention was safe, well, I'm going to say can be done safely, and compared with usual care awake prone positioning significantly reduced the intubation rates, so odds ratio 0.72. About a 28% reduction ending up on that ventilator. They reported that all eight RCTs had high-quality of evidence, which really supported the reliability of the meta-analysis results. Remdesivir if we're still in the first 10 days, immune modulation with things like tocilizumab in some patients, and again let's not do harmful things.

A few things here to wrap us up in the Long COVID, the late phase. The article, *“*Melatonin Effects on Sleep Quality of COVID-19 Patients: A Protocol for Systematic Review and Meta-analysis of Randomized Controlled Trials with Trial Sequential Analysis.” was published in *BMJ Open*. I was a little disappointed. This is a publication where they announce and describe that they will search for RCT type studies of melatonin in the treatment of sleep disturbances in patients with COVID-19. No results yet, but I look forward to the results and anticipate discussing them when available.

The mini-review article, “Female Reproductive Health Impacts of Long COVID and Associated Illnesses Including ME/CFS, POTS, and Connective Tissue Disorders: A Literature Review,” was recently published in *Frontiers in Rehabilitation Sciences*. Lots of interesting information as review, but one section that caught my eye was section 2.3, Long COVID and pregnancy. Here they mention a small but they say important control match prospective cohort study in Brazil, n=88, so not huge, where they followed pregnant women after testing positive for COVID-19, finding that in this, they report 75.9% developed Long COVID. It's a very high number. That was concerning.

The study also found that patients given glucocorticoids to treat COVID-19 during pregnancy were at higher risk of persistent fatigue, which is a key and debilitating Long COVID symptom. I'll leave a link into the referenced article. It also references a number of other studies as well.

I'm going to wrap us up with the article, “Incident Autoimmune Diseases in Association with SARS-CoV-2 Infection: A Matched Cohort Study,” recently published in *Clinical Rheumatology*. Here, the researchers set out to investigate whether the risk of developing an incident autoimmune disease is increased in patients with prior COVID-19 disease compared to those without.

These results of a study looking at a large cohort selected from German routine healthcare data, in total 641,704 patients with COVID-19 were included, comparing the incident rates in the COVID-19 and match control groups, matched as well as they could. They found a 42.63% higher likelihood of acquiring autoimmunity for patients who had suffered from COVID-19. This estimate was similar for common autoimmune diseases such as Hashimoto thyroiditis, rheumatoid arthritis, or Sjogren’s syndrome. The highest incident rate ratio was observed for autoimmune diseases of the vasculitis group, interesting, with a more severe course of COVID-19, putting folks at greater risk for incident autoimmune disease.

I will close this out with low and middle-income countries. I've been repeating also for about three years, "No one is safe until everyone is safe, have a plan for global equity." I do want to encourage everyone to pause right here, go to parasiteswithoutborders.com and click ‘Donate.’ We are about two-thirds of the way through our Foundation International Medical Relief of Children fundraiser. May, June, and July donations made to PWB will be matched and doubled up to a potential donation of $20,000 from PWB to FIMRC. It's going slow, we need your help, folks. We've only got about a month to go.

VR: It's time for your questions for Daniel. You can send them to Daniel@microbe.tv. Lisa writes, "I live in Sarasota County, Florida. We have recently had two confirmed malaria cases in this area, and hearing this news, I'm thinking, 'Malaria in the U.S.?' It's reported that this species is less fatal than others, but it's still worrisome to me. I'm wondering if you can shed any helpful thoughts or information." Lisa is an APRN and PNP-PC in Venice."

DG: Lisa, thank you for writing. We have this on the radar. One of the things I think is to understand malaria, now suddenly have to understand malaria living in Florida, this is acquired by the bite of a female Anopheles mosquito. The Anopheles female mosquitoes tend to be night biters and even not just night biters, but darkness biters. When you're out and about, there is an encouragement to avoid mosquito bites a little bit, use the sprays.

We'll actually be talking about problems with insecticide and mosquitoes, and malaria on the next *This Week in Parasitism*. Try to avoid those nighttime biting, just try to reconsider some of your decisions about putting yourself in harm's way now. We do not expect this to this time become an entrenched disease again, but for the time being, until it's clear that this is no longer a problem, just exercise a little bit more caution.

VR: Russ writes, "On your June 16 update, one of the questions posed to you was regards to flecainide and Paxlovid," is that the way you say it, Daniel?

DG: Flecainide.

VR: Flecainide and Paxlovid. "I thought it would be good to communicate to your listeners some clarification. You spoke of having a plan, however, you didn't specifically address flecainide. This is a medication you cannot simply stop to start Paxlovid, as you can with many others. Flecainide has too long of a half-life, as you know well, it's an antiarrhythmic, and stopping it may allow her to revert to AFib. It's worth noting as well that three of the other antiarrhythmic commonly used for AFib, amiodarone, propafenone, and dronedarone, make the person taking it be unable to take Paxlovid. Metoprolol was also mentioned in the question, this medication is okay to take with Paxlovid. If I were the primary care provider for that patient, I would advise her first and foremost is up to date on vaccinations. Secondly, she should look into remdesivir. I would advise her regarding molnupiravir, as an option I would encourage you to seek testing at first symptoms by having home testing kits available." Any thoughts, Daniel?

DG: This is great. Thank you, Russ, for bringing this up. When I get a med list that starts to go into medicines like this, I will actually sit down at a computer with the Liverpool COVID-19 medication interaction checker, and I'll put each of the medicines into this. I've a patient recently - it took me about half an hour, so he and I worked through, "What medicine you're on, let's go through."

When you identify a medicine like flecainide, maybe amiodarone, some of the other commonly used ones, you plug them in, and if it turns out there's an interaction, then yes, as Russ recommends, hopefully, he's getting this from listening to *This Week in Virology*, clinical updates, but you may, in certain situations, not be able to do the Paxlovid. Not every drug-drug interaction can be easily navigated, and you may need to look at another option, such as, we discussed here, the three-day remdesivir, maybe molnupiravir. It takes a little time, and when you start getting outside the world of statins and a few other familiar medicines, a clinician needs to take that time and make those determinations.

VR: Russ, also wants you to address the benefits of boosters on T-cell responses. "I've read there are data indicating T-cell response has a twofold increase after an updated booster regardless of prior infection. Can you address this?"

DG: This is something that comes up several times. I know, Vincent, when you've asked about this, people just complained that it's really hard to test those T-cell responses, so - There seems to be a significant correlation between T-cell immunity and the protection against severe disease, I would love more data here. What does the twofold increase actually mean? Does that translate into something clinically significant?

I think one of the things I will say, and this will be a challenge for us going forward, when we look at boosters, often we get data back, one month, two months, three months. We do expect, particularly if we get a well-matched booster with a circulating variant, if we're able to generate neutralizing IgA that we will get some protection against infection. That will translate into some period of time where if you don't get infected, you reduce that risk, you reduce your risk of severe disease. I, like Vincent, like you, Russ, would love to see more information about the T-cell response of the boosters.

VR: Brandon writes, "In a previous episode, you sounded optimistic that those with Long COVID who stuck with pacing were more likely to recover, but aren't patients more likely to stick with pacing if they're actually recovering? I'm just thinking the causality arrow could easily point the other way."

DG: Yes. Brandon, that was actually one of the critiques that, not only a lot of people made, but also one that echoes with me. Basically, people who are doing better are doing better. People who are doing better are going to be able to stick with pacing, people who are just struggling and not doing well are going to stop with the pacing. Is pacing and the ability to get better just a marker that you're participating in getting better, or is it really that pacing is a better approach? This is something we are going to continue to have a look at, and be scientifically critical, don't just get excited about confirmation bias.

VR: It's a long-standing controversy about pacing and ME/CFS, where some physicians in the UK feel it's beneficial, and many, many people feel that it's not. David Tuller has written a lot about that at *virology blog*. It's not a straightforward issue there. That's *TWiV,* weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

DG: Thank you. Everyone, be safe.

[music]