This Week in Virology

TWiV 1034 Clinical Update

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Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick. From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1034, recorded on August 10, 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: Does the COVID case numbers continue to rise, Daniel?

DG: I have to say the COVID case numbers are getting high enough now. Actually, the hospital admissions high enough, actually we're having a discussion. Do we need to have a COVID ward just because so many folks are getting admitted? The numbers are still increasing. This is happening in several areas of the country. We have our theories, just standard infection things. Transmission. People are inside. They're gathered. This is a respiratory pathogen.

VR: I think the answer is, Daniel, that August is the new December.

DG: [laughs] Is that what it is? OK. I see you wearing orange because orange is the new black. [laughter] All right. Let me jump right in with our quotation. “Gatsby believed in the green light, the orgastic future that year by year recedes before us. It eluded us then, but that's no matter. Tomorrow we will run faster, stretch out our arms farther, and then one fine morning - So we beat on, boats against the current, borne back ceaselessly into the past.”

A couple of reasons why that F. Scott Fitzgerald quotation from the end of *The Great Gatsby* will be relevant today. Maybe one of them was the one you just brought up. So many people thought we were through this. Now I'm getting a lot of people saying, "I sort of wished I could forget about COVID, but now I feel like I need to be up to date on what's going on."

We're still here. After a couple of mentions of RSV and influenza, we'll get right into COVID, but first, I think this is on a lot of people's mind, a lot of questions about this. The U.S. CDC Advisory Committee unanimously recommended routine use of Beyfortus, that's the nirsevimab, to protect infants against RSV disease. Actually, this is quite sweeping. What did the advisory committee recommend? I had to read this a couple of times, but recommendation for use in all infants below 8 months of age.

Also, unanimously to include Beyfortus in the Vaccines for Children Program, supporting equitable access for all eligible infants. Interesting. This is a MAB, a monoclonal antibody, but it's being put in the vaccines, it's being treated like a vaccine. The Beyfortus approved for protection of all infants will be, I think this is important, they say available ahead of the 2023-2024 RSV season.

Just to sort of put this together, the U.S. Centers for CDC and P, so it's Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices voted unanimously, 10 to zero, to recommend the routine use of nirsevimab, Beyfortus, so this is Sanofi and AstraZeneca's product, for the prevention of RSV, lower respiratory tract disease for newborns and infants below 8 months of age, born during or entering their first RSV season.

These provisional ACIP recommendations will be forwarded to the director of the CDC and the U.S. Department of Health and Human Services for review and possible approval. The official recommendation will then be published in the CDC's *MMWR, Morbidity and Mortality Weekly Report*.

VR: We had a good discussion of this by Paul Offit on the most recent *Beyond the Noise*.

DG: All right. Excellent. I haven't listened to that yet. Somehow I've got to get it to where it comes up as a feed and I hear it right away. I look forward to hearing that. All right. Flu. It's already August and flu season will be here soon. Some people may already be thinking about the coming influenza season. We have the article, "Immunogenicity, Safety, and Preliminary Efficacy Evaluation of OVX836, a Nucleoprotein-based Universal Influenza A Vaccine Candidate: A Randomized, Double-blind, Placebo-controlled, Phase 2a Trial," published in *The Lancet Infectious Diseases*.

In this Phase 2a randomized, double-blinded, placebo-controlled study, they recruited 137 healthy adults aged 18 to 55 years in a single center in Belgium. Participants were randomly assigned to receive one single intramuscular administration of the OVX836 influenza vaccine at three doses. The two primary endpoints were the safety and the cell-mediated immune responses to OVX836 at the three doses in terms of change in nucleoprotein-specific interferon-gamma spot-forming cell frequencies in the peripheral blood population.

They're measuring interferon-gamma ELISpot at Day 8 versus pre-injection baseline Day 1. The OVX836 increased the frequency of these nuclear protein-specific interferon-gamma cells, SFCs, so spot-forming cells, per million PBMCs from Days 1 to 8, that's the primary endpoint, in a dose-dependent manner compared to placebo. Dose-dependent and polyfunctional nuclear protein-specific CD4 T cell responses were observed. CD8 T cell responses were elicited at the 300-microgram and the 480-microgram as secondary endpoints.

They concluded, quite encouraging, OVX836 appears to be a safe and well-tolerated candidate vaccine that elicits humoral and cellular nuclear protein-specific immune responses, including CD8 T cells at the highest dose levels and showed a preliminary signal of protection against influenza. OVX836 is a promising vaccine candidate for universal influenza A prevention that they say, and I agree, warrants further trials. Unfortunately, this, like so many great articles, is behind a paywall.

VR: They will have to do an efficacy trial to see if it actually prevents influenza.

DG: Yes. I mean, this is interesting. This is Phase 2a. So we really need that Phase 3 efficacy trial. It's great. It's safe. We're seeing these immune responses, but yes, what we really want to know is, does it work?

Now we're into COVID and a lot of questions now. I think when COVID numbers and COVID hospitalizations rise, people suddenly sort of come back and ask what's going on.

One of the things that's been in the press, in the news lately is Eris or EG.5, but also what about FL.1.51? Here in the Northeast, is it the end of the XBB period? A big question is how will changes in the variants impact our booster plans? The whole idea is let's make some XBB variants, sort of trying to predict the future, as Yogi Berra says, the hardest thing to do. If you look at our Region 2, that's where we live here in the Northeast, but you can actually look at variants across the country and believe in a link, you can actually see that EG.5 and FL.1.5.1 are actually really making some inroads relative to all the XBB variants that we've been living with for quite some time.

Moving on to post-exposure testing. How do you keep yourself safe? Well, this is a fun article, a little bit gross, for the children that might be listening. We have the article "Why Not to Pick Your Nose: Association Between Nose Picking and SARS-CoV-2 Incidents, a Cohort Study in Hospital Health Care Workers" published in *PLOS One*. For those parents, and well, just all of us who need another reason to discourage nose-picking, these are results of a cohort study where they looked at 404 healthcare workers in two university medical centers in the Netherlands.

SARS-CoV-2 specific antibodies were prospectively measured during the first phase of the pandemic. For this study, healthcare workers received a retrospective survey regarding behavioral and physical features. Now, only about 52%, only about half of the healthcare workers, completed the survey. And 15.5% became SARS-CoV-2 seropositive during follow-up from March 2020 till October 2020.

Now, the majority of health care workers, are you ready for this, Vincent, 84.5% reported picking their nose, at least incidentally, with frequency varying, between monthly, all right, weekly, and daily. SARS-CoV-2 incidents was highest in the nose-picking healthcare workers compared to participants who refrain from nose-picking, 17.3 % versus 5.9. Now, that's an odds ratio of 3.8. What I did find was, well, maybe this is - I wish they'd found this as well because I'm also a stickler for people who are chewing on their nails, but no association observed between the nail biters, those that wore glasses, or those with beards and the incidence of SARS-CoV-2 infection.

VR: I wonder how they posed this question. They just said, "Do you pick your nose," or do they say -

DG: I think that was the binary.

VR: That's it.

DG: "Do you pick your nose?"

VR: Yes or no?

DG: Then it was, "How often? Is it just incidental? Is it once a month? Do you do this every week? Are you doing it every day?"

VR: Daniel, do you pick your nose?

DG: [laughs] Of course not. That's disgusting.

VR: I have a feeling that many people do, but they don't realize it.

DG: Yes. I think that's sort of interesting. Yes. There's people who pick their nose and there's people who lie about it.

VR: The idea would be that you have some virus on your fingers that you got from someone else and then you put it in your nose by picking your nose, right?

DG: I think that would be the idea here because we're looking at people getting it. You're not getting it by picking your nose, you're getting it by introducing it into your nose. This is in transmission to others. The other side would be observing people who pick their nose, are they more super spreaders than those of us who deny picking their noses?

VR: I suspect this would apply to many respiratory infections, right?

DG: Yes. Yes. It is interesting that the nail-biting wasn't associated, just something about the transmission here.

VR: I'm happy about the beard result.

DG: I was looking at your beard [laughs] as I was going through that. That actually came up today as this interesting issue that you need to be fit-tested for the N95 masks, right? They go on, they form a seal, but if you have certain facial hair patterns, the CDC basically says that's not going to work. You're not going to be able to get a good seal. Your beard, a proper beard, that's not going to work.

I was talking to Brian Laird and he's kind of got this goatee thing going, which maybe you can get a mask to surround that and still form a good seal, but no, it's a bit of a problem. If your job requires you to be in a situation where you need the benefit of an N95 and your facial hair doesn't give you a proper seal, then yes, you're going to be at risk in those settings.

VR: Well, now that we don't mask any longer, the beard is not really going to have an impact, right?

DG: Yes. It's really the healthcare workers, those of us that are still going into the rooms, and spending some time breathing in and trying to keep ourselves safe. All right. The article "Effective COVID-19 Vaccination and Booster on Maternal Fetal Outcomes: A Retrospective Cohort study" was published in *Lancet Digital Health*. I will warn, I warned the other one was gross where we talked about nose-picking, this is going to be where I get emotional and you get opprobrium, but repetition is critical in this arena.

Here we have the results of a retrospective multi-center cohort study on the impact of COVID-19 vaccination on maternal-fetal outcomes for people who delivered at Providence St. Joseph Health. That's an N of 106,428 across seven Western U.S states from January 26, 2021 to October 26, 2022. This is really this question of, is it important for pregnant individuals to get vaccinated? Is this going to protect them? Is it going to protect the unborn child?

Well, cohorts were defined by vaccination status at delivery. We had vaccinated, we had folks with two or more doses of mRNA-1273 Moderna or the Pfizer-BioNTech. Then we had unvaccinated. Unvaccinated propensity score matched. We had boosted, vaccinated, unboosted. The primary outcome was maternal SARS-CoV-2 infection, COVID-19 vaccination status at delivery, COVID-19-related health care, preterm birth, stillbirth, and very low birth weight were calculated as secondary outcome.

Maybe I'm not as interested in this first outcome, but I will comment. They found that vaccinated pregnant people had lower rates of COVID-19 during pregnancy compared with unvaccinated people. All right. Now, this is the take-home message and why I'm going to actually stand on my soapbox and say it is irresponsible to discourage women from getting vaccinated.

They found that unvaccinated people were more likely to have, one, preterm birth; two, they were twice as likely to have a stillbirth, 50% more likely to have a very low birth weight neonate. So, not only do we protect the pregnant individual, but we actually protect the unborn child from dying, from not actually surviving the pregnancy. I just want to point that out because your professional society recommends that you advise pregnant individuals to get vaccinated. I know there's some OBs out there who are not really on board.

All right. I should point out while we're talking about vaccines, we are hearing that those updated vaccines will be available by the end of September. We'll be giving people updates in time regarding the potential benefits, which populations would benefit from those, but one of the other things about vaccination is inflammation.

Inflammation is not good, right? Well, we also have the article "Dynamics of Inflammatory Responses after SARS-CoV-2 Infection by Vaccination Status in the USA: A Prospective Cohort Study," published in *The Lancet Microbe.* OK, some sorts of inflammation are good, but let's see what we're looking at here. This is a very simple study with an important result. These are the results of a longitudinal prospective cohort study where blood samples were used from participants enrolled in a multi-center, randomized trial assessing the efficacy of convalescent plasma for ambulatory COVID-19.

The trial was conducted in 23 outpatient sites in the USA. In this study, participants were 18 or older, those who had COVID-19 before vaccination or with infections post-vaccination, who had blood samples and symptom data collected at screening, so a pre-transfusion, a Day 14 and a Day 90 visit. Association between COVID-19 vaccination status and concentrations of 21 cytokines and chemokines were examined using this multivariate linear mixed effects regression model that they adjusted for AIDS, sex, BMI, hypertension, diabetes, et cetera.

They found that the concentrations of a number of the interleukins, as well as interferon-gamma-inducible protein-10, monocyte chemoattractant protein-1, and TNF alpha were

significantly lower among the fully vaccinated than the unvaccinated group. On Day 90, fully vaccinated participants had approximately 20% lower concentrations of IL-7, IL-8, vascular endothelial growth factor-A than the unvaccinated. Right up front, that vaccination is preventing you from having this cytokine storm, and also protecting you when you follow folks out over time.

Now, moving into the early viral upper respiratory non-hypoxic phase. You've tested positive. Either you've tested positive, your patient has tested positive. I know there's a bunch of folks that are coming back to listen again now that COVID is becoming more of a thing. Number one, what do we recommend? Paxlovid in anyone who has a high risk of progressions. That's over the age of 50, a number of comorbidities. It's an easy lift, remember, twice a day for five days. We're looking at renal function. We're looking at drug-drug interactions and working through those.

Number two, remdesivir, three-day early IV access. Molnupiravir, Thor's hammer, sort of our third option, maybe about a 30% reduction compared to that 80% to 90% reduction progression we saw. Convalescent plasma, really restricted to the early outpatient treatment of immunocompromised individuals. We're not doing harmful or unuseful things, but one of the big things people keep asking is, "Yes, I don't really think I'm going to end up in the hospital. I don't really think I'm going to end up on a ventilator or not survive this, but I'm really worried about Long COVID."

The big question is around what we can do during this early viral phase that might provide protection. I got a call just yesterday from one of my partners, Dr. Lee. Apparently, metformin is out there on social media. We've discussed the potential benefit of Paxlovid, the limited evidence from the COVID-OUT trial that metformin may be an inferior option with an associated complicated dosing regimen for those that cannot access Paxlovid, remdesivir, or molnupiravir, but what about early treatment with monoclonal antibodies?

The article, "Does Monoclonal Antibody Treatment for COVID-19 Impact Short and Long-term Outcomes in a Large Generalisable Population? A Retrospective Cohort Study in the USA," was recently published in *BMJ Open*. As the first author, I'm a bit partial to this one. Not really the answer I wanted, but here are the results. A sample of 3,809 individuals who received monoclonal antibodies and a matched one-to-one comparison group from a set of 327,079 eligible patients who did not receive monoclonal antibody treatment was selected from a deidentified administrative data set. We found that individuals who received MAb, for some good news, were 28% less likely to be hospitalized. This is real world. You're not always getting it in those first three to five days like you would ideally want. That's a hazard ratio of 0.72; 41% less likely to be admitted to the ICU, hazard ratio of 0.59. But then we found that a higher proportion of individuals who received MAb therapy received care for clinical sequelae in the post-acute phase, and that was a p-value of less than 0.02.

While we again verified in this large generalizable population real world that monoclonal antibody therapy was associated with benefits in the acute period, the benefit did not extend into the post-acute period, did not reduce the risk for clinical sequelae.

VR: Seems that 28% is rather low, Daniel. What do you think is the reason for that, not getting it early enough?

DG: I think that's the biggest issue, is a lot of people, and we tried as much as possible, in the trials, you're getting people in and the median time in those trials was about three days from symptom onset, but when you start looking at real-world logistics, I mean, a lot of places, you go online, the doctor puts stuff in, the patient gets a call, they get scheduled two to three days later, maybe it's even worse on the weekend. A lot of folks were not getting it as early as we really need to get these therapies in there.

Moving on to the second, now the patient has ended up in the hospital, a refresher for those coming back to join us. You end up in the hospital, that oxidation saturation is less than 94%. Dexamethasone, six milligrams a day times six days, please update those order sets. Number two, anticoagulation, we have recommendations from American Society of Hematology. In general, I think most people are doing a prophylactic dose, but in some individuals who sort of match what we saw earlier in the pandemic, a full dose.

Pulmonary support, still have that proning out there. Remdesivir, if you're in the first 10 days, but once you're past that, we're really not seeing benefit. Immune modulation, certain patients will benefit from tocilizumab, the IL-6 receptor blocker. Avoid those unnecessary antibiotics, proven and unproven therapies. Remember, this is a virus, not something we want to throw antibiotics at willy-nilly.

All right, and moving on to the part which I sort of expected would become a significant chunk, but Long COVID, late phase. The article, "Persistent Endothelial Dysfunction in Post-COVID-19 Syndrome and its Associations with Symptom Severity and Chronic Inflammation," was recently published in the journal *Angiogenesis*. These are the results of a prospective observational cohort study where they analyzed retinal microcirculation using this retinal vessel analysis in a cohort of patients with PCS, that's post-COVID syndrome or Long COVID, compared to an age and gender-matched healthy cohort.

The PCS patients exhibit persistent endothelial dysfunction as indicated by significantly lower venular flicker-induced dilation. That's a new one for a lot of us. Narrower central retinal artery equivalent and lower arteriolar-venular ratio. When they combine these scores, they reached a good ability to discriminate the groups, and the association of microvascular changes with PCS severity were amplified in PCS patients exhibiting higher levels of inflammatory parameters.

I'm not an ophthalmologist, so I love having the graphical abstract to help me here, and I do recommend, take a look at this. Apparently, the RVA, this analysis was performed using this commercial product made by the Germans. They used another product to do the SVA measurements. Before the examination, the pupils were dilated. They were seated in a quiet, dark room for a 10-minute rest period, and then they used this mydriatic retinal camera. We actually get to see some of the images in the abstract here. Yes, a little bit of information support for the ongoing concern about persistent endothelial dysfunction in COVID-19.

VR: I have to say, Daniel, this curve they have of this reduced flicker-induced dilation, the curves are exactly the same, except the peak in the healthy people is 104%, and the peak in the people with Long COVID is 103%. So, 1%, I don't know if that is of any clinical significance because I don't know this assay at all, but it seems pretty close to me, doesn't it?

DG: It's pretty close. You need that statistician to work with us to help, but we were getting p-values, they tell us 0.02, 0.01, 0.007. I mean, they're seeing statistically significant. Now, clinically, that becomes the issue. I think this supports the theory of an ongoing endothelial dysfunction, inflamed endothelial driving this, but no, I think that's a well-placed comment.

That's it. I guess it's all endothelial dysfunction. We have the answer. Is Long COVID all about endothelial dysfunction? Well, we also have the article, "Core Mitochondrial Genes are Down-regulated during SARS-CoV-2 Infection of Rodent and Human Hosts," published in *Science Translational Medicine*. There's a nice editor's summary by Orla Smith. I'll read that.

SARS-CoV-2 needs host cells to generate molecules for viral replication and propagation. In this article, Guarnieri *et al*.- probably pronouncing that wrong. Can you pronounce that, Vincent? Was that -

VR: It's Guarnieri.

DG: Perfect. Now show [laughs] that the virus is able to block expression of both nuclear-encoded and mitochondrial-encoded mitochondrial genes, resulting in impaired host mitochondrial function. The authors analyzed human nasopharyngeal samples and autopsy tissues from patients with COVID-19 and tissues from hamsters and mice, them's the rodents, infected with SARS-CoV-2.

Host cells attempt to compensate, here they're anthropomorphizing, by activating innate immune defenses and mitochondrial gene expression, but chronically impaired mitochondrial function ultimately may result in serious COVID-19 sequelae, such as organ failure. I'm sorry that Orla Smith anthropomorphized there, but all right. SARS-CoV-2 viral proteins appear to bind to host mitochondrial proteins, such as OXPHOS stimulating glycolysis.

Here the investigators analyzed mitochondrial gene expression in, as I mentioned, nasopharyngeal and autopsy tissues from patients with COVID-19. In nasopharyngeal samples with declining viral titers, the virus was associated with blocking of the transcription of a subset of nuclear DNA-encoded mitochondrial OXPHOS genes, induced the expression of microRNA 2392, activated HIF-1-alpha to induce glycolysis, and activated host immune defenses, including the integrated stress response.

I think it's important to break this down. I'm going to do this because people just sort of want a binary here, but timing has always mattered in COVID-19. In autopsy tissues from patients with COVID-19, SARS-CoV-2, the virus, was no longer present, and mitochondrial gene transcription had recovered in the lungs. However, nuclear DNA mitochondrial gene expression remained suppressed in autopsy tissue from heart, and to a lesser extent, kidney and liver, whereas mitochondrial DNA transcription was induced and host immune defense pathways were activated.

During early SARS-CoV-2 infection of hamsters with peak lung viral load, mitochondrial gene expression in the lung was minimally perturbed but was downregulated in the cerebellum, upregulated in the striatum, even though no SARS-CoV-2 was detected in the brain. During the mid-phase of SARS-CoV-2 infection of mice, mitochondrial gene expression was starting to recover in mouse lungs.

The authors say that these data suggest that the viral titer first peaks, there's a systemic host response, then we get viral suppression of mitochondrial gene transcription, induction of glycolysis, leading to the deployment of antiviral immune responses. Even when the virus was cleared and lung mitochondrial function had recovered, mitochondrial function in the heart, the kidney, the liver, and the lymph nodes remained impaired, as they say, potentially leading to severe COVID-19 pathology.

Also, again, a great graphical abstract. Unfortunately, this is behind a paywall. Thanks to my Columbia access, but again, a nice breakdown where you really see the distinction between early stage, late stage, and the different tissues.

VR: I would have liked to see a comparison with another virus to see how general this effect is, or if it's specific to this virus.

DG: I like that actually. Yes. Maybe we're starting to just learn a little bit about virology in general. How much of what we're learning translates to other viral infections? All right, we will wrap it up here. Hopefully, we're still within your attention span. As I've been saying for a number of years now, no one is safe until everyone is safe.

I do want everyone to pause the recording right here, go to parasiteswithoutborders.com and click Donate. We are now doing our Floating Doctors fundraiser for August, September, and October, where we double your donations up to a potential maximum donation of $20,000 to help Floating Doctors continue to do their work in Panama.

VR: Time for your questions for Daniel. You can send them to daniel@microbe.tv. Mary writes, "My question is, I was able to get a just-in-case prescription of Paxlovid to start immediately if COVID should get through despite my precautions. If I have a rebound, I know it's not a Paxlovid rebound, would it be helpful to take a second course of Paxlovid or might it be worth seeking out remdesivir? I'm not so much concerned about a severe initial case of COVID because I'm vaxxed with the most recent booster in May, although I hate to be sick with anything, but I'm interested in avoiding the long-term sequelae of long COVID organ damage, et cetera."

DG: All right, we visited this many times, but I'm glad, repetition is going to really matter here. Think about what you're doing. The first week is when you have significant viral replication. That's the perfect time for an antiviral. That's why it's five days. That's why three days with remdesivir during the first week is appropriate.

Now, the viral replication goes down. Maybe you're getting an antigen test that's positive-negative. You're not seeing millions and millions of copies of the virus. You're not seeing significant viral replication when during that second week, you start to get symptoms. That second week is an inflammatory response. That's when we start thinking about treating with steroids. Early in the pandemic, this was a huge mistake that people made. They were trying antivirals during week two, during week three.

They were showing no benefit, actually, potentially all the harms that come with jumping in with an antiviral that has effects, but no benefit. I know several prominent people have gone ahead, have taken Paxlovid during that second week, all kinds of ideas and hand-waving about maybe it prevents Long COVID, et cetera, but this is an antiviral. The first week, the first five

days is the ideal time to take it. If you start to get an early inflammatory response, which is after the viral replication has really shut down, there's no evidence to support that, and there is the potential for harm. I would recommend against taking another course of any antiviral.

VR: Katherine writes, "Thank you for making yourself available as a resource for all physicians trying to do our best in caring for patients. My partners and I, pediatricians, are curious about the recommendations for RSV vaccination with Beyfortus when a mother has had the RSV vaccine during pregnancy. Should we give Beyfortus as additional protection, or would it be better to hold off until their second season for RSV? Do you think insurance companies will pay for the vaccine for babies if moms also received the RSV vaccine during pregnancy?"

DG: This is a great question. Just sort of walk through the science. We know that that vaccination during the last trimester is going to provide protection for the newborns, so that's great. We also know that the nirsevimab, the Beyfortus, is going to provide pretty robust protection for these infants under 8 months of age. There's no reason to think that you're not going to get extra benefit.

Really, the data was persuasive to the point that they're actually looking at this, treating this as a passive vaccination. Yes, what would the science support, what would be my thought, is don't limit your use of nirsevimab just because the pregnant individual got the vaccine. I think we're going to see benefits to both being given.

VR: Louise writes, "I'm a family physician from suburban Philadelphia. I have a patient with inflammatory bowel disease and immunosuppressive therapy who just had a Pap with positive HPV. Her gynecologist recommends Gardasil vaccine, but it is only indicated for up to age 45. Any suggestions?"

DG: Yes, that was an interesting expansion. That was pre-COVID-19 pandemic, actually, I think 2018 was when the FDA expanded, sort of realizing that there may be benefit and there was some evidence supporting that. These are situations where clinical judgment, it is reasonable to think that this may be a helpful suggestion, the data is not compelling to the point that it's been FDA approved above that age, but I think that's a reasonable recommendation that's being made.

VR: Carolyn writes, "Could you please talk a bit about nirsevimab timing for infants? News reports state it will be out before RSV season in October. However, hasn't RSV season been earlier this past two years since COVID? RSV went around my older child's class in September last year, and I'm concerned nirsevimab won't be available before my infant is exposed. As parents, I know we don't have control over the timing, but any info you could provide on RSV seasonality and the nirsevimab availability process would be appreciated."

DG: Yes, this is great email. Thank you for asking this because right as I started right up front, we're being told it's going to be ready for the RSV season. Well, when is the RSV season? Things have changed quite a bit. What happens if RSV comes early this year like it did last year? What if we start seeing cases in September? Is it going to be ready for then, or are they talking about the typical October delivery of this? Really, as soon as it's available, people should go out there, get the benefit that's going to be there, but you make a really good point.

When is RSV going to be here? Saying that it's going to be here before the season is predicting the future.

VR: Diana writes, "Dr. Griffin, the hospital where my physician affiliates does not carry remdesivir because they say it is ineffective. Is this true? I don't think I can swallow Paxlovid. Do I have any options other than to end up on a ventilator? This is upsetting."

DG: Yes, no, this is very upsetting. Here maybe I'll vent a little bit. I remember during the pandemic, having conversations with medical directors of different facilities who had - they were not boarded in infectious disease. They did not have the background, but they had an administrative title and they were making comments, for instance, about when we weren't allowed to use tocilizumab without their approval, the approval of an administrative person, not necessarily a board-certified infectious disease doctor.

When I hear this, "They have decided," I'm very curious who “they” are. I'm very curious who is having input into this. I know that the early outpatient remdesivir is in most situations, not really financially in the best interest of the institution, but it is in the best interest of the patient. I applaud institutions that go ahead and do that.

A couple of things, just to say, the PINETREE data, you get remdesivir within the first seven days, 87% reduction in progression. That's fantastic. If you can get remdesivir within the first 10 days, and there are going to be patients who end up in the hospital, then there is benefit. Once you get past 10 days, once you end up in an ICU, on a ventilator, okay, then the window has closed, but there's subtleties here and remdesivir at the right time, in the right patient, can be a tremendous tool.

VR: I don't know what to say to Diana then, right?

DG: Move to New York. [*laughter]*

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

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