This Week in Virology

TWiV 1062 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 18 November 2023

pdf of this transcript available (link)

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

[music]

From MicrobeTV, this is *TWiV. This Week in Virology*, Episode 1062, recorded on November 16, 2023. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today here at the incubator in New York City, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Good to have you back again, Daniel.

DG: Yes, it's nice to be spending some time. After this, we're going to go to the Dickson Despommier book signing.

VR: That's very exciting. Dickson should be in his element, right?

DG: [laughs] He will be in his element.

VR: What's on your tie today, Daniel?

DG: This is a virus. Notice a nice -

VR: I do.

DG: - symmetry, almost like a corona of spikes around the outside there.

VR: Is it coronavirus?

DG: Sure. [laughs]

VR: How do they sell it? It starts CoV-2 or coronavirus?

DG: Actually, they sell this as HIV.

VR: You're serious?

DG: Yes. I'm going with coronavirus. Maybe that's gp160 or something.

VR: Well, HIV has the conical cords and that just doesn't.

DG That's a problem when you get artists doing the viruses.

VR: It depends what they start with. Anyway, it's a nice tie. Black and tan I guess.

DG: Yes, that's my fancy, going to -

VR: Is that a drink, black and tan?

DG: Yes.

VR: You take Guinness and mix some -

DG: Yes, you mix a light beer and then you get -

VR: That seems like a heresy, doesn't it?

DG: Yes.

VR: OK.

[laughter]

VR: OK, enough beer.

DG: All right. Let us start with a Jack Kerouac quotation, "Great things are not accomplished by those who yield to trends and fads and popular opinion." Let's start off with apparently the fad these days is to not protect our children with vaccines. That's it. I will start off with that disturbing news. The *MMWR,* "Coverage with Selected Vaccines and Exemption from School Vaccine Requirements among Children in Kindergarten, United States 2022-23 School Year." This is basically last year, 2022 through 2023 school year.

The exemption rate increased to 3% across this country. Exemptions increased in 41 states exceeding 5% in 10 states. This is available, cdc.gov. We'll leave in a link, but you can go through and you can find your state. Vincent and I pulled a few out for you just to highlight. Who's the winner when it comes to losing? Idaho at 12.1%.

VR: Idaho.

DG: Kind of crazy, and Arizona 7.4, Wisconsin 7.2. Washington, they're a great Pacific state, and we got 4%. Who's winning when it comes to winning? New York 0.1.

VR: Hey, we're in New York right now. I'm proud of it.

DG: I'm proud of New York. Joe Manchin country, West Virginia, less than 0.1.

VR: These are exemptions that have been granted to children to not be vaccinated to go to school.

DG: Yes.

VR: Are they medical exemptions mostly?

DG: No, philosophical. That's this new thing.

VR: Philosophical.

DG: Philosophical. I just don't believe in protecting my children against these vaccine-preventable diseases.

VR: I think that in order to have a philosophical objection, you should have to answer a 20-question test on vaccines. You need to pass, and I bet none of them would pass. Come and make up the test. You and I will make up the test, all right?

DG: That's it. All right. It sounds good. It's really disturbing. We were discussing this on the last urgent care call this week, and just prepare to start seeing stuff that we thought we weren't going to see so much anymore.

VR: Well, the good news is if you have a child and you vaccinate them, they'll be protected from disease. Unfortunately, the kids don't have a say in this matter and they'll get sick and they may have lifelong disabilities as a consequence.

DG: Unfortunately, the parents, they're not bad people. They're the victims of this massive misinformation campaign that is not benefiting them but is benefiting certain people who are filling their coffers. All right. Flu, looks like a little bit of a rise in flu. Puerto Rico is getting hit hard with 42 flu deaths already, more than 900 hospitalizations, over 13,000 cases, six times the number of cases compared to this time last year on this little island of only 3 million people. Mostly hitting kids, 19 and younger seems to be what we're seeing so far.

Most of the U.S. not really seeing much of a rise, but we've got New Mexico, we've got Alaska, Florida is jumping in with high levels. We're starting to see an increase particularly in those little kids, 4 and under. I'll mention so far of the isolates, it's looking like 90% are H1 viruses.

VR: That's good because those are less virulent than the H3 viruses, right?

DG: We'll see how it goes, but I don't know, six times the number of cases in Puerto Rico, a lot of predictions that this might be a challenging winter ahead of us. All right. Moving into Candida auris. I can't skip when I hear something about Candida auris. A total of 1,313 cases have been reported in Nevada so far this year. Of those, 492 were clinical cases, actual infections, not just colonization, but this time last year, Nevada had a total of 774, we're almost double that. There were cases reported in 28 states and the District of Columbia.

In addition to Nevada the hardest hit, California 359 cases, Florida 349 cases, New York 326. We're losing, stop washing your hands so much. Illinois 276, and Texas 160. I joked washing our hands, but that's not probably going to be enough. This is a very difficult fungus to get rid of. At IDWeek, Chuck Knirsch and I were at a meeting where they were talking about some ideas about what might be going on.

I'll quote, Arturo Casadevall, “If you were a tree, you'd be terrified of fungi.” Does Arturo say that? It's about this, we call the thermal gap or the temperature barrier. There's this whole idea that the reason that mammals are warm is to basically protect us from fungi that really have trouble at this higher temperature, but a couple of things that were being discussed at IDWeek with global warming, which apparently is a thing, the fungi are now living in higher temperatures, thriving in higher temperatures.

There was a whole discussion that human beings are a little colder than we used to be. Apparently, we used to be a little bit warmer. I don't know if that's true. That was actually a bit of the discussion.

VR: I think the main thing is that with global warming, the fungi are getting adapted to higher temperatures, and it's inevitable.

DG: I think that's the thing. All right. Moving into COVID. I just want to point this out, we are still at over 200 deaths a day. We're still at over 1,400 deaths a week, just think about that number. In the United States, there have been some horrible things happening recently, and that 1,400 might ring a bell for some people. Over 1,000 people, over 200 people every day are still dying.

What is happening? We're starting to see a rise in the Southeast, starting to see a rise in the West, we're starting to see a rise in the Northeast. I think, as predicted, we're expecting a rise this winter, but that brings me to my next - What will the future hold? In recent discussions, I've realized there seems to be a consensus that COVID-19 will settle into some seasonality, but interesting to me that everyone expects the seasonality to be that of influenza or RSV and not necessarily that of the other coronaviruses.

I am going to encourage everyone to listen to *TWiV 1061*, which I enjoyed. There is a really deep dive into the article seasonality of endemic COVID-19 that had recently been published in virology. A couple of things they point out is the four common coronaviruses actually have slightly different seasonality from RSV and influenza. I think we've discussed, RSV starts in the South, and actually to my dismay, there are already hospitals in Texas with 95% capacity due to RSV.

We talked about all these great tools, Beyfortus, vaccination during the last trimester of pregnancy, older individuals getting vaccines, we're not seeing those tools come to bear, so RSV is starting off in Texas, Florida, the South and then it moves its way northward for usually a slightly earlier peak than we see with influenza. Influenza often peaks either right after Thanksgiving, right after Christmas, or a delayed peak in the spring.

As we can see with some of the common, common coronaviruses is what folks have called them. 229E is a late bloomer, a February, March when we see that really rise. NL63 may be a little closer to flu, and they're actually predicting actually SARS-CoV-2 will have this interesting - they are predicting that over time, it might be more of a February peak.

VR: Like HKU-1, right?

DG: Yes.

VR: The modeling was done specifically with these human coronaviruses. They didn't model it on flu. That wasn't even part of the study. It would be interesting to know, RSV or something else, but then again, it is a coronavirus, so maybe that makes sense.

DG: Yes. It'll be interesting. There's a nice figure, Figure 3, and this is where they do the Yogi Berra thing. They predict the future. This is what do they think the seasonality, the pattern is going to be of SARS-CoV-2 in the future. It's interesting. Amsterdam is such a place of transit that people are always coming and going. It's going to basically be almost constant year-round.

VR: It's flat like the lowlands.

[laughter]

DG: Lowlands like the country itself. [laughs] Then you see or you see Edinburgh up in the UK having that little bit of a late peak in February, and then you see a little bit of a difference, Rochester, USA, out there in Minnesota, not the New York one. Then New York, New York.

VR: Of course, Dickson thought it was Rochester, New York. [laughs]

DG: Yes, I'm sure he did. [laughs] Really interesting. We'll see, we are at this point however the seasonality settles in, we're predicting at least for this winter, December, January, February, we're going to see a rise and we're already at 200 deaths a day.

VR: Why do we care about what the seasonality is, Daniel?

DG: I think we care for a couple of things. One is there may be a public health advantage to a timed booster, particularly for high-risk individuals, so it's timed. The other is we were having a discussion earlier this week about pharmacy stocking antivirals. We have this tragic thing where you decide you want to actually use an antimicrobial agent and you run out.

I remember an early flu season in Colorado where we had a couple of adolescents die in Fort Collins, Colorado, and there was a shortage of antivirals at the time. It can be vaccine, it can be public health things, it can actually be antivirals.

All right. Moving into children COVID and other vulnerable populations. I do not think I can share enough science in this area, but the article, “mRNA SARS-CoV-2 Vaccination Before versus During Pregnancy and Omicron Infection Among Infants,” published in *JAMA Pediatrics*. We need to look at this article carefully because their efficacy is for infection, not disease. That's important.

A lot of times with the little kids, that's what you're doing because there's a lot more infections, you don't need this massive study to do that. We read in this national population-based cohort study of 7,292 infants aged 6 months or younger in Singapore. The estimated vaccine effectiveness in infants against Omicron SARS-CoV-2 variants including XBB from maternal messenger mRNA SARS-CoV-2 vaccination was 42%.

A lower risk of infection was only found in infants when the vaccine was administered during pregnancy but let's put this under a finer lens. Infants of mothers who received vaccination

prior to pregnancy did not have a lower risk of infection. The vaccine efficacy was only about 15.4%, really wide confidence intervals. A lower risk for Omicron XBB infection was observed among mothers vaccinated with the booster antenatally, and there we're seeing, when you look just at that population, 76.7% reduction in infection in these little kids.

VR: They really immunize kids less than 6 months of age?

[laughter]

DG: No. They're immunizing mom.

VR: In the other study, didn't they say a VE in infants 6 months and younger? They weren't immunized, they were just -

DG: Yes. They're vaccinating mom during the last trimester, and then the kids get this 77% reduction in even getting infected.

VR: You say here, a lower risk of infection was only found in infants when the vaccine was administered during pregnancy. That's why I'm asking. It was either administered or not, so the moms who didn't get it -

DG: The moms who got the vaccine prior to pregnancy -

VR: They weren't protecting the babies, yes.

DG: Minimal protection, not even statistically sick, maybe 15%, but not a significant confidence interval.

VR: Not surprising because pregnancy is long, and by that time, the antibody levels have gone down, not enough to prevent. That's a great advocacy for getting vaccinated in the third trimester.

DG: I think we need to start making this, you get the flu, you get the RCV, you get the COVID vaccine that last trimester.

VR: Interesting.

DG: We don't need these kids under 6 months of age ending up in the hospital having these - How did they assess infection in these babies? Did they actually swab them?

DG: Yes.

VR: That's amazing. I guess they're a captive population.

DG: Yes, you stick the little thing up their nose.

[laughter]

VR: You don't have to get them to come in, their moms bring them in, or their dads.

DG: Yes. Unlike my cocker spaniel, you don't have to worry about them biting your fingers off. [laughs]

VR: All right, good.

DG: A little bit of crying afterwards. All right. The article, "Extracting Symptoms from Free-text Responses Using ChatGPT Among COVID-19 Cases in Hong Kong," was recently published in *CMI.* Why am I talking about this? The thing I want to point out here is a lot of times when we see these studies where they're looking for the physician coding all these different symptoms, Long COVID, et cetera, the problem is, once you get four diagnoses, you're done, you can't send in anymore.

A lot of times when we're charting, when we're coding, things get dropped and we don't necessarily capture them. Here, they extracted symptoms from 300 de-identified symptom narratives of COVID-19 patients using this computer-based matching algorithm, and prompt engineering in ChatGPT. They report that GPT-4 achieved high specificity for all symptoms, high sensitivity for common symptoms, and moderate sensitivity for less common symptoms. Using AI here to make sure they capture all these symptoms.

Then we are going to move on to the meat of today's session, the controversial paper. When I wrote this, I say a few people, I should say many people interested in the *Annals of Internal Medicine* article, "SARS-CoV-2 Virologic Rebound with Nirmatrelvir–Ritonavir Therapy. An Observational Study." With all this interest, let's spend a little time, you and I, discussing this. I want to keep an open mind, so let's walk through.

In this observational cohort study, they looked at ambulatory adults with acute COVID-19 with and without use of nirmatrelvir–ritonavir therapy. In total, there were untreated persons, 55, treated with Paxlovid, 72. Some important things before we get into the results, not a great job of matching. As we read, if we look at those who were untreated, median age 39, those who were treated, almost twice as old, 57.

More often, so the people that got treated, about a third of them had immunosuppression, 32%, versus the untreated, only 9%. These are really immunosuppressed individuals. We've got individuals here with leukemia, lymphoma, solid organ bone marrow transplant. Those on immunosuppressive therapies, corticosteroids, interferon-gamma inhibitors, cytotoxic therapies.

We're now going to get clinical information, and we're going to get viral kinetics. First, clinical outcomes. No one that got Paxlovid died, no reports of progression of disease in this high-risk cohort in getting Paxlovid, so far so good.

VR: All right, so no difference clinically in the Paxlovid and non-Paxlovid treated, correct?

DG: The interesting thing, so yes, except for the fact that the younger 39-year-old, they were going to do fine anyway, but this high-risk group got Paxlovid, and they all did great, which is really the goal. That's what we're treating people with Paxlovid. We don't want them to progress to the hospital. Look at this, these are high-risk individuals, and none of them progressed, none of them died. From a clinician's standpoint, I'm happy so far because that's my goal.

Now we move on to the viral kinetics. They are going to go ahead, and they are going to redefine viral rebound. Instead of this being my patient felt better, and now they feel worse and are teeming with virus, they're going to come up with a new definition of viral rebound. Either, one, a positive SARS-CoV-2 viral culture result after a prior negative result. They're going to be checking these people three times a week, trying to culture virus. If you fail to culture virus on, let's say, a Tuesday, and then you could do it on Thursday, that's going to count as rebound. It doesn't have to be a lot of virus, you just have to fail one day and then succeed the next.

Two, sustained elevated viral load. What do they mean by that? Characterized by the combination of a nadir viral load below 4 log10, so below 10,000, followed by an increase in viral load that was at least one log higher. If you get it down to 100 and the next one is 1,000, that's rebound.

VR: I see.

DG: If you get them down to 1,000 and the next one is 10,000, that also counts as rebound.

VR: That's not fair. It's really not fair.

DG: At this point, I'm like, "Come on, I'm crying foul. This is rigged." First off, I'm going to take issue with this definition, I'm going to cry foul, and I'm going to suggest the game is rigged. What are they trying to accomplish here? They tell us that when we restricted our analysis to three time points based on viral load, it was done in prior studies, we detected a 2.4% rate of viral rebound.

That's fine. They confirmed the prior stuff. It's 2.4, it's nice and low, everyone does fine. No one ends up in the hospital, no one dies, but now they're going to game the system, apply their new definition and testing protocol. They're going to check everyone three times per week. A person could be asymptomatic, have started with a CT value on average here of 21.9, which is an RNA copy number of about 10 million, and as we mentioned, if they get an RNA copy number down to, say, 1,000, and then 10,000, oop, we're going to call that rebound. The person on no treatment who stays above a million can't have rebound because the RNA number dropped.

We'll just start off with the first one. How do we do when we look at Figure 3 and we look at participants with positive viral culture results? If you look at the people that got the nirmatrelvir by about day three or four, majority of them, culture result negative. By the time you get out to day eight, they're all culture-negative. Now, if you look at the people who get no therapy, you don't get down to 50% until a little bit later, and you still have some folks who are culture-positive past day 10.

So far, I'm thinking that this is encouraging me. People did great. We get a quicker reduction in culture result negativity, but now we're going to get into the weeds. We will look at Figure 1. You can access this paper, so maybe people pause and follow along. It's a little bit of a thing. You got to go in, you got to register your email, but you can get it, and you can look at the figures.

Now we're going to look at Figure 1 and we're going to look at viral load with no therapy, and we're going to look at culture, viral culture with TCID50. That's good. I'm glad they did this. If we look at the folks that got no therapy, you can see it really takes quite a while for these numbers to come down. There's not a great slope here. You go out today about day seven, day eight, you're still pretty solid up there. You look at the viral culture, and as we discussed, you still got some people at day 10 still with these positive cultures.

Now let's look at the nirmatrelvir treated. Now we're at Panel C and D. If we look at the viral load in general, a much quicker drop in the viral load when we compare it to the not treated, but we do have a number of individuals that actually are still above this, 10 to the 4th, 10 to the 6th in some cases, but again, nobody's up at 10 to the 8th, which was actually the average at inclusion in the study. If we go and we look at the viral culture and the TCID50, yes, there are some positives that go out a little bit.

VR: We should point out, though, that for the viral load, it's in log10 copies, so you have at least two log increase, that's 100-fold, but if you look at viral culture, it's twofold increase in infectivity. Obviously, there's not a direct correlation between RNA levels and infectivity. You could be misled by saying, "Oh, my gosh, 100-fold more RNA," but it's actually only twofold more infectivity. It's clearly different from the untreated, but there may be some other explanation for that. The real question is, is it of any clinical significance?

DG: Let's hit on that because I think that's really - When we read a couple of these things. Let's think about in our head, when you hear Paxlovid rebound, what are you thinking about? Clinicians who say, "Oh, I see this, it's much higher there," but they're thinking of individuals who get started on treatment, feel completely better, and then have a second week when theoretically, the symptoms come raging back, worse than the first couple of days. The viral load is - they're teeming with virus.

VR: Which is done by PCR or - ?

DG: Well, they're teeming with viruses. Interesting enough, sometimes they're looking at the color of your antigen test and there's some crazy people out there that tell you, you can look at the color and tell you how many people you're going to infect that day, which is not true.

VR: Wow. Oh, my gosh.

DG: I've seen this on social media where they're like, "Look, 12 people and 33 people, based upon the darkness of the line." No, none of that's true. There's this concept of rebound where you start off with 10 million RNA copy numbers, it's all gone, and then the second week, it comes raging back. You feel horrible, you end up having to go to the hospital.

One of the first things I'm going to point out when I keep saying that Paxlovid rebound is not a thing is these people that report symptoms, these people, as we see here who have positive viral culture, who have the RNA copy numbers, they don't go to the hospital, they don't die, they do much better. 90% reduction in bad outcomes during that second week.

Sure, you can culture some virus. Sure, there's some RNA copy number. Sure, some people - and this is, I think, really interesting, is they tell us that the majority of those reporting symptom rebouncing, oh, man, that second week, the symptoms really came back. Majority

of those people did not experience even this really expansive viral rebound definition. These are people having the early inflammatory response.

When the doctor says, "About 20% of my patients, they get Paxlovid, they feel better, and then the second week, they have some symptoms." Well, what we're seeing here is evidence that the majority of the time, that's early inflammatory, that is not a viral rebound.

VR: I think we're confusing two different things that happen. We're talking about the clinicians who see patients getting less well, and here they're making a very detailed observation of RNA and infectivity, but we have no connection between that and clinical symptoms.

DG: Well, no, I think that's critical. Here they tell us only eight of the people that meet their definition of viral rebound, only eight of them had any symptoms during this period.

VR: Eight out of 72 or something like that?

DG: Yes. It's small.

VR: Daniel, something is going on in the Paxlovid-treated group. All right?

DG: Yes.

VR: Clearly, because you see higher PCR and higher infectivity, but I don't know what it is. I don't know what's causing that. It may be some artifact. It may be that with Paxlovid, there's sequestration of virus in the respiratory tract, which you can pick up in different swab days. It's something that may be interesting to look at, but from the numbers, it doesn't seem to me that this is of any clinical significance. As you know, they're claiming that this is causing transmission, but there's zero evidence for that.

DG: That's a big thing. You can read this paper in detail, you can read the discussion, and actually, Mark Siedner actually has a video. You can watch a video where he gives you a recap of what he thinks this demonstrates, and why is he worried and why is this so important that this get us out there. They're suggesting that this RNA copy number of greater than 10,000, this ability to culture a virus is a surrogate for infectiousness. They're suggesting that this percent of people that have this are a public health threat.

The argument from them is the patients are fine, they're doing fine with five days, but from a public health perspective, we should potentially force them to stay off their other medicines and do 10 days for the betterment of our society.

VR: Hey, wait a minute. I think this has all changed because my original understanding was doctors didn't want to prescribe Paxlovid because they felt it made some of their patients get worse after they recovered. It had nothing to do with transmission, but now we're talking about transmission.

DG: Well, unfortunately, they're not able to find that Paxlovid is associated with any harm.

VR: OK, so they're doing something else.

DG: The rebound is fine. Everyone does great. No one goes to the hospital.

VR: Got it.

DG: That horse left the barn. Now, it's that you've got to protect other people. These people are a menace. Got to keep them from -

VR: This is an important accusation and it needs better data. You can't say, "We think this leads to transmission." That's not doing a public health service.

DG: I'm actually very concerned about that because they're raising, they're saying, "This is why this is so important." You're seeing this article discussed all over. 20%, one in five people have Paxlovid rebound. This is going to result in high-risk individuals not getting this incredibly effective number one recommended NIH guideline therapy. You're going to end up with more people ending up in the hospital, you're going to end up with an increased number of people dying. Their argument is, "Oh, we're worried about public health."

As we saw, if you really want to get that RNA copy number down, the quickest way to get them viral-culture negative is by treating them with an antiviral. The argument doesn't make any sense.

VR: Also, Daniel, when these patients have this increase in infectivity, it's typically on one day.

DG: [laughs] Yes.

VR: Which would make it harder to transmit because it's more of a crapshoot.

DG: Where the other people just stay infectious for twice as long, and apparently that's OK because there's no rebound because they never had a period when they felt better and stopped.

VR: More importantly, are they saying we should not use Paxlovid because it might increase transmissibility, or we should keep people who were on Paxlovid isolated for a longer period of time?

DG: Or maybe the other, which I think is a reasonable question is, maybe there's certain situations where instead of five days, 10 days, except the issue is that 10 days, as we know, is not necessarily going to help our patients. We start off with remdesivir at 10 days, we study 10 versus five with that antiviral, five is better. Actually, if it's the first week, three is fine, you're already getting your almost 90% reduction.

Are they saying, "Let's put certain people on for 10 days, keeping off their other medicines for the betterment of your neighbors?" We're not seeing any documentation that these people are transmitting onward. That's a huge problem.

The other, which is the other takeaway is they're saying, "Well, maybe just the immunocompromised, maybe they're the ones." If you actually look at one of their figures, Figure 2, and you compare the immunocompromised to the non-immunocompromised, actually the immunocompromised had half the rate of their viral rebound definitions. That doesn't make sense either, but I will say, this is science. There are several studies going on. I'll leave links to it. Looking at, are there advantages to 10 days, 15 days, versus five.

There's the, “OPtimization of Antiviral Therapy in Immunocompromised COVID-19 Patients.” There's also a study to learn about these study medicines. This is where they're looking at again, five, 10, 15. We are looking at this, but right now, there's no evidence that there's benefit going more than five days, and there is potential harm.

VR: I think they ought to also look at correlations between the cycle thresholds that you see in transmission.

DG: I think that's a big thing, particularly timing. As we've talked about, 85%, 90% of the transmission is occurring in the first five days. We see a little bit of transmission maybe day five through 10, but we're not seeing much past day 10.

VR: Let me just take a group of people who've been treated with Paxlovid, and if they're in family situations, you can study transmission.

DG: You certainly can.

VR: It's very easy to do. Before you say this is a big problem, you should do that.

DG: In this article, I have to say, it's going to undermine. There will be less Paxlovid prescribing because of this article. More people end up in hospital, more people will die.

VR: We can look at the weekly death rate and see if it goes up now after the publication, although that's not an easy study because there are a lot of confounding factors, obviously.

DG: It's going to go up.

VR: That could just be the season anyway, right?

DG: Yes, it's also going to go up because of the season.

VR: Wow.

DG: All right. Not happy about that. Not happy about the way the media is putting this out there. Let's not undermine our most effective tool.

VR: Well, the problem is, Daniel, that it's not easy to read the paper and get out all these nuances. Most people look at the headline and say, "Ah, that's it." They don't look at the data.

DG: I ran into it today. I had a patient that was discharged from the hospital, unfortunately, during their hospital stay acquired COVID. Now they're in a facility. I talked to them, and I said, "Well, we got to start this individual on the Paxlovid." She said, "Oh, their primary care doc doesn't really like the Paxlovid." I said, "Who's their primary care doc?" What does that mean? That woman's been started on Paxlovid, but this is not going to help in situations like that.

VR: Isn't that one of the things that a doctor should never say, in my opinion?

DG: In my opinion. [laughs]

VR: In my experience?

DG: In my experience. All right. Moving on to remdesivir, as we've discussed, if you're within that first seven days, it's a three-day IV therapy. Here we have the, “Evaluation of the Safety Profile and Therapeutic Efficacy of Remdesivir in Children with SARS-CoV-2 infection - A Single-center, Retrospective, Cohort Study,” published in the *European Journal of Pediatrics*.

Here we're getting safety information on remdesivir administered to 64 children.

Basically, remdesivir is a safe treatment option for high-risk children with COVID-19. We have Thor's hammer, molnupiravir, convalescent plasma in certain contexts. We have isolation for the infected. It's pretty much five days. How many people are actually isolating for those five days?

VR: Very few.

DG: Yes, very few. The second week, the cytokine storm week, the early inflammatory phase, if the oxygen saturation get less than 94, steroids in the right patient at the right time, anticoagulation if they end up in the hospital, pulmonary support, remdesivir, if we're still in the first 10 days, we talked about that, immune modulation. The best data is for tocilizumab if we're going to do that, and remember, avoid those unnecessary antibiotics.

All right. I'll spend a little time on this. It was an article, “Effect of Neutralizing Monoclonal Antibody Treatment on Early Trajectories of Virologic and Immunologic Biomarkers in Patients Hospitalized With COVID-19,” published in *JID*. Really the big issue here is this article focuses on the importance of timing, and they also focus on the issue of, if you get this, are you still going to get that good antibody response?

It's really this interesting concern that people have like, "Oh my gosh, here's my COVID infection. Here's my chance to get that natural immunity. So much cheaper than the vaccines that they're now charging for." Here they show that actually if you get that monoclonal antibody, you're going to blunt that big inflammatory response, but you're still going to get those antibodies that are going to come up.

All right. We will close as I do now before we get to our questions with what I've been saying for a while, no one is safe until everyone is safe. This is Vincent's favorite time of the year. I want everyone to pause the recording right here. Go to parasiteswithoutborders.com, and click ‘Donate.’ We are now doing our MicrobeTV fundraiser, where for November, December, and January, we double your donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Craig writes, “Can you talk about fever?”

DG: [laughs] All right.

VR: “How important it is to diagnose these? Why some people seem to get infections without fever? Do some people really run lower than 98.6? Is that why they seem not to have a fever when they are well above their baseline?”

DG: Any poor medical students, residents, fellows who've rounded with me know that I always love to talk about fever. Actually, I have to admit, I love this at IDWeek, and there became this passionate exchange about like, what is normal body temperature? There was this famous study where 10,000 people had their temperature measured, the thermometers are in this museum over in the UK. It's all very exciting.

Well, a medical student a few years back was like, "This is great. We got these thermometers. We should see if they work. Let's check them out." They check out these thermometers. No, they're terrible. They're not accurate. They're poorly calibrated. They realize, "Oh, that's a bit of a problem. Maybe we should repeat that study and find out what actually is a normal body temperature."

Because fever is going to be a change from normal. One is they realize 98.6, "Yes, that's not actually right. Maybe more about a 98.2 is actually a typical body temperature." Then they realize, there's a lot of subtleties here. Some of these will be easy for people to remember. Every person is not the same temperature. The different sexes, women are hotter than men, just by the way, men, as they get older, become cooler.

VR: They're hotter because of the - No, I'm actually serious. For various biological reasons, they have a higher temperature, right?

DG: Yes. There might be certain biology why women, in general. The average body temperature of a female and a man is different. Your body temperature goes down as you get older. A lot of times when we say, "Ooh, they're only 99.9, it's not really a fever." Well, in an older male, their normal body temperature might be down around 97.2. At 99.9, in an older male, maybe. Aso, time of day, lowest temperature in the morning, highest temperature at night. Male, female, time of day, age. Yes, what is a fever? A fever is a significant change from your baseline temperature.

VR: Which you don't know necessarily if you show up at the OR. [laughs]

DG: You do have people who come and say, "Hey, normally I'm 97.2. 99.9 for me is a big change." You know what? We used to all say, "Oh, you can't trust people. We got to measure." That's not true. Eighty, 90% of the time, if someone says that they've been having fevers, they've been having fevers.

VR: In your opinion, if you don't have a baseline, what temperature would you consider a fever?

DG: For positive blood cultures, it's this 100.6F, it's 38.3, but then you've got to use your judgment. If you've got an older individual, they look infected, the body temperature isn't quite at those numbers, you may call it a fever a little bit lower. Then as we've learned, as we get older, this immunosenescence, you may not mount a fever, you may be bacteremiac and still not have a fever.

VR: What is the highest fever that you could get and still live?

DG: Again, it has to do with age. Young kids, they get 106 and be absolutely just fine, maybe they have a seizure. As you get older, your ability to tolerate these high temperatures without a permanent cognitive impact actually decreases.

VR: You say it's OK with kids to have a seizure. Isn't a seizure bad though?

[laughter]

DG: It's interesting. They'll have febrile seizures. That's always a big question when a child has a seizure. Was it during a fever? Because that's not uncommon. An older individual - get an older individual like the person I was describing, a man in their 90s, gets up to 106, that can be associated with some ongoing neurological issues.

VR: All right. Craig goes on and talk about Celsius versus Fahrenheit, but we'll leave that for another time. Is that OK with you?

DG: Yes.

VR: All right. Theodore writes, "Greetings from Athens, Greece. I would like to ask you about a relative of mine. COVID vaccination. She's 93, fully vaccinated and boosted last year, bivalent BA.4-5. Apart from atrial fibrillation, no other health issues, fully independent, loves to go to taverns on the weekend.

DG: All right.

VR: "She came down with COVID nine days ago, a few days before her XBB1.5 vaccination. Due to extreme weakness, she could be officially diagnosed and registered a week after symptom onset. Unfortunately, Paxlovid still has a special emergency authorization status in Greece, is distributed only at hospitals, positive test required. Of course, after a week, Paxlovid won't do much.

"Thankfully, the "unsung heroes," (call me T-cells) must have done their job. She's way better and everything looks that she will be fine. Taking into account her age and her heart problem, what would you suggest? The immunity is sufficient, doesn't need vaccination this year? Should she wait three months and get XBB1.5?

DG: The general recommendation is to wait three months and go ahead and do that. This is an individual who's in that higher-risk category, so they're an individual – (aside) I'll put my computer back open here, otherwise, we're getting a beep on our screen for HDMI input.

This is an individual that we would recommend three months, go ahead, but we're honest, right? What you just saw is that enduring protection that you get from having that baseline vaccination series. Get a little bit more, and as we've discussed, COVID-19 has not really settled into that seasonality. Three months from now, here we are. Look at our fundraiser, November, December, January, we're in February. We still expect there to be a fair amount of SARS-CoV-2 circulating. Reasonable to try to get a little bit of a boost there.

VR: Brian writes, "I have a patient who underwent a bone marrow transplant for multiple myeloma last year. She now takes daratumumab." Well, daratumumab, I can't say it. Can you say it?

DG: Yes, you did well. Let's say monoclonal antibody. A MAB targeting a receptor on plasma cell. She got her anti-plasma cell MAB.

VR: And Revlimid -

DG: That's a small molecule that affects angiogenesis, small molecule.

VR: - that's prescribed by her oncologist. He recently advised her not to get either the flu or COVID vaccines because her therapy will make them ineffective. Do you agree with this? I advised her to take both because she'll likely get some T-cell immunity and perhaps a bit of B-cell, but what are your thoughts?

DG: I actually agree with our email writer. You're going to definitely have compromised B-cell responsiveness because of her underlying disease, her therapies, but you may get some benefit. Again, we're talking about diminishing returns, this is a high-risk individual, every little bit counts. Yes, I think it's reasonable to go ahead with vaccines.

VR: All right. Our last is from Kim, who sent photos of her pediatric office staff in their Halloween costumes. "We had a blast being superheroes and the younger kids do believe we can fly. The teens rolled their eyes but smiled." They're great photos of the capes and the spike shirts. I didn't put them in the show notes, but I will. As far as her question goes, "As far as GAS," I guess Group A Strep?

DG: Group A Strep.

VR: "After being in solo rural practice for 34 years and looking into a lot of throats, I find that the presence of petechiae clinically correlates much more with culture-proven strep throat than exudates do, but the more recent strains of Coxsackievirus causing hand, foot and mouth disease present with more petechiae than they did decades ago. Do you agree with that?" [chuckles]

DG: [chuckles] I'm not sure. It is interesting. We talked last week about a couple of the different criteria, the modified Centor, and then there's even updated criteria for making this clinical diagnosis of strep throat. I've never seen any kind of validated comparison here, but it's interesting. No reason to stop doing the studies. That would be a reasonable thing to look at, but there certainly has been a change. We've seen some more aggressive Group A Strep. We've seen some more aggressive Coxsackie issues. Yes, these pathogens evolve, and they have a much quicker replication cycle than we have.

VR: "Lastly, would you review any need for outpatient treatment of COVID with antivirals in children?"

DG: Yes. There are children that are high-risk. We've talked about the fact that about 1,000 children died from COVID, not just by the way died and had COVID. That's the conservative estimate. There were certain issues. There are individuals that have cardio or pulmonary risk

factors. Down syndrome is considered a risk factor. There really is a whole list on the CDC website. If your child is younger and has these risk factors, then remdesivir is an option for some of the youngest individuals.

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

DG: Oh, thank you, and everyone, be safe.

[music]

[00:47:14] [END OF AUDIO]