This Week in Virology

TWiV 984 Clinical Update

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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 984, recorded on February 16, 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: I haven't seen you in a long time, Daniel.

DG: [laughs] It's been minutes.

VR: And then I spent two hours recording something else just now. We're tired of hearing each other, but hopefully, you're not. [laughs]

DG: Yes. All right. Well, let's get right into it. We have a lot to cover today. Yes, there will be one point in time when, hopefully, I do not say that, but we will start off with our quotation. "When people talk, listen completely. Don't be thinking what you're going to say. Most people never listen." That's from Ernest Hemingway, *Across the River and into the Trees,* written in 1967, the year I was born. I will admit to being a huge Ernest Hemingway fan.

Let us start off with the brief report, “The Political Polarization of COVID-19 Treatments among Physicians and Laypeople in the United States,” published in *PNAS*. The most disturbing part of this study is that it underscores that many physicians, so-called experts, are forming their opinions based not on reading the actual scientific publications, but rather instead from the media.

In this study, the participants read an abridged research abstract, that's for the physicians, or a research summary written in a journalistic style, that was for the laypeople, both of which reported the results of the TOGETHER trial, a well-powered, randomized control trial that failed to find evidence that an anonymized therapeutic GL-22 was effective for treating COVID-19. First, they elicited beliefs about the study's informativeness, its methodological

rigor, and the likelihood that its authors were biased. Then they identified the GL-22 as ivermectin.

Participants, who were more conservative, now reported that the evidence was less informative, the study was less methodologically rigorous and the authors were more likely to be biased. The preference for a certain misinformation source, which will not be renamed, was a significant predictor. This preference was also associated with physicians prescribing other therapeutics that lacked evidence of benefit and evidence of potential harm such as hydroxychloroquine.

Now, I will say there is a local infectious disease physician here who will often have the details a bit off from the actual numbers in a study, and they are drawing their information from a news article about the study rather than reading the actual study. It can be painful to see physicians claiming expertise when they're just parroting an article by a science writer rather than reading the science for themselves with the appropriate time and rigor one should demand from a member of our profession.

Now, I do want to say, I want to make sure to mention that many science journalists do a great job of getting the science right and of making the science accessible. I also know many journalists who are very careful and have the integrity to mostly avoid quoting physicians and scientists that left the bench in the bedside years ago and are now just talking heads desperate to stay relevant.

Now for physicians and scientists, if one is going to - This is my soapbox, by the way. For physicians and scientists, if one is going to claim to be an expert, one really needs to take that responsibility seriously and take the time and effort to read the actual science critically. Otherwise, dare I suggest, opinions voiced by physicians need to be qualified with the comment that they did not actually take the time to read the science for themselves and are merely parroting back an article that they recently read.

Unfortunately, when the administrators and board members of hospitals, I'll put a link into this, read *The New York Times* or watch *Fox News*, a physician or scientist that parrots this back comes off well in those circles. Now that we seem to return to the Gilded Age with the majority of physicians now employees, proletariats of the capitalists who run the show, I have concerns. I have previously talked about evidence-based medicine, eminence-based medicine, eloquence-based medicine, diffidence, nervousness, providence, vehemence, confidence-based medicine, and now I must add media-based medicine.

VR: I love it. I love that phrase, Daniel. That's great.

DG: [laughs] Media-based medicine.

VR: I love it. It's terrific.

DG: I'm also going to put a link into the article, “Seven Alternatives to Evidence-Based Medicine,” published as a short report in the *BMJ*. I have to say, it's a one-pager. It's a fun read. There's a lot of tongue-in-cheek. They talk about eminence. They also talk about how some of this is to some degree evidence-based. You can look at the radiance of the white

hair with a luminometer, and based upon the optical density, you can determine whether or not to believe them. [laughs]

VR: I don't have any gray hair, so you shouldn't believe me, right?

DG: Yes, let's not listen to him.

[laughter]

VR: Now, what do we do with you who has no hair at all?

DG: Yes, exactly. That's why I got to read the science All right. RSV Influenza. Now, U.S. flu activity remains low, but I do want to point out a sobering fact. Pediatric deaths have passed 100. Influenza A so far this year was responsible for 109 pediatric deaths. 83% of those were H3N2. Something I think that was touched on in a most recent *TWiV* is that as much as we malign the influenza vaccines, most of these children that died were not vaccinated. I will say CDC recommends a yearly flu vaccination for everyone 6 months and older. Flu shots can be given to your child 6 months and older. The nasal spray can be given to people 2 through 49 years of age. Just want to share that sobering fact.

Cholera, for those paying attention, Malawi's cholera death toll just crossed 1,300. Its deadliest outbreak on record. Over 40,000 cholera cases. The country is averaging over 500 new cases per day. Then this has actually hit the mainstream media a little bit. Equatorial Guinea is having its first outbreak of the hemorrhagic fever virus, Marburg. The African CDC has actually deployed a team of experts to support response efforts in the country. There was some discussion about whether or not this had crossed into Cameroon, but I will just say, so far, it has not spread to Cameroon.

All right. Something that has been keeping me and other folks busy lately, norovirus. Actually, we've got a bunch of folks in the hospital. I say that with a bit of a smile because these folks are going to be OK, but norovirus, this little virus has been in the news lately and in lots of people's GI tracts. We have the ability to do PCR tests on stool. Based on CDC data, all throughout the U.S., we're seeing a rising number of percent of these PCR tests positive for norovirus.

As far as transmission, this is almost exclusively contact, but if a person vomits or due to the ventilation dynamics on a cruise ship, for instance, we can actually get this by breathing. A couple of things I want to discuss. Now, do those alcohol-based hand sanitizers work against this pathogen?

VR: No, they do not, Daniel.

[laughter]

DG: But on the cruise ships, there's all that alcohol.

VR: That's not really good spending of their money, Daniel.

[laughter]

DG: OK. Yes, you must use soap and water. I was joking with my wife, who thinks I shouldn't joke about such things, that this will be a true test of which of my colleagues in the hospital actually wash their hands. All those folks calling in over this weekend sick with vomiting and diarrhea, yes, you need to keep washing those hands. An infected person can produce billions of these little variants, and it only takes maybe 100 to get infected.

Classically people are presenting with diarrhea. They tend to have vomiting. As mentioned, the vomiting can aerosolize the pathogen. Fortunately, this disease, in general, only lasts about one to three days, is self-limited. You don't need antibiotics to treat this virus. The big thing here is to stay hydrated. Yes, you can get norovirus more than once. I got nothing to say on the UFOs. Nothing to say on the balloons. I'm going to stay in my lane. [laughs]

VR: Yes, that's not our lane. You're absolutely right.

DG: All right. COVID, sobering, is we are getting estimates on how many people died during the last two months after China ended its zero COVID policy in the range of 1 to 1.5 million people. I'll leave in some links for people that might want to look into that and see how those estimates are being generated. Moving into children, COVID and other vulnerable populations. I try to make a point of keeping this information in front of our listeners every week, and the article, "Impact of Human Coronavirus Infections on Pediatric Patients at a Tertiary Pediatric Hospital: A Retrospective Study of the Pre-pandemic Era," was published in *The Journal of Hospital Infectio*n.

This article looks at human coronaviruses in general, remember that the dates here are going to be before, and reinforces or for some, points out, that young children less than 5 can have severe disease, even with the common cold coronaviruses such as OC43, 229E. These are the results of a retrospective review of all encounters of children with known common human coronavirus infection at a tertiary pediatric hospital from January 2015 to January 2018, so pre-COVID-19 pandemic. Electronic health records were reviewed looking at a number of different issues, demographic data, which type of coronavirus, viral co-pathogens, time to testing, need for hospitalization, requirement for higher-level of care, including ending up in the ICU requiring supplemental oxygen, et cetera.

Now, the investigators analyzed 450 encounters for 430 different patients with 85% being inpatient. OC43 was the most common human coronavirus. Younger patients less than 5 had higher probability of hospitalization with an adjusted odds ratio of 2.2, requiring higher level of care adjusted odd ratio of 1.8. Presence of lower respiratory tract findings on chest radiograph, 1.7. Length of stay, interesting enough, was longer for 229. Actually, there was even some suggestion of nosocomial infections. I'm going to agree here with the authors when they suggest that human coronaviruses are important respiratory pathogens in the pediatric population. Especially patients less than 5 years of age who are, as we see here, at increased risk for disease severity.

Now, what to do? The article, "Maternal mRNA COVID-19 Vaccination During Pregnancy and Delta or Omicron Infection or Hospital Admission and Infants: Test Negative Design Study," was recently published in the *BMJ.* These results of another test negative design study that looked at infants less than 6 months of age. 8,809 infants met eligibility criteria. Infant vaccine effectiveness from two maternal doses was 95% against Delta infection and 97%

against infant hospital admission due to Delta, 45% against Omicron infection, and 53% against hospital admission due to Omicron. But vaccine effectiveness for three doses was 73% against Omicron and 80% against hospital admission due to Omicron.

Vaccine effectiveness for two doses against infant Omicron was highest if you got that second dose in the third trimester. I'm going to see that take-home message here in the time of Omicron makes sense to get that third shot. It also looks like timing it as we thought during that last third trimester makes sense. I will also say vaccine effectiveness for the two doses against infant Omicron infection decreased from between birth and 8 weeks once you got out to 16 weeks of age. Really getting most of that protection right upfront.

VR: It seems to me, Daniel, that if you're fully vaccinated and you're pregnant, you could just get a booster in your third trimester and that would probably help the infant as well.

DG: I think that makes a lot of sense. Pre-exposure period transmission testing, have a plan. A lot on transmission today, so warn you upfront. I want to encourage people to read the article, "Yes, Masks Reduce the Risk of Spreading COVID, Despite a Review Saying They Don't." That was the title. I love that. This was published in *Conversation* and republished in *TVO Today*. That's the name of the journal, *TVO Today*.

I do not feel that I will have time to do justice here. I'm actually going to recommend, go ahead, read this. I'm going to leave in a link. The authors are, written by C Raina MacIntyre, Professor of Global Biosecurity. We've got Abrar Chughtai, we've got David Fisman, we've got Trish Greenhalgh, great channeling of Mark Crislip in this article as they point out the flaws with the *Cochrane Review*, methodology of lumping all the apples and oranges along with some cow pies and then telling us not to eat apples because they're full of partially digested alfalfa.

The issue with including large, poor quality studies where people were asked to wear masks but did not. All this does is prove that asking people nicely to do the right thing does not work if they don't do it. We've discussed the large RCT for Bangladesh that found face masks reduced the risk of infection overall, even more so in people over 60. Also, the compelling evidence that in hospitals where we had expected excellent ventilation standards, the compelling and high level of protection afforded by N95s.

I want to suggest that one of the biggest public health communication and guidance issues for future pandemics is updating the outdated binary distinction between droplet and airborne transmission, and instead making that binary at the level of contact and respiratory. Instead of continuing to fight using the outdated paradigm of droplet and airborne, may I suggest this effort and passion goes into moving infection control from the 1910s and Chaplain's binary to the 21st century before the next respiratory pandemic has us rehashing the same issue.

As people may have heard the New York State Department of Health let masking requirements in healthcare facilities expire on February 12. Some settings they actually, those masks are no longer mandated in other settings. I will say at Optum, we are still mandating masks when we take care of our patients. I, also, am going to put in a link to the

article, ”COVID-19 and Airborne Transmission: Science Rejected, Lives Lost. Can Society Do Better?” Published in *CID*. Lots of social media attention around this article.

The authors referenced the article, “What Were the Historical Reasons for the Resistance to Recognizing Airborne Transmission During the COVID-19 Pandemic?” I feel the author does a really good job here, as published in the *International Journal of Indoor Environment and Health*, of laying out the history that led to how we ended up with this outdated binary, all the language around respiratory transmission, including droplet and airborne.

I understand that much regulation surrounds the term airborne and this leads to obligations on employers to supply proper protective equipment such as N95s, but I'm going to keep asking that we address this issue. When we have crowded hospitals full of patients during the next flu pandemic, with H5N1 or H1N1, with a higher mortality rate perhaps, maybe multi-occupancy rooms. Does flu then become an airborne pathogen? Do I then get an N95 to wear or do we stick with the idea that flu is all droplets if I walk around only wearing a surgical mask while in the room? I'm going to say now is the time to update our language and thinking.

All right. COVID vaccination, we actually have a bunch here. Let us start this section by discussing the preprint, “A Randomized Trial Comparing Omicron-containing Boosters with the Original COVID-19 Vaccine mRNA-1273.” What got me interested in this article actually was some social media posts, the idea that the majority of immunologists agree, comments like that. The issue addressed here is, how important is it to be updating these boosters and vaccines? How critical is it that we get it just right?

These are the results of a phase 3 randomized, observer-blind, active-controlled trial in the UK that evaluated immunogenicity and safety of 50 microgram doses of Omicron-BA.1-monovalent and bivalent mRNA booster vaccines compared with the 50 microgram mRNA-1273, the good old original administrative boosters in individuals 16 years of age and older. Participants had previously received two doses of any authorized, approved COVID-19 vaccine with or without an mRNA vaccine booster. Safety and immunogenicity were primary objectives. Immunogenicity was assessed in all participants with analysis conducted on prior infection status. Infection of COVID-19 post-boost was a secondary or exploratory objective.

What did they find? I've got some figures here that hopefully, I'm distracting Vincent with. In part 1 of the study, 719 participants received mRNA. I'm just going to say 719 participants got the Omicron bivalent BA.1 booster, or we got a bunch of folks that got the mRNA-1273 monovalent booster. In part 2, a bunch of folks receive the updated bivalent booster targeting BA.4, BA.5, or the mRNA-1273 monovalent booster. You can see we're comparing the BA.1 booster to the original and we're comparing the bivalent booster to the original.

Now, the median duration between the most recent COVID-19 vaccine and study boosters were similar in the different groups. The incidence rates per thousand persons of COVID-19 trended lower with the mRNA-1273.529 That's the Omicron bivalent BA.1, than with the mRNA-1273 and the mRNA-1273.214. That's the updated bivalent over the mRNA original. I want people to actually, well, Vincent and I are going to look at the actual data. What do you think, Vincent, is it earth-shattering? Are those lines very well separated, or are they basically overlapping?

VR: I think, with this data, there are no error bars. It's hard to say, but they're very close. It's not earth-shattering, right?

DG: Yes, it's really not actually. I think one of the interesting things here is that you would need a statistician to tell you whether or not these lines are actually different. Very, very similar when you follow them out over time.

VR: What is the endpoint again that we're looking at here? Is this infection?

DG: These are cumulative event rates. These are people actually getting sick, so not necessarily ending up in the hospital.

VR: Not just a positive test, right?

DG: Yes. This would be symptomatic. Cumulative event rate for symptomatic. Really, at the end, they basically, the two lines overlap at the end. You see them back and forth and -

VR: Yes. When you go out so many days, it gets to be the same. This study, as Paul Offit has pointed out, could only be done in the UK where they still have the original mRNA-1273 booster. We can't do this study in the U.S.

DG: All right, let me add another here. A preprint out of David Ho's lab, "SARS-CoV-2 Neutralizing Antibodies After Bivalent vs. Monovalent Booster*."* Here, they assessed serum virus neutralizing titers in 41 participants who received three monovalent mRNA vaccine doses followed by the bivalent booster, a monovalent booster, or they actually got a BA.5 post-vaccine infection at one month and three months after the last vaccine dose. They didn't get the infections twice. They're measuring the antibodies at one and three months. There were no significant differences at one month and three months post-booster for the two booster cohorts.

The BA.5 though infected patients did exhibit significantly higher neutralizing antibody titers at three months against all Omicron subvariants tested compared against the monovalent and the bivalent. There was a twofold drop in the mean neutralizing antibody titers in the booster cohorts between one- and three-month time points. They were not seeing discernible waning of titers in the folks that got BA.5 post-vaccine infections over the same period of time.

VR: Daniel, as a pull-off, I would say it's not clear that these differences are clinically relevant.

DG: Yes. Well, actually here, they're not even different. Hard to be clinically relevant when basically they're at the same level. I think that's an interesting issue. What about Novavax? Moving on. The traditional protein-based vaccine, dare I say, at the last FDA meeting, there were several comments about why the FDA was so mRNA focused. The article, "Safety and Efficacy of Novavax Coronavirus Disease 2019 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Control Trial." This is published in *CID.*

These are the results, as right there in the title, a phase 3, randomized, observer-blinded, placebo-controlled trial in the UK. Adults, this is a 1:1. They were monitored for virologically

confirmed mild, moderate, or severe COVID-19 at a maximum of 7.5 months, a median 4.5. They reported vaccine efficacy was 100% against severe disease and 76.3% against even asymptomatic disease. There's a nice Kaplan–Meier plot, so not bad data.

VR: What virus is circulating when this is done? Is it early Omicron or even before Omicron?

DG: Yes, I think that's an important question. When were most of these infections, when did most of these occur? Because, yes, vaccine efficacy is definitely going to be impacted by circulating variant. I will comment, not sure what triggered this, but the U.S. government is purchasing another 1.5 million doses of the Novavax COVID vaccine. I say I'm not sure what to make of this because according to federal data only about 77,500 doses of Novavax COVID-19 vaccine have been administered out of the more than 1 million doses that we already bought.

The initial lot of Novavax vaccines purchased are set to expire toward the end of February. The Biden administration purchased 3.2 million doses of Novavax's protein-based coronavirus vaccine in July of 2022. What does Novavax tell us? This agreement acknowledges the need to offer the American people a diverse COVID-19 vaccine portfolio and underscores the importance of Novavax's partnership with the U.S. government to ensure continuous access to a protein-based option as a part of public health measures.

This actual article, this is what we discuss around the Griffin household. The article, "The Impacts of SARS-CoV-2 Vaccine Dose Separation and Targeting on the COVID-19 Epidemic in England," was published in *Nature Communications*. What's the story here? In late 2020, the Joint Committee on Vaccination and Immunisation, which provides advice to the Department of Health and Social Care in England, made two important recommendations for the initial rollout of the COVID-19 vaccination in the UK.

First was to increase the interval between the first and second doses from the three months that were studied to 12 weeks. The second was vaccines should be targeted to older and vulnerable people, with the aim of maximally preventing disease rather than infections. Here, the authors are going to ask, were these good decisions? Did these have a good impact? Was it a good idea? Did it provide net overall benefit to increase that interval from three to 12 weeks? Then two, what was the best population to target? They're going to do mathematical modeling.

We'll start off with the first. By increasing this interval, was this really going to allow for more primary shots? Also, would this give the immune system more time to improve that boost where you're going to get a better response? Here, they actually estimated that this increased interval averted between 32 and 72,000 hospital admissions and 4 to 9,000 deaths over the first 10 months of the campaign.

Now, who to vaccinate first? Did it turn out that older and vulnerable people with the aim of maximally preventing disease rather than infection was an effective approach? This gets a little bit more complicated in their modeling. Their results suggest that the policy of vaccinating the oldest and most vulnerable first led to a faster decline in hospital admissions, in deaths. However, when they actually looked at subsequent waves, they suggested that a younger-first policy might have been more effective in the subsequent

Delta wave when it came to looking at lowering hospital admissions. There's a lot going on here. It's modeling. Vincent, I don't know if this is something that has -

VR: The problem with modeling is you're making assumptions about what you're modeling. For example, spacing out the doses, you're making some assumption on how much diversification and increase in titer you're getting, and that may not be appropriate. I think you have to take this with a very large grain of salt in my opinion.

DG: Yes, it's interesting. This is what we, discussing around the dinner table, what do we do the next pandemic. Do we follow the science? Sort of the this was studied, this dose, then this dose three weeks later. Do we think we know enough to extend that to three months? These are going to be interesting questions that we will face again at some point in the future.

VR: Also, I think we put the first doses three weeks apart because we wanted to get the vaccine into a lot of people, spreading it out. We know that that booster spread out does a lot, but it's not clear if it's going to apply to another virus, so it's very difficult, I think, to extrapolate.

DG: Yes. I look forward to the day when we say things like, this is not COVID.

VR: Yes, that's right.

DG: Stop comparing this new virus to the COVID.

VR: Well, you don't look forward to it, but it's going to happen.

DG: All right. What about those variants? Actually, I think Amy may have sent this my way. The article, "Intra-Host Evolution Provides for the Continuous Emergence of SARS-CoV-2 Variants," published in *mBio*. Here they investigated 94 patients who were repeatedly PCR-positive for SARS-CoV-2. Based on this data, they estimated then as much as 2% of hospitalized COVID-19 cases variants with multiple mutations in the spike glycoprotein emerge in as little as one month of persistent intra-host virus replication. I hope they mean mutations in the code, the codes for the spike glycoprotein.

This suggests that continued local emergence of variants with multiple nonsynonymous single nucleotide variations even in patients without overt immune deficiency. Now, my one criticism is that they fail to name these variants after monsters, so I am calling these Godzilla and Mothra. Just joking by the way.

All right, let's move into COVID the early viral upper respiratory phase, and I am going to talk about Paxlovid. For those not aware that Paxlovid actually works, I've got a couple of articles, "Real-world Use of Nirmatrelvir-ritonavir in Outpatients with COVID-19 During the Era of Omicron Variants Including BA.4 and BA.5 in Colorado, USA: A Retrospective Cohort Study." Actually, just because maybe some people are not prescribing Paxlovid because they're not sure how to pronounce nirmatrelvir so it's like Norma but with the U, so nirmatrelvir.

VR: There you go. We just learned that today.

DG: [laughs] This was published in *The Lancet Infectious Diseases*. For all those providers and patients that are worried about a bad taste or misinformed about the concept of rebound versus the intrinsic biphasic nature of COVID with week two being the early inflammatory phase, we have the results of a propensity-matched, retrospective, observational cohort study of non-hospitalized adult patients infected with SARS-CoV-2 between March 26 and August 25, 2022 using records from a statewide health system in Colorado.

Among 28,167 patients infected with SARS-CoV-2, 21,493 met the study criteria, 9,881 patients received treatment with nirmatrelvir-ritonavir, Paxlovid, and 11,612 were untreated. Treatment was associated with reduced 28-day all-cause hospitalization compared with no antiviral treatment, odds ratio of 0.45, and Paxlovid treatment was associated with reduced 28-day all-cause mortality adjusted 0.85, so 85% reduction in your chance of dying. Using subsequent ER department visits as a surrogate for clinically significant relapse, we observed a decrease after Paxlovid treatment, so 26% reduction.

VR: Is this both vaccinated and unvaccinated people, all ages?

DG: Yes. It's a mix actually. You've got to think where we are. We're in Colorado and we're in March going into August of 2022, so this is recent data. As we know, at this point, the majority of these individuals have been vaccinated, infected, or both. *The Lancet Infectious Diseases* article, "Viral Burden Rebound in Hospitalised Patients with COVID-19 Receiving Oral Antivirals in Hong Kong: A Population-wide Retrospective Cohort Study." These are the results of a retrospective cohort study of hospitalized patients with a confirmed diagnosis of COVID in Hong Kong, China, for an observation period from February 26 to July 3, 2022, so overlapping periods of time during the Omicron BA.2.2 variant wave.

In these 4,592 hospitalized patients with non-oxygen dependent COVID-19, viral burden rebound rates are similar between patients with antiviral treatment and those without, and they have some really nice curves. We can actually follow the CT values in folks that got Paxlovid, folks that got molnupiravir, folks that got nothing.

VR: I don't know. I don't see rebound here, Daniel.

DG: Yes, you're not seeing that where it goes down and then it's - Oh yes, I'm not seeing it either. Nothing to see here.

VR: Move on.

DG: OK, number two, remdesivir, number three, unfortunately, not much here for the monoclonals, but I am going to mention something next week and I will, molnupiravir. Then just to tip our hat to convalescent plasma, the article, Guidance on the Use of Convalescent Plasma to Treat Immunocompromised Patients with COVID-19," was published in *CID.* This is exactly what it is, guidance on using convalescent plasma in immunocompromised patients with COVID.

The guidance is that for optimal effect CCP, so COVID convalescent plasma, should be recently and locally collected to match circulating variants. It should be considered for the treatment of immunocompromised patients with acute and protracted COVID-19. The

dosage depends on the clinical setting, whether it's acute or protracted, and the CCP should have high titers SARS-CoV-2 antibodies with activity against these circulating SARS-CoV-2 variants.

VR: What does high titer mean? Do they have a number? I hope so.

DG: They actually do. They do. I don't mention it here, but yes in the article, they actually mentioned what this high titer is.

VR: Next week on *TWiV,* Arturo Casadevall will come and talk about what's happening with convalescent plasma.

DG: Oh, exciting. All right, I will look forward to listening. Unfortunately, if we wait to see how folks do, we are still seeing individuals progress to severe disease hospitalization, and about well, 3,000 to 4,000 folks death per week. So steroids at the right time, anticoagulation, pulmonary support, remdesivir if not on a ventilator, if early enough, immune modulation made with tocilizumab. Avoid those unnecessary, unproven therapies.

Unfortunately, as much as we do, there are still folks who three months out are still struggling. It's been a little tough this week. I don't know what the media has been doing, but I had one patient that I saw this week, urgent-care provider desperately trying to figure out how she can get well enough to return to work. She's got bills piling up, and she mentioned several times her son, who she loves dearly, is training up at the MGH, where, as he informed her, they have debunked the myth of Long COVID. She felt a little, I think, personally attacked as if she was now a malingerer among the rest of them, as apparently they are teaching in Boston.

Also, another patient was quite upset with apparently stories about Long COVID only happens to overweight and people who don't exercise. I just want to say none of this is true. This is heartless to be spreading such misinformation. I take care of a lot of these individuals. They just desperately want to understand what's going on and how to get better. I will close by saying low- and middle-income countries, no one is safe until everyone is safe. I do have a quick bullet point summary for those people who are driving and do not want to crash into people as they turn left, or crash into the car in front of them when they are looking down.

Today, we covered the problem of media-based medicine, U.S. flu activity remaining low, but kids death passing 100, cholera in Malawi and Marburg hemorrhagic fever in Equatorial Guinea, norovirus being very prevalent in the U.S., that estimation of over a million deaths in the last couple months in China, the impact of coronavirus infections on children, benefits of vaccine during pregnancy, efficacy of and controversies around masks, the issue with language around respiratory transmission, vaccine boosters do boost but not so overwhelming that we've got to get it exactly right, vaccines might do better with more time between first and second doses, variance keep it coming and I guess they keep needing names, Paxlovid works and Paxlovid rebound is still not a thing, it never was, and CCP guidelines as well as Long COVID is a thing and we need to stop being dismissive and focus on being more caring and inquisitive.

VR: Don't you want to say something about your fundraiser?

DG: Oh, yes, I do want to encourage everyone. Pause the recording right here. Thank you, Vincent. We are now having our American Society of Tropical Medicine fundraiser, so February, March, and April, go to parasiteswithoutborders.com, click on that 'Donate' button. Things will be doubled by Parasites Without Borders up to a maximum donation of $30,000 from Parasites Without Borders to the American Society of Tropical Medicine and Hygiene.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Janet writes, "I work at a rural urgent care clinic. We offer outpatient COVID therapy. Until this fall we offered monoclonal therapy and now remdesivir. Our guidelines have a hard stop for a creatinine clearance of less than 30. We are unable to offer these patients Paxlovid or remdesivir, yet these patients are at high risk for complications of COVID. When I search for data about remdesivir/COVID/less than 30 GFR outpatient prophylaxis, I'm mainly finding data about severely ill hospitalized patients, not ones who need prophylaxis. What do you think? Do you think that remdesivir three-day infusion is safe for this patient population? Do you have references to share with my admin?"

DG: Yes, so I think this is a great question. This was a great situation when we had effective monoclonals. There are a number of studies out there, "Clinical Effectiveness and Safety of Remdesivir in Hemodialysis Patients with COVID-19," that was published in *Kidney International Reports*. There's a few others, but I'm going to put this in context. This is always going to be a judgment and what they're going to say here is you always want to make a clinical judgment. This is now a licensed medication. A physician can say, "OK, I'm going to go ahead and I feel that the benefit is worth any risk in treating a patient for this three-day or even five-day course of therapy, so short course remdesivir.

I have to say this is something that we are routinely doing here in the Northeast, but, yes, we could use more data. There are few studies out there, some from India, some from Hong Kong, some as I mentioned.

VR: Linda writes, "Should a high-risk individual, elderly-elderly 85 years old who tests positive for COVID but is asymptomatic, tested due to exposure from a family member who was positive and symptomatic, should that elderly person pursue Paxlovid or remdesivir? Is this person who is asymptomatic still at risk to progress to hospitalization on week two?"

DG: This is an interesting issue. I think I'm going to sort of bring up this. Things like remdesivir, Paxlovid, these are authorized for treatment of COVID-19, so if you run into this little area here where a person, we're not authorizing these for PCR positivity, they're for someone who has some symptoms: I feel fatigue, I have a headache. You got to have at least something is really the approval here.

Can you take remdesivir? As I mentioned, it's licensed to use it a little bit off-label. Just, yes, I'll just say that there. What about the choice? What about if you're making a choice in someone who is symptomatic, someone who has COVID-19? This actually came up just earlier this week at the hospital. One of the providers was asking about this. Remdesivir, the PINETREE data was about 87% reduction in progression. Paxlovid got authorization based upon interim analysis of the EPIC-HR. The full results are actually before the FDA as we speak. In that interim analysis, we've got it within the first three days, 89%. If you got it

within five days, 86%. We're really seeing pretty similar efficacy here between your Paxlovid and your remdesivir. Paxlovid, it's oral, it's easy to take. Remdesivir, there's a lot more to lift, so that's why Paxlovid is always number one, but really followed closely by remdesivir.

VR: Finally, Roman writes, "Daniel, the advice that I give clients about restarting medications after Paxlovid is different. With Justin's question, I would have him restarting atorvastatin two days after completing Paxlovid. This recommendation would be based on the Science Table COVID-19 Advisory for Toronto." Provides a link for that. "The University of Liverpool Drug Interaction Checker would have me restarting atorvastatin three days after completing Paxlovid." Provides a link for that. "It's interesting that we have three sources giving three different restart dates."

DG: It is interesting. The fact that we're not all on the same page here. You can look at what is the issue with Paxlovid and these medications. It's the CYP3A. Actually, there's a bit to think about CYP3A here. One is when you're on ritonavir, ritonavir is going to inhibit CYP3A, metabolism by CYP3A. That's on purpose so that the nirmatrelvir can stay at a high level. The other interesting, let's say a person is on a medicine that is inducing the CYP3A, basically counteracting the ritonavir.

Here's a patient, you're trying to give them Paxlovid and it's dropping down, but in a lot of times what we're thinking is now you've stopped the medicine, is there a residual effect of ritonavir? The ritonavir, we're dosing that twice a day because the half-life is just not that long. The recommendations here in the U.S. is this 10-day but when you start looking at the pharmacology, I think you can actually start using your judgment and start looking at, do I need to stick with a rigid guidance of 10 days, or depending upon the importance of being on that medicine, can I actually restart it sooner?

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

DG: Thank you. Everyone, be safe.

[music]

[00:45:01] [END OF AUDIO]