This Week in Virology

TWiV 998 Clinical Update

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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

[music]

VR: From MicrobeTV, this *TWiV*, *This Week in Virology,* Episode 998, recorded on April 5, 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: Wow, 998, Daniel, that's something because when the pandemic started, we just hit 600, as we said last time. I'm amazed at how many episodes we have in but I don't think we're going to make 2,000.

[laughter]

DG: 400-plus episodes since the pandemic started. That's amazing. The next clinical update will be part of *TWiV* 1,000. Probably, small parts, I'll save up some stuff for what *TWiV* 1,001 - [crosstalk]

VR: Yes, we have to skip next week's clinical update to synchronize for 1,000. Otherwise, it would be all messed up. Tomorrow, Friday, we're doing the last regular *TWiV*, that'll be 999. Then we'll do 1,000, and then we'll get back to the next 1,000, yes.

DG: [chuckles] OK. Let me jump right into my quotation. I've got a lot to say today, I seem always to, but let's go right with the quotation. "Let not anyone pacify his conscience by the delusion that he can do no harm if he takes no part and forms no opinion. Bad men need nothing more to compass their ends, than that good man should look on and do nothing. He's not a good man who without a protest, allows wrong to be committed in his name and with the means which he helps to supply because he will not trouble himself to use his mind on this subject." That's John Stuart Mill.

I'd like to update this with people, but I agree with the sentiment, but it brings me right into the article, "'If We Don't, Others Will': White House COVID Adviser Calls on Doctors to Combat a Vacuum of Medical Information," published in *STAT* by Elizabeth Cooney.

I always want to rename these things. It shouldn't be just doctors, it should be doctors, scientists, and the like. I'll just read one of the parts of this article, "'What we have seen is the widespread propagation of misinformation and disinformation. And the reason it has taken root is because there was an information vacuum,' Jha said to the group convened by the Massachusetts Medical Society with support from the New England Journal of Medicine Group. 'I come back to our role as physicians. It is critical that we fill that vacuum because if we don't, others will.'"

VR: Daniel, aren't we filling the vacuum? Why don't they acknowledge what we're doing?

DG: I think when he was giving this talk, he left a link to our podcast.

VR: Really?

DG: I say that jokingly, but it is amazing, they go up and they say this, and then the next step is, "OK, so is anyone doing this? Can we help them get the message out?" We have, as we just mentioned, over 400 of our episodes. Mine are maybe 30, 45 minutes. Some of the deeper dives are a couple of hours. There are hundreds and hundreds of hours of information that we've created. Yes, this is happening. It would be nice -

VR: Maybe he has no idea that we're doing this. That's the problem. Yes, I agree, there's misinformation and disinformation, but he also is uninformed because he doesn't know the hundreds of hours that we have programmed with virologists and clinicians who know what they are talking about. I'm sorry, Jha, people are trying to do this.

DG: Yes, help us. Help us. Not just us, I love to, what is it, ring our bell. I'm not great with expressions but toot our horn. Is that what it is? It's something -

VR: Or you could ring your own bell, that's fine.

DG: You could ring your bell and toot your horn. Paul Offit, I was just reading his-- He's got a new Substack apparently. That's the thing. I don't know.

VR: Yes. I've been told I need a Substack now.

DG: I think people make money off Substack. Anyway, I thought it was quite informative. I may even have a reference to it later on, but let us jump into some pre-- This is the pre-COVID stuff. I don't know if people still remember. Hopefully, people still care about the severe cases of hepatitis in children. A couple of articles. The first article, "Adeno-associated Virus Type 2 in U.S. Children with Acute Severe Hepatitis," was published in *Nature*.

Vincent, I'm looking forward to your take on this and it will suggest this reinforces my, perhaps now famous quotation, "Occam may have had a razor but he was not a physician. John Hickam was a physician and a patient may have as many diseases as they darn well please." We just got the unedited version, and as far as background, let me remind everyone that by the end of summer 2022, clusters of acute severe hepatitis of unknown etiology in children had been reported from 35 countries, including the United States.

Previous studies had found human adenoviruses in the blood from cases in Europe and the U.S. Here they used PCR testing, viral enrichment-based sequencing, agnostic metagenomic sequencing, I love that, to analyze the samples from 16 of these positive cases from October 1, 2021 to May 22, 2022, in parallel with 113 controls. In blood from 14 cases, adeno-associated virus 2 sequences were detected in 93% compared to only 3.5% in the controls and 0 of 30 patients with hepatitis of defined etiology.

In controls, the HAdV-41. I want everyone to remember that. The human adenovirus 41 was detected in blood from 39% of the 23 patients with acute gastroenteritis without hepatitis, including eight of nine with positive stool testing, but co-infection with adeno-associated virus 2 was observed in only 13% of those 23 patients versus 93% of the cases. You saw some co-infections by EBV, HHV-6, enterovirus A71.

I would agree, I'm going to wrap up this first. I would agree with the authors that these findings suggest that the severity of the disease is related to co-infections involving adeno-associated virus 2 and one or more helper viruses. I was also excited to see a second article, "Genomic Investigations of Unexplained Acute Hepatitis in Children," also published in *Nature*. As we mentioned, I'm going to expand on this background because they do.

Since the first identification in Scotland, over 1,000 cases of unexplained pediatric hepatitis in children had been reported worldwide, including almost 300 cases in the UK. Here, they investigated 38 cases with 66 aged-matched controls, 21 immunocompromised comparator subjects. They used a combination of genomic, transcriptomic, proteomic, and immunohistochemical methods.

Again, they detected high levels of adeno-associated virus 2, DNA in liver, blood, plasma, stool from 27 of the 28 cases. They found low levels of human adenovirus, 23 over 31, and Human Herpesvirus 6B in 16 of 23 cases. In contrast, the adeno-associated virus 2 was infrequently detected at low titer in blood or liver from the control children, even in those that were profoundly immunosuppressed. We had some histological analyses of the explanted livers which showed enrichment for T-cells and B-cell, B-lineage cells.

Proteomic comparison of liver tissue from cases, healthy controls, identified increased expression of HLA class 2, immunoglobulin variable regions, and complement proteins. I'll just wrap up this one as well. They hypothesize that the high levels of abnormal adeno-associated virus 2 replication products aided by human adenovirus infection, and in severe cases, HHV-6B, may have triggered immune-mediated hepatic disease genetically and immunologically predisposed children.

VR: I just want to point out that last year, I interviewed Emma Thompson at a meeting in Manchester about this work, which at the time was under review at *Nature*, and that was published on *TWiV* 937. She's really good and you want to hear her talk about how the story developed. You should check that out.

DG: Excellent, man. Well, it's nice to get some more information. I never say closure in science because there's never closure in science, we just keep moving forward. Sometimes a step back, two steps forward. Polio, I got a few comments about our comments last week, I'm really curious to see the sequence data on the vaccine-derived polio cases from the

updated type 2 vaccine-associated cases. I had a few thoughts in my head, did it really revert or they're just rare people out there that develop paralytic polio from an attenuated infection? I'm very excited to get that data. Any more thoughts on - You got a few more cases reported in the last week here, Vincent?

VR: We need to see these data, I don't know why they're not being released. Stop hiding stuff whoever you are, and release it. Your question, did it revert? The five prime end is probably not reverting, other parts of the genome might. These are typically going to be recombinant with other enteroviruses in the gut so they could acquire neurovirulence. That way, I would guess it's not the people. I think the people who get this are simply not vaccinated, and it's the virus that has somehow acquired neurovirulence.

However, Daniel, only 1 in 100, or a few 100 people, get polio of all the people infected. I've always thought it was some other genetic anomaly in certain individuals, a snip of some sort in a certain gene that predisposes them to paralysis, but no one has ever really sorted that out.

DG: It's going to be hard to sort out but looking for more information here. Norovirus, winter vomiting disease, are we on a mission to Mars? Just keeps going up. What is it about washing your hands that people seem not to be interested? Just think about it, you can say the alphabet twice, and get your hands good and washed, and you can avoid winter vomiting disease.

All right, moving right into COVID, how do we know what's going on? Because people always ask me, and I had to say, I'm not sure. I don't have as much information as I'd like, but we do have wastewater monitoring, I'll leave in a link. We do have excess mortality, but we're having some issues here with getting updates. I was getting amused a bit about the book that I'm reading. Right now I'm reading *Journal of the Plague Year* by Daniel Defoe. That's why I get invited to parties all the time because I'm just such an upbeat guy reading all this optimistic stuff.

Actually, it's interesting in the early part of this, this is how people got a sense that the plague had come to different areas. They would basically say, in my parish, how many funerals are happening. Even when people were dying of some mysterious spotted disease, and obviously not the plague, when they noticed that those burials went from 100 up to 300 in a week, people were aware that something was happening.

Actually, we'll leave in a link to the CDC site, but you can actually see over time, so it was a little bit delayed here. There's an expected number of weekly deaths from all causes, but then you can actually see the different spikes, when it goes up you can actually see. Omicron starts to spread, and actually the peak in January of 2022, after Omicron, the "mild variant" had come, it was just as high as it was the year before.

All right, and moving into, this is fun, "Surveillance of SARS-CoV-2 at the Huanan Seafood Market," posted on *ChinaXiv*. They're doing that same thing, funny thing with the X being the archive. Here they share the SARS-CoV-2 detection results of 1,380 samples collected from the environment since the first of January and animals since the 18th of January, within the market in early 2020. They use SARS-CoV-2 specific RT-qPCR.

They looked at environmental samples that tested positive for SARS-CoV-2, although, actually they say here, three live viruses were successfully isolated. I guess they've settled that viruses are now alive, Vincent. The viruses from the market shared nucleotide identity of 99.99% to 100% with the human isolate, and that's the HCoV-19/Wuhan/IVDC HB-01/2019. What I'm going to say here, which I think is the most interesting part, we've heard that there were none of those prohibited highly susceptible mammals here, but somehow there was lots and lots of genetic material from different vertebrate genera there.

I'm going to actually go right to the nice piece in science that helps explain this story a little bit better, and I'm going to leave in a link. As they explained, the Chinese team's initial preprint argued that the market data consisted of genetic sequences found in 923 samples collected in or near the market in early 2020, highly suggests human brought the coronavirus there and made no mention of the evidence that SARS-CoV-2 susceptible mammals were present.

Their updated preprint acknowledges the genetic evidence of the animals and now says the collected samples don't resolve whether infected animals or humans or even contaminated food, introduce the virus into the market where the first cluster of COVID-19 cases surfaced.

VR: This Daniel, is the best evidence for spillover at the market because they're trying to cover it up. They released the sequence data last year, and they missed the fact that there were animal mitochondrial sequences in it. Then when few people picked it up a few weeks ago, they right away, pulled down the sequences, did the analysis themself, and now they've published their own preprint, which is fine. To say it doesn't prove that the animals were the source is so missing the point because there's a preponderance of evidence. You have this one part of the market, first of all, the market is the epicenter of the outbreak. It clearly started there.

DG: I mean, very, very compelling science that that's -

VR: It's not that a few humans brought it in. I mean, you had a huge outbreak right there. Then these susceptible animals were all in a certain part of the market. That's where the environmental specimens were, and that's where these mitochondrial specimens were, that are all SARS-CoV-2 positive, it's overwhelming. I just don't understand what they're saying, and neither do many other people like Eddie Holmes, get why they're saying this, but I think it's because they want to deflect attention from the market because that's where it started.

DG: They weren't supposed to do these. They weren't supposed to have these-

VR: No, they were not supposed to do these.

DG: They weren't supposed to have these highly susceptible mammals all stuck there together. It was supposed to have come in on the frozen fish that that guy with the yellow hat and rain suit brings in from America. All right, I'm not buying that.

Children, COVID, vulnerable populations. I thought this was important because this has become a controversy this last week. I'll say due to some misrepresentation of some WHO comments. but the article, "Vaccine Effectiveness against Hospitalization among Adolescent

and Pediatric SARS-CoV-2 Cases between May 2021 and January 2022 in Ontario, Canada: A Retrospective Cohort Study," was recently published in *PLOS ONE*.

We've talked about different outcomes that might be impacted by vaccination, and by how in children, hospitalization and post-acute sequelae are probably the endpoints to be looking at. Here are these investigators sought to quantify the protection conferred by mRNA vaccination against hospitalization due to SARS-CoV-2 in adolescent and pediatric populations included 62 hospitalized, 27,674 no-hospitalized SARS-CoV-2 cases, with disease onset from May 28, 2021, to December 4, 2021. That's right in that pre-Omicron, right there at the end of November, early December when we see Omicron.

From December 23, 2021 to January 9, 2022, when we have entered the Omicron period. Among adolescents, two mRNA vaccine doses were associated with an 85% lower likelihood of hospitalization in those cases caused by Omicron. They even saw pretty impressive efficacy, when they looked at folks that just got one vaccine dose. This is really, I have to say, impressive data.

We've talked about the thousands of children that were hospitalized, not just with but due to COVID-19, and an 85% reduction with just two doses adds up to a pretty big number, suggesting that this is a three-dose series and we may see even more efficacy when we get there. As a parent of a child who was hospitalized several times, not for COVID, I would want to do everything I can to prevent my child from ending up in the hospital, and vaccination is something that can do that.

Also excited to see the article," Effectiveness of BNT162b2," that's the BioNTech-Pfizer vaccine, "After Extending the Primary Series Dosing Interval in Children and Adolescents Aged 5 to 17," published in *Nature Communications*.

For a while, we've asked this question, are we doing three shots because we just did that second dose too close? Could we do that second dose maybe out at six months? We've talked a lot about how in the height of the pandemic, there was an urgency to get those first couple of doses in to get that protection. Here, the authors suggest that extended intervals between the first and second doses might reduce the risk of myocarditis. We're not going to actually get data on that here, but they are going to suggest that maybe this increased interval is going to impact effectiveness.

To examine this potential variable effectiveness, they conducted a population-based, nested case-control study of children and adolescents aged 5 to 17 who had received two doses of the mRNA vaccine in Hong Kong from January 1 to August 15, 2022. 5,396 COVID-19 cases and 202 COVID-19-related hospitalization were identified and matched with 21,577 and 808 controls, respectively.

Here's what they found. For vaccine recipients with extended intervals, so greater than 28 days, the adjusted odds ratio was 0.718. That's about a 29% reduced risk of COVID-19 infection compared to those with that shorter, that 21 to 27 days. If the threshold was set at eight weeks, then the risk reduction was increased to 43.5%.

VR: Yes, that close spacing of those first two doses is probably interrupting somatic hypermutation and affinity maturation. You have an antigen coming in and the lymph node is like, "Wait a minute, what's this?" and drops what it's doing. [laughs]

DG: I'm not quite through, but I was listening to the latest discussion on *Immune* about how this ongoing germinal center activity out six months. You jump it at three weeks. It's probably too soon. I have to say we are learning a lot of immunology thanks to COVID. I also wanted to spend some time on the article. It's right up front here, right? I'm doing this in the young adult section, but it was sent my way by Yonatan Mehlman at Columbia. Not so much sent my way as put up on the big screen during morning rounds one day.

"Dr. Griffin, what do you think of this article?"

“Prevalence and Characteristics Associated with Post-COVID-19 Condition among Non-hospitalized Adolescents and Young Adults,” recently published in *JAMA Network Open*. As I mentioned, we just talked about hospitalization, but what about post-COVID conditions? In the introduction, they point out that in the aftermath of a wide array of infectious diseases such as mono, Q fever, giardiasis. Multiple prospective studies report about a 10% to 15% incidents of patients with moderate to severe disability meeting the diagnostic criteria for what we have termed post-infective fatigue syndrome.

This is actually in line with some of the current studies about post-COVID conditions. They comment that studies of post-infective fatigue syndrome have benefited from an international case definition that is centered around the symptom of fatigue, which should be, as the definition is persistent from onset of the acute infectious event, severely affecting daily activities not caused by any other condition, and diagnosed individuals in this strict definition need to experience at least four of eight additional symptoms such as headache, concentration, memory problems.

In contrast, the WHO has a very broad case definition for post-COVID conditions. Here what they were doing is looking at this very broad WHO definition and then asking some questions. I tend to agree with some of their comments. What we see in this cohort that included 382 SARS-CoV-2 positive individuals and a control group of 82 SARS-CoV-2 negative individuals aged 12 to 25 who were assessed at the early convalescent stage and at six months follow-up. When you apply the really broad WHO case definition of post-COVID conditions, prevalence at six months was 49%, but it was 47% in the control group. I'm going to comment that a definition ceases to be useful, actually becomes a problem if it's too broad, it loses its specificity.

I do worry, the way I've seen this article taken on social media, is that people will take away from this article what they want. They'll use it as ammunition for those that are tending to say that Long COVID is not a thing. Here in their mind is more evidence that it's not a thing. For the millions that are suffering post-COVID, understanding, properly identifying, having ways to treat, post-acute sequelae COVID, remains a health emergency.

VR: Basically, the WHO definition is inadequate, right?

DG: It's just too broad. It's just everyone has it. I think that's the problem. When 50% of your control group meets criteria, it just lacks any specificity. All right, and we will move on to

COVID active vaccination. The article, Within-host Genetic Diversity of SARS-CoV-2 Lineages in Unvaccinated and Vaccinated Individuals," was recently published in *Nature Communications*. I like to say perhaps this paper will get a deeper dive during a live stream on *TWiEVO* from Nels Elde Studios and MicrobeTV? [laughs] I think all our listeners are familiar with the ongoing evolution of SARS-CoV-2 that is happening right before our eyes with all the variants we have heard about.

I don't know if you know, Vincent, but there's even a Griffin family of COVID variants. Yes, they're actually calling the descendants of XBB, the Griffin family of variants. I believe we can thank Ryan Gregory for this catchy moniker. In this investigation, the researchers are looking at specific amino acid changes that result from mutations in individuals. The investigators analyzed deep sequencing data from about 3,000 SARS-CoV-2 respiratory samples with different viral lineages to describe the patterns within host diversity under different conditions, including infections after vaccine.

In unvaccinated individuals, variants of concern, Alpha, Delta, and Omicron respiratory samples were found to have higher within-host diversity and were under neutral to purifying selection at the full genome level. Infections after vaccination with two-dose or three-dose Comirnaty and CoronaVac vaccinated individuals did not increase levels of non-synonymous mutations and did not change the direction of selection pressure. Interesting, I'm going to swing back to the implication here. Vaccine-induced antibody or T-cell responses did not appear to have significant impact on within-host SARS-CoV-2 sequence diversification.

The authors say that these findings suggest that vaccination does not increase exploration of SARS-CoV-2 protein sequence space, and may, from this work, it appears that unvaccinated are the ones that may have facilitated emergence of the viral variants. I'm not sure about this paper. One is, I feel like there's some finger pointing here. I actually worry that a lot of the viral evolution may be taking place in immuno-compromised individuals. This is a really brief summary. There are significant public health implications. The data even suggests that three-dose vaccinations may be potentially limiting T-cell escape mutants. Lots of beautiful color data-rich figures, but very sophisticated and complex article.

VR: I think what limits T-cell escape is that it doesn't help outside of the host that it happens in. This is not a persistent infection. You see it in HEP C and HIV on a population level. In a host, T-cell escape is not going to matter. You're not going to see it, although this is within-host. Maybe that's what they're saying here, within-host genetic diversity.

DG: I think it's pretty - Yes. Let's go to - I wish I was a Syrian hamster. The article, "Live-attenuated Vaccine sCPD9 Elicits Superior Mucosal and Systemic Immunity to SARS-CoV-2 Variants in Hamsters," published in *Nature Microbiology*. This has gotten a lot of attention. Here, the investigators compared immune responses and pre-clinical efficacy of the mRNA vaccine, BNT162b2. Everyone should know what that is by now, right? That's Pfizer-BioNTech. The Adenovirus vectored-spike vaccine, AD2-spike, and the attenuated virus vaccine candidate sCPD9 in Syrian hamsters using both homogeneous and heterologous vaccination regimens.

Comparing vaccine efficacy was assessed by employing readouts from virus titrations to single-cell RNA sequencing. The authors say that their results show that CPD9 vaccination, so attenuated virus vaccine, elicited the most robust immunity, including rapid viral clearance, reduced tissue damage, fast differentiation of pre-plasma blast, strong systemic and mucosal immune responses and rapid recall of memory T-cells from lung tissue after challenge with heterologous SARS-CoV-2 in Syrian hamsters. This is exciting stuff and it looks like rather than cockroaches out-surviving, it will be the mice and Syrian hamsters. I joke, but this is a very good and very detailed paper that's worth reading.

VR: How are these mice immunized? Where is the vaccine going, Daniel? I'm trying to find it here.

DG: Let me see here. I'm going to actually bring it up while we're chatting.

VR: Methods.

DG: I believe it's actually a nasal, but let me just check the methods here while we're -

VR: Intranasal installation. Right.

DG: Yes, intranasal. I say I've got some great pathology of the lungs where you see less impact.

VR: If infection cannot maintain high nasal mucosa antibodies, I don't see why this will. They didn't look long-term and that's part of the issue here.

DG: That's always the problem. What durability? If you can't get a year, if you have to -

VR: In the review article by Crotty and Sette that we did on *Immune*, they say the intramuscular vaccines do not give you great mucosal immunity. Natural infection does, so an infection with an attenuated virus could potentially as well. The question is whether this is as good as infection plus mRNA vaccine. In fact, infection plus mRNA vaccine is fabulous. It's the best immunity ever, the so-called hybrid.

DG: The only problem is it protects you against infection, but you have to get infection for the protection. It's odd. It's like crashing your car to stay out of a car crash.

VR: Presumably you get the vaccine first, you get the full three doses, and then when you get infected, you're going to have a mild course. Most people will have a mild course and then you're going to get that fabulous mucosal immunity on top of it.

DG: All right. Fingers crossed. Also in *Nature Microbiology*, the article, "Fc Gamma R-dependent Antibody Effector Functions are Required for Vaccine-mediated Protection against Antigen-shifted Variants of SARS-CoV-2."" Here they're using passive and active immunization approaches in wild type and these Fc gamma receptor knockout mice. These investigators determined that the requirement for the Fc effector functions to control the SARS-CoV-2 infections. Maybe get a little background here before we go further.

Remember, we've talked about how antibodies can actually directly neutralize but there also can be effector functions. Think of that antibody as a slingshot. This is coming from that handle of the slingshot, actually allows antibodies to pull other cells in. The antiviral activity of passively transferred immune serum was lost against multiple SARS-CoV-2 variants in mice that didn't have these activating Fc receptors. Particularly the Fc gamma R3, so CD16 or when they depleted alveolar macrophages.

Alveolar macrophages express these receptors, allow them to work with those antibodies. After immunization with the preclinical mRNA 1273 vaccine, Moderna, control of Omicron BA.5 infection in the respiratory tract also was lost in mice lacking the Fc receptor three. What are all these studies? The passive and active immunization studies suggest that this Fc receptor engagement and alveolar macrophages are important for vaccine-induced antibody-mediated protection against infection by some of the antigenically changed SARS-CoV-2 variants, including all those Omicron sub-variants.

VR: This is a theme now we've seen in multiple papers where Fc functions are important for protection. Daniel, if this is right, then we don't need Omicron-specific boosters, do we?

DG: [laughs] Vincent, you may need Omicron-specific boosters for the marketing aspect. I don't know if you've been involved in this, but if you ask people, do you want the original - This is like one day we'll bring back original Coke. I'm sure that'll never happen. If you ask people if they want the original vaccine or they want the updated Omicron-specific, what do people want?

VR: Of course, they want the updated. I think it's -

DG: It's like getting that new iPhone. You're like, "Why do I need a new iPhone?" because of course you do.

VR: In certain populations, I could see it. In very vulnerable populations and so forth, but not as a population-wide thing because if we're saying that the Fc takes care of it even in Omicron, then that means that Omicron-specific boosters are not going to help.

DG: It makes me worry, too, about the way we threw our monoclonals away just when the neutralization data…

VR: Exactly. I asked you a few months ago, is there any evidence that the monoclonals would work, even if there's no neutralization and maybe they should do an animal study to figure it out, right?

DG: Yes. There is some data that maybe sotrovimab, the last - It may actually still work, it just may lose its neutralization, but it still may have the Fc-mediated effectiveness.

All right, so moving on to the early viral upper respiratory phase. You got infected, what do you do? Number one, we have -- I should point out, we're talking about people that have a solid risk of progression. We're not at the point here where we have the most compelling evidence to say, "I can give you advice on how to prevent Long COVID." I'm hoping we get there. Here we are, people who are at risk of moderate severe degree disease progression.

Number one, Paxlovid, two, remdesivir. We said we've lost our monoclonals. Maybe that's true. Molnupiravir, not the most impressive data out there. Convalescent plasma, remember, this is an early treatment option for the treatment of immunosuppressed COVID-19 patients at high risk for progression, of severe disease, who have no other treatment options. I'm going to mention an article here, "COVID-19 Convalescent Plasma Utilization in the United States: Data from the National Inpatient Sample," was recently published in *CID*. Here, the investigators, including our friend Arturo Casadevall. I should mention Arturo Casadevall published a lot of stuff on fungi and C. auris.

VR: He's a fungal guy. That's what he is. He always has been a fungal guy.

DG: He's all set for the next pandemic, by the way.

VR: That's right.

DG: Looking at the COVID-19 convalescent plasma use between October and December 2020, they used the National Inpatient Sample database. The COVID Convalescent Plasma, CCP, was administered in 18% of COVID-19-associated hospitalizations and was strongly associated with older age, increased disease severity and they did find that there were disparities in the receipt of CCP by race, ethnicity, geography, and insurance.

What is this NIS database? It's the largest available all-payer inpatient database. We're talking about millions of patients here. They reported that CCP use was rare in pediatric patients but about 18%, as I mentioned, hospitalized adults got CCP. A few disturbing things were observed. Sick white males were the most likely to get CCP and being female or a minority was associated with lower use of CCP.

If you had private insurance, you were almost twice as likely to get CCP compared to those with Medicaid. Also looks like CCP was most likely to get used in the most severe patients who, as we have repeatedly discussed, are mostly past the window when we have any evidence to suggest CCP is helpful and less likely to get used early, and the patients admitted with less severe disease.

The authors themselves point out that this is looking at in-hospital use, which, while extensive, CCP is optimally effective when it's administered early in the course of infection. I will comment here, this is when the public health emergency ends and the access is through an Investigational New Drug application, IND, this will most certainly limit access for early use in immunosuppressed individuals.

VR: When is that going to end, Daniel?

DG: Any day. Any day. Apparently, there's a bill and President Biden says he's going to sign it and that will end it. There's some reassuring things I've heard with regard to some things. For instance, Paxlovid, there's enough of that stockpiled around that will probably make it to when it gets fully licensed next month. All right, the early inflammatory, the cytokine storm week two, no rebounds here. Number one, steroids.

We talked about the right dose, right patient, not overdoing it. Anticoagulation guidelines from ASH. I think we have some upcoming meetings, so maybe some new guidelines will

come out. Pulmonary support, maybe remdesivir, immune modulation. Hot off the press. I just added this in, Vincent. 4/4 so that's Tuesday, the fourth of April. The FDA authorized Gohibic. Who named that? That is the brand name of vilobelimab injection for the treatment of COVID-19.

There are some articles, "Anti-C5a Antibody IFX-1 (Vilobelimab) Treatment versus Best Supportive Care for Patients with Severe COVID-19, (PANAMO): An Exploratory, Open-Label, Phase 2 Randomized Controlled Trial," that was published in *Lancet* back in the fall, and "Anti-C5a Antibody (Vilobelimab) Therapy for Critically Ill, Invasively Mechanically Ventilated Patients with COVID-19 (PANAMO): A Multicenter, Double-blind, Randomized, Placebo-controlled, Phase 3 Trial," published in *Lancet Respiratory Medicine*.

What will I have to say? This medicine appears to be safe from the first paper, as well as the second. In this PANAMO trial, the all-cause mortality rate at 28 days was 32% in the vilobelimab group, and 42% in the placebo group, so hazard ratio of 0.73. That's a relative risk reduction about 27%. Reduced all-cause mortality at 28 days, that's a hazard ratio of 0.67, so a 33% relative reduction there.

We're only seeing smaller absolute risk. It's an EUA, so I'm interested in how this is going to be impacted by the end of the health emergency. I did just get an email earlier today from Bruce P. Burnett, PhD, the vice president head of medical affairs, so I'll talk to him a little bit. I'm curious where this drug will fit in because this is really for sick mechanically ventilated patients in the ICU, and try to figure out who would benefit and how this might get used.

Now, this was an interesting article, "Triple Combination Therapy with Two Antivirals and Monoclonal Antibodies for Persistent or Relapse SARS-CoV-2 Infection in Immunocompromised Patients," published in *CID*. What about those immunocompromised folks who have prolonged or relapsed COVID-19? Here, they're going to go ahead and treat them with couple antiviral, so remdesivir plus Paxlovid, or molnupiravir in the case of renal failure, plus if available, those monoclonal antibodies. This is between February and October, 2022.

The main outcomes were virological response at day 14. You got to have a negative SARS-CoV-2 swab and virological and clinical response being alive, free of symptoms, and that negative swab at day 30, and the last follow-up. Basically, this is a description of a number of cases and the success that they had. Twenty-two patients, Omicron variant in 17 of 18. 18 received full combination of two antivirals and mAbs, four got two antivirals only, 91%, two antivirals were Paxlovid plus remdesivir. Going through a bunch of different things here. They tell us response rate at day 14, 30, and last follow-up were 75%, 73%, and 82%. Interesting.

We will finish off with the late phase. The NIH has a nice web page to which we can leave a link, and has resources about what Long COVID is, symptoms of Long COVID, what we know so far, information about research and resources. We also got another preprint this last week, "The Breadth of the Neutralizing Antibody Response to Original SARS-CoV-2 Infection is Linked to the Presence of Long COVID Symptoms," posted on *medRxiv*.

I've been trying to limit discussion of preprints, but I like the paradigm here. We've discussed how at a population level, elevated antibody levels are correlative protection. I've been a little critical that there's a particular threshold at which an individual should feel like they cannot get infected and exposed to the virus. Here, the investigators are actually looking at the potential negative of these antibodies. Perhaps this connects to the story featured on *TWiV* 993, COVID Drives Autoimmunity.

In this investigation, they looked at longitudinal, neutralizing, and cross-neutralizing antibody responses to pre- and post-SARS-CoV-2 Omicron variants in participants infected during the early waves of the SARS, of the COVID-19 pandemic prior to widespread rollout of the vaccines. They report to have identified several novel relationships between SARS-CoV-2 antibody neutralization and the presence of Long COVID symptoms.

Specifically, they show that cross-neutralization ID50 levels to the Omicron BA.5 variant, approximately four months following acute infection, were independently and significantly associated with greater odds of Long COVID and with persistent gastrointestinal and neurological symptoms. They did some longitudinal modeling that demonstrated significant associations in the overall levels and rates of decay of neutralizing capacity with Long COVID phenotypes. A higher proportion of participants had antibodies capable of neutralizing Omicron BA.5 compared with BA.1 or XBB.1.5 variants.

Let me try to translate this. What they're suggesting is, the breadth of the antibody neutralization responses and the persistence over time may be related to, may actually be a mechanism behind certain cases and types of Long COVID. I'm going to suggest that people look at Figure 3 - Panel B, everyone's pausing now, where we see that people who got infected early on with a pre-vaccine variant infection with Omicron have a significant odds ratio of Long COVID symptoms, neurocognitive symptoms, and GI symptoms, and leave people to take a look at.

It's you get infected with a pre-vaccine variant. What they're doing here is they're saying, "How high is this ID50? Is it above 90% to BA.5?" The idea you've got this broad neutralization, this maybe overexuberant, overbroad response. When they look at people with Omicron BA.5 ID50 greater than 90, who are not infected with Omicron BA.5, but got an early infection, you see about a fourfold and a statistically significant risk.

VR: Is this because the broad response includes auto-antibodies? That's the only thing that would make sense to me.

DG: think that's the theory here. I don't want to say all forms of post-COVID conditions are due to auto-antibodies, but this is a suggestion that there may be certain ones, particularly neurocognitive, maybe the GI phenotype may be related to the generation of auto-antibodies.

Our last article, the article, “Pathogenesis Underlying Neurological Manifestations of Long COVID Syndrome and Potential Therapeutics,” recently published in the journal, *Cells*. Not cell, but C*ells*, plural. I have mixed comments about this paper. I have to say, I do wonder sometimes when people share papers on social media if they actually take the time to read

the whole paper or they just share it because they see a few keywords that seem to provide confirmation bias. I think I know the answer.

This is another widely shared paper on Long COVID by a well-known social media influencer, but I want to point out, it's a hypothesis paper. Just a reminder to our listeners that a well-articulated hypothesis is just that. My repeated warning, not to be taken in by eloquence-based medicine. Why do more research when the eminent, eloquent physician has already made their pronouncement and thrown their darts at the board? The reason I will suggest is that people continue to suffer. The time of bloodletting, enemas, snake oil should be behind and not ahead of us.

Experience, if carefully inspected, should teach us humility. If we pay attention, we see that so many brilliant ideas are later to be shown to be harmful misadventures. We do need more evidence to guide us in terms of Long COVID. I will finish by saying let's look at it, the rest of the world. No one is safe until everyone is safe. I know people paused before to look at that figure.

Pause again now. Go to parasiteswithoutborders.com and click Donate. We are still in the middle of our ASTMH fundraiser February, March, and April. Our donations will be doubled up to a potential maximum donation of $30,000 from PWB to ASTMH, and we need your help to get there, so click away.

VR: Time for your questions for Daniel. You can send them to daniel@microbe.tv. Tracy writes, "My husband tested positive for COVID for the first time since the start of the pandemic. He's a 63-year-old lifelong smoker, high blood pressure, elevated cholesterol. All the drugs he takes are contraindicated for Paxlovid. He opted to stay on his regular drugs, skip Paxlovid. His doctor told him the alternative, molnupiravir, has been proven completely ineffective for COVID in clinical trials. This sounds erroneous to me. With his health history, it seems he should try molnupiravir to avoid severe outcomes, would you weigh in?"

DG: Yes, I think people have to be careful with their wording and that's just not true. I don't think that clinical trials have proven a lack of efficacy for molnupiravir. We have our randomized control trial. It was less than impressive. It was only about a 30% reduction in progression. Yes, it's not as great as some of the other options, but it still is evidence-based to go ahead. It is guideline-based to go ahead. You described someone who's a high-risk individual. It certainly would make sense to consider molnupiravir, particularly because it's so hard to access outpatient IV remdesivir.

VR: Shay writes, "I know people can get Long COVID/PASC from reinfections, but do we have evidence that it's less likely than from first infections, given the documented change in Long COVID risk from different variants/vaccination? Is it even possible to know this?"

DG: Yes, no, that's great. The epistemological question, the like, can we know this? Over time we have seen that when people get infected, lower risk of death, lower risk of getting them in the hospital, less reporting of Long COVID. Is that because the most vulnerable people have died? Is that because the most vulnerable people already have Long COVID? Is that because there's been changes in the virus itself? Is that because there's been a lot less toxic snake oil thrown at folks?

In general, it looks like we are seeing less COVID from infections now, but we're still seeing it and I think that's really important. People who are getting repeat infections, if they didn't get Long COVID the first time, they still can get it the next time. The picture does look rosy. The picture does look like the risk is decreasing.

VR: OK. J writes, "During a *TWiV* update that dropped on 4/1, you shared a lot of compelling evidence for taking Paxlovid. However, it's still not clear to me to whom this applies. Are the data now so compelling that anyone who gets COVID should take Pax within the first five days of symptoms or anyone 40-plus or only those 65-plus with comorbidities. As a relatively healthy 47-year-old, albeit not a very physically active one, with mild asthma history of depression, am I and others like me in the "Yes, take Pax," category or are we squarely in the, No, Pax is for the very immunocompromised folks, those with serious medical conditions and or very advanced age? "

You recommend everyone have a plan. I'm trying to make a plan, have asked my PCP about this, but I cannot get a good database answer on risk-benefit or general recommendation."

I think there are millions of folks in similar circumstances. Any light you can shed would be wonderful.

DG: OK. Yes. From a science, and I think, you know next month at some point Paxlovid will be licensed and we'll be getting more and more information. The machinery at big pharma will be spreading information. A couple of things to comment on. The science is compelling that this prevents progression to hospitalization, to severe disease. We're not sure there's this suggestion, a signal that maybe this prevents Long COVID, but that's not the indication. That won't be the licensing, that's not the message. The message is preventing progression to severe disease.

The other message is, let's keep getting more information to figure the rest of this out. This is a medication that, potentially has side effects, potentially has drug-drug interactions. You are doing something, so you've got to be asking risk-benefit questions all the time. Age cutoff is 50 if you're using age just alone. We're always trying to do this metric to figure out is there a solid finite real risk that you're going to progress to severe disease? If you're under 50, if you don't have health problems, if you're fit, that risk is so small that we're not suggesting, we're not recommending it for that lowest risk group.

VR: Nanette writes, "Is there any evidence to support the use of low- or regular-strength aspirin for one month during the period of highest risk for stroke, heart attack, or death after COVID infection?"

DG: Yes, it, there isn't actually, and we've looked at this and people have been very emotional on either side of this, but no. We've looked at it for the individual that does not end up in the hospital, that experiences COVID in the outpatient setting. We have no compelling evidence that there's a benefit to being on aspirin. If there isn't some other reason that you're on, I'll say no. If you end up in the hospital, then there's a whole bunch of different scoring systems we'll use and make certain recommendations about what you might want to do to reduce your clotting risk.

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

DG: Thank you and everyone, enjoy the holidays. Be safe.

[music]

[00:55:19] [END OF AUDIO]