This Week in Virology

TWiV 1001 Clinical Update

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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 is *TWIV*, *This Week in Virology*, Episode 1,001, recorded on April 19, 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: It's so weird to say 1,001, Daniel.

DG: It's like *Space Odyssey*, but it's *Viral Odyssey 1,001*.

VR: When we hit Episode 2,001, we can do *2,001 a Viral Odyssey*, right?

DG: Yes. I think at that point right, are we going to be propping you up like *Weekend at Bernie's* or something?

VR: I'll be fine.

DG: All right. Let's jump right into it because we have a lot to talk about. It's been a little while since I've done my clinical update, or it's been, well, it has been a little while. "There are risks and costs to action, but they are far less than the long-range risks of comfortable inaction," and that's John F. Kennedy. Perhaps people can tell I've been helping out my son with his AP U.S. history.

Let's start right off with polio. Vincent, I was listening to *TWIV* #2.

VR: Oh my god.

DG: Polio is not dead. It was like I was reminiscing. Maybe I was getting ready for the trivia night listening to *TWIV* 1,2,3, but this episode, "Polio is not Dead," we'll leave a link in. It's only 40 minutes. It's a really great episode. Interesting to hear Vincent's take from about 15 years ago.

VR: Wow. It's probably different from my current take.

DG: Yes. Let us start with the *MMWR,* "Update on Vaccine-derived Polio Virus Outbreaks - Worldwide, January, 2021 through December, 2022." For background, as we've discussed, circulating vaccine-derived, poliovirus outbreaks can occur when oral polio virus from the vaccine, the vaccine oral poliovirus containing one or more Sabin-strain serotypes 1,2 and 3, undergo reversion to neurovirulence. You can jump in and tell us if we're using the right terminology.

Then prolonged circulation in under-vaccinated populations. Here in the U.S., we saw not an outbreak, but an individual case where a revertant circulating vaccine-derived poliovirus type 2 infected a non-immune unvaccinated individual resulting in paralysis. In this report, we read that during this period of time, 76, and they say cVDPV, so circulating vaccine derived polio virus type 2 outbreaks occurred in 42 countries. Since 2020, the number of paralytic cases and emergencies has declined following the introduction of, as they say, a safer novel type 2 oral polio virus vaccine for outbreak control.

We've talked a little bit about how this is safer. The number of these circulating vaccine-derived polio virus, and they say here, type 1 outbreaks, increased during 2021 to 2022 as COVID-19 pandemic-associated global routine immunization coverage declined.

I'm going to engage you, Vincent, here and ask about the path forward. Maybe I'll just stop there and engage you. What is your thoughts? Where do we go from here?

VR: We have a lot of circulating vaccine derived type 2. It's gone up ever since the type 2 was removed from OPV, so now we just use types 1 and 3. When there is an outbreak of circulating vaccine-derived type 2, we vaccinate with OPV type 2. We keep feeding the virus into the environment.

Now, recently, nOPV2 has been developed, which has a lower acquisition of neurovirulence, but it's not zero. The hopes is that that will eliminate the circulating vaccine derived polio 2. We don't know if that's the case or not, WHO is very optimistic, but I'm not sure it's an optimism based on any data.

I think as long as they put even nOPV2 into kids, we're going to have circulating nOPV2, and I think that will be really hard to get rid of.

DG: Yes. There was a recent NPR piece that I was going to leave a link to as well. "The Dream of Wiping out Polio Might Need a Rethink." I think this piece is worth reading, but I'll just hit a few highlights, read a little bit. I encourage everyone, despite the time, read the whole article. When the Global Polio Eradication Initiative was launched in 1988, the goal was to extinguish polio by the year 2000. At the time, polio was still paralyzing hundreds of thousands of people a year. Some cases were even fatal. In the first three months of this year, there have been 15 cases, total, the entire world.

This sounds like we're almost there but then comes the challenge we keep alluding to. Countries, particularly in Africa, were declared polio free only to have polio pop up again years, even decades later. We've mentioned last year the United States, which had officially eliminated polio in 1979, had a case of the paralytic disease. The virus has also been found

in sewage samples in London, Finland, and Jerusalem, all places where it supposedly was extinguished decades ago.

Then the problem, as we've discussed on a few of our clinical updates, is as just mentioned, we are now using an oral polio vaccine that in the human gut changes back to a neurovirulent virus that ends up in the community as a danger to those who are not immunized. The update from this article last year, there were 30 cases of wild polio detected, while there were nearly 800 cases of vaccine-derived polio. Of the 15 cases reported in the first quarter of 2023, the last three months, 14 are from the virus that mutated from the oral polio vaccine used in lower income countries.

I did want to edit, I think it's an excellent article, but I did want to edit, and, Vincent, you could tell me if this is a proper edit. The last two sentences they say, "But the virus spreading in wastewater can also cause paralytic disease. This is most likely what happened last year in the case of an unvaccinated man in New York being paralyzed by a vaccine-derived strain of the virus." I do want to point out that wastewater does not end up in the drinking water in the U.S. Someone who is shedding the revertant vaccine-derived virus toilets, fails to wash their hands, then maybe shakes your hand, touches something, and virus ends up being transmitted.

Wastewater in the U.S. is a monitoring opportunity, not a transmission opportunity.

VR: Absolutely. I want to just say the idea that in 1979, after that polio was eradicated in the U.S., is not correct because we never looked in wastewater to see if there were viruses there. All we did was eradicate paralytic disease. If you want to get rid of the virus, which is the goal of WHO, you have to look, and you can't actually look in every sewer globally. It's impossible to eradicate a virus with so many asymptomatic infections. That's something that D.A. Henderson, who architected the smallpox eradication program, always said, it cannot have a lot of asymptomatic infections.

I used to think that it was possible, but now given the circulating vaccine-derived type 2, I don't think we can eradicate this virus. This NPR article, by the way, is very good because it has that same idea. We need to rethink.

DG: Yes. All right. Moving into influenza. The article, “Risk of Death in Patients Hospitalized for COVID-19 vs Seasonal Influenza in Fall-Winter 2022-2023,” was published. It's actually gotten a lot of press, published in *JAMA*. In the first year of the COVID-19 pandemic, two U.S. studies suggested that people hospitalized for COVID-19 had nearly five times the risk of 30-day mortality compared with those hospitalized for seasonal influenza. These investigators use the electronic health databases of the U.S. Department of Veterans Affairs, the VA, I should mention that was my first paying job as an MD, working for the VA.

Between October 1, 2022 and January 31, 2023, enrolled all individuals with at least one hospital admission record between two days before and 10 days after a positive test for SARS-COVID-2 or influenza, and an admission diagnosis for COVID-19 or seasonal influenza. Basically, they're comparing here, flu and COVID-19. I still remember that Roxanne Khamsi article, “COVID is Bad. Comparing it to the Flu is Worse.” Well, here they're doing that, the

death rate at 30 days in a VA population in fall winter was 5.97% for COVID-19 and 3.75% for influenza, with an excess death rate of 2.23%.

Compare with hospitalization for influenza, hospitalization for COVID-19 was associated with a higher risk of death, 1.6, so 1.6 times higher. As they comment here, these findings should be interpreted in the context of a two- to three-times greater number of people being hospitalized for COVID-19 versus flu. We actually end up without four times as many people hospitalized dying from COVID than from the flu. We're not quite there yet with getting this to the background of the flu. They have a really nice figure where you can actually break down the hazard ratio.

Really what I think we've been saying for a while, which is really true, the biggest issue here, the biggest hazard ratio, death rates, percentage of excess deaths, is in those over 65, in those unvaccinated. There's still some of those around, those who did not get outpatient COVID-19 antiviral treatment.

VR: Daniel is the VA population representative of the general U.S. population?

DG: I think there are quite a number of differences. I think that's a reasonable comment. If anything, you're going to be seeing an older age group. I think it's good that they broke it down that way. It's interesting whether or not there are more comorbidities.

All right. Mpox. Oh my god, what are we doing talking about mpox? Isn't that over? Just want to plug *CIDRAP* out of University of Minnesota. This is a plug, not an endorsement. They do a great job of keeping on top of things and sending out very accessible newsletters.

Recently, they had the news brief, "Recent French Mpox Cluster Includes Fully Vaccinated Patients." Here they shared, explain a recently posted update by the French about an mpox cluster that occurred in the Center-Val de Loir region, with 17 cases reported since the first of the year, including 14 since March 1. Five of the patients had received two of the mpox vaccine doses. Also five had received one smallpox dose during childhood, plus one dose in 2022. They reported that 59% of the infected people had been vaccinated.

We'll put in a link to that. Why am I talking about this? Well, we also have the article, *The Lancet Infectious Diseases,* "Two Individuals with Potential Monkeypox Virus Reinfection." You can get reinfected, and you can get infected after vaccination. Here we read the description of two men that had PCR confirmed mpox with typical signs and symptoms. Following resolution, both men had negative PCR tests after a symptom-free interval of one and four months. One developed proctitis, the other a typical lesion with general involvement.

On further investigation, they tested positive for mpox virus again.

There's a third such possible reinfection reported in the *BMJ* journal, sexually transmitted infections of a patient who had completely recovered from a primary mpox infection four months previously, despite receiving a complete two-dose course of vaccination between the two presentations.

VR: I just want to emphasize that, it wouldn't be surprising if they got infected. The key here is they develop disease. That's what the first infection should have prevented.

DG: We would hope, this is we're talking about hybrid here in the one case. So, yes.

The last thing for this mpox section, and don't worry, we'll put a timestamp for when this is over. Some people don't like hearing about mpox. The *MMWR* "Epidemiology and Clinical Features of Mpox-associated Deaths - United States, May 10, 2020 through March 7, 2023." Yes, deaths from mpox, people may have missed that, but we read that CDC received reports of 52 deaths among persons with confirmed or probable mpox.

Thirty-eight deaths were classified as mpox-associated, 6% were non-mpox-associated, and some of those, interesting causes of death included suicide and drug overdose, and 21% of deaths still being investigated. The authors comment that findings in this report are subject to limitations, and deaths may have actually been undercounted. I do want to point out that mpox can be a horrible, painful, disfiguring disease, and it can be deadly. Actually, this is a report on dozens of deaths. There's a bunch of interesting things here, but I do want to point this out. I think this is important.

Nearly all the decedents with complete data on HIV infection were HIV positive, so 94%. We're basically talking about individuals here that did not have an intact immune system. Among the 24 deceased with HIV, 100% had CD4 counts less than 200, most of them quite a bit below 200. Among the two immunocompromised folks that died who did not have HIV, one was thought to be immunocompromised as a consequence of undiagnosed diabetes. This patient experienced diabetic ketoacidosis at the time of the mpox diagnosis, and the second decedent was severely immunocompromised from a recent renal transplant complicated by acute rejection. What will happen with mpox in the future? We will let you know come summer.

All right, norovirus winter vomiting disease. I thought we were almost over this. Things were starting to come down, and now we have a little bit of a climb again, so we'll let you know. Winter is almost over, so people will hopefully stop vomiting soon.

OK, here we are, timestamp, 16 minutes in, and we are to COVID. Let me say this right up front, have a plan. A plan to stay safe, keep from getting sick, and a plan for what to do if you get an infection.

Our government has a new plan, project Next Generation or NextGen. We hear that the Biden administration has announced a $5 billion program to accelerate the development of next-generation COVID-19 vaccines and treatments, and I quote, "Like Operation Warp Speed, which developed and distributed vaccines in the early days of the pandemic, Project NextGen will cut across government agencies and involve public-private collaborations." We hear that this plan will develop a roadmap too, and I have some criticisms. Develop a nasal vaccine to prevent infection as well as severe diseases.

Develop longer-lasting vaccines and create broader vaccines that protect against all variants and several coronaviruses, and funding to develop more durable monoclonal antibodies

resistant to new variants. I'll leave in an article to a *USA TODAY* news article by Karen Weintraub.

Vincent, I thought you might have some comments here.

VR: Boy, are they going to go crazy over this $5 billion. Whether or not it's going to work or not, the scientists want the money. First of all, we're not going to develop a vaccine to prevent infection. It doesn't work that way. The immune system doesn't come up quickly enough to prevent infection once those antibodies have contracted. It's a waste of money.

Preventing severe disease. The vaccines already do that, don't they, Daniel?

DG: They do, and I think that that's something that is - Well, I don't think it's lost in our listeners. I enjoyed the *TWiV* 1,000 discussions with our audience attendees. People get it. Our listeners get it. The vaccines are durable when it comes to protecting against severe disease, that 90% reduction. Protection against infection is transient, three to four months. That special superpower. Has anyone heard of Flumist? That's that nasal spray for flu. I pretty much think that changed the world.

I say that, and, one, I'm worried that we're wasting money, and the other is I worry about the opportunity costs. Are we spending money on a flying car instead of spending money on things that are realistic and viable?

VR: It's a good point. That's a really good point. This, develop longer-lasting vaccines, well, we don't even know how long these last. It's very hard to do that. Broader vaccines, that could be a good project where people are already working on that, and durable monoclonals resistant to new variants could be done. Well, they have to be not directed at the ACE2, but it could be done. I think those are reasonable. It's not like people aren't doing these. People are doing this. I do agree with you 100%. It's going to be a waste of money to try some of these other things that we've mentioned.

DG: Yes, but they've talked to some very intelligent people who are not infectious disease or virology experts or even epidemiologists, but they are very confident. OK, right up front is a mention of the end of the public health emergency. What does that exactly mean? One question people have is about telehealth. During the public health emergency, providers were able to reach out across state lines. I know the Office of Civil Rights is providing a 90-day transition period, and this is going to actually be in effect beginning May 12, and will expire 11:59 PM on August 9.

We'll see what we can do there, because I think telehealth access has really been tremendous. Well, it's been tremendous for some people. It also has been abused by some others. That will need to be properly addressed.

Other news, on Tuesday, April 18, FDA authorizes changes to simplify use of bivalent mRNA, COVID-19 vaccines. I think I tweeted this out. They have simplified and made it more complicated. Let's go through this. Here, the FDA amended the emergency use authorizations, I thought we just ended our public health emergency, of the Moderna and Pfizer BioNTech COVID-19 bivalent mRNA vaccines authorizing the current bivalent vaccines,

this is that mix of original and Omicron, to be used for all doses administered to individual 6 months of age and older, including for an additional dose or doses for certain populations.

The mono valents, they're gone, no longer authorized for use in the United States. In a sense, it's simpler. All those mRNA vaccine doses, they're all the same. Number one, what are the things? Number one, previously vaccinated with a monovalent COVID-19 vaccine who have not gotten a dose of the bivalent vaccine, go ahead, get a single dose of the bivalent vaccine that's authorized.

Unvaccinated, this is interesting. Unvaccinated individuals can receive a single dose of the bivalent vaccine rather than multiple doses of the original monovalent mRNA vaccines. The logic here is the idea that they already have preexisting immunity. For them, it's a boost. Then this is what people really were watching for, the headline about additional boosters. That was just making it easy. It's all the same. You've got the same shot for everything.

Individuals 65 years of age and older who received a single dose of bivalent vaccine may receive one additional dose at least four months following their initial bivalent dose. Just folks 65 and older, just folks, as we're about to see certain kinds of immunocompromised, who received a bivalent COVID-19 vaccine, can get an additional dose here at least two months later.

Then this is a big comment here by the FDA, and I hit on this a little. Most individuals who have already received a single dose of the bivalent vaccine are not currently eligible for another dose. The FDA intends to make decisions about future vaccination after receiving recommendations on the fall strain composition and an FDA advisory committee in June.

To put this together, there was several articles, but recent *New York Times* article by Christina Jewett, and I'm going to quote a couple of folks here. Dr. Peter Marks, the FDA vaccine chief, said the available data continue to demonstrate, as we've discussed, that vaccines prevent the most serious outcomes of COVID-19, which are severe illness, hospitalization, and death, and then the decision to offer the booster to the most vulnerable this spring is sound for two reasons, said Dr. Daniel Griffin, an infectious disease specialist at Columbia University, who y'all may know.

One is the traditional reason for vaccines. It protects people from severe disease, but there is what I call the superpower, where for a matter of three or four months, you get an extra benefit of reducing your risk of even getting infected. I will say that we should be reassured as we've discussed, and in Dr. Marks, and we have pointed out many times, the vaccines are very successful and have durability in this traditional vaccine efficacy of providing protection against disease, including severity of illness, prevention of hospitalization and death, also Long COVID for higher risk individuals.

Boosters do boost, and this superpower of protection against infection can, for three to four months, give one the extra benefit of reducing the risk of even getting infected. If you don't get infected, you don't get disease.

Thoughts, Vincent? Are you over 65? Can I ask that? Is that a personal question?

VR: Yes, I am. I'm not getting this. I don't think the benefits are there. I have not seen any data that say this is any better than what I've had. I have three doses. The original two, which were too close together, three weeks, four weeks, whatever, then I got the third one, which was properly spaced out. According to the data, that's good enough to get the broadened antibody response.

Then I had a natural infection, which, in the words of Crotty and Sette, I'm a superpower, and so I'm not getting anything out.

DG: You've already been boosted.

VR: If I tested positive again, I would take Paxlovid. I am not taking another bivalent vaccine. There's no reason for me to do that. I'm healthy, as you said before, I'm going to last another 10 years at least for *TWiV* 2,000. No more vaccines, at least COVID vaccines for me.

DG: All right. Variants, just I'll mention this. The latest SARS COVID 2 variant in the Omicron XBB Gryphon family is Arcturus (XBB 1.16). We actually know Arcturus, we know the star here in the Griffin household as Hokulea, the Hawaiian star of gladness. They've moved away from these scary names. This is the star the Polynesians used to navigate by, and the name of my last sailboat. Currently X BB 0.1 0.5, (the Kraken is dominant), but Hokulea, or Arcturus, as it is being called, is picking up.

Moving into COVID children, other vulnerable populations, what I was thinking about Vincent, people have that short attention span. If you want, you could break this into like two or three pieces. That way you could listen to the whole thing in two or three parts. Alright, COVID other vulnerable populations. For those of you who are still with us, the article, "SARS-CoV-2 During Omicron Variant Predominance among Infants Born to People with SARS-CoV-2," was published in the journal *Pediatrics.* During the period before Omicron variant predominance, the incident rate of positive SARS-CoV-2 tests among infants age zero to 6 months, born to people with SARS-CoV-2 infection during pregnancy, was 3.1 per 100 person years. During the period of Omicron variant predominance, the rate, what is when something goes up fivefold, five-duple, what's the word there?

VR: Quintupled.

DG: Quintupled to 15.3 per 100 person years. That was a fivefold increase. Restricted to infants born to pregnant individuals who had SARS-CoV-2 pre Omicron, the IRR increased to 5.83. A lot more infected pregnant mother to child transmission pre Omicron. The proportion of infants infected less than 14 days after delivery with maternal infections less than 14 days before delivery declined from 31.4% pre Omicron to 0.8% during Omicron predominance, suggesting the increased rate of infection was not due to increased perinatal transmission. They've got a nice graph where you can look at the incidence there. You really see the Omicron period and the huge spike for the kids once we get into the early period of the Omicron.

Also, the article, "Severe Maternal Morbidity and Mortality of Pregnant Patients with COVID-19 Infection During the Early Pandemic Period in the U.S.", was published in *JAMA Network Open*. As we've been pointing out, pregnancy is a high-risk condition. Here, we see that pregnant patients with COVID-19 infection at delivery were more likely to develop

severe maternal morbidity compared with those without, adjusted odds ratio of 2.6. What are these bad outcomes? More than twice as likely to end up with a tracheostomy, that's a hole in a tube in your throat. Respiratory distress syndrome, ending up on a ventilator, developing an acute myocardial infarction, sepsis shock, cardiac arrest, and coagulopathy. The mortality risk of pregnant patients with COVID-19 at delivery was 14 times higher compared to those without. Hope our OB-GYN colleagues are listening.

The traditional you test positive period pre-exposure transmission testing, there were some interesting comments on social media. I don't know if you saw any of these, Vincent, about our recent *TWiV* 1,000, and the mask wearing or not wearing by some folks there. I think it's really interesting, and I don't want to spend too much time on this, but we've talked about this before, about the fact that we're in a different situation now. It was actually this week that Optum actually, the care delivery organization I work for, has moved to a mask optional user judgment when wearing the mask.

Later episodes maybe we'll have a little bit more of a discussion, but I am curious about people's take on the ethics here from the article, “Sickness Presenteeism in Healthcare Workers during the Coronavirus Disease 2019 (COVID-19) Pandemic: An Observational Cohort Study,” published in *Infection Control & Hospital Epidemiology*. In this observational cohort study that included all healthcare workers at the Veterans’ Affairs, I feel like we're beaten up on the VA folks, Boston Healthcare System, who tested positive for SARS-CoV-2 infection by PCR between December 1, 2020 and September 30, 2021, they report about 50% went to work with symptomatic COVID-19. Then they go ahead and suggest this may contribute to the nosocomial transmission of SARS-CoV-2 to this high risk population, and following this reasoning, to the death of a portion of those veterans.

I know how I feel about the ethics here, but I will leave judgment up to our listeners.

*The MMWR, “*Ventilation Improvements among K-12 Public School Districts - United States, August-December 2022” is worth a read. Here, we hear to reduce school transmission of SARS-CoV-2, K through 12 public school districts implemented ventilation improvements, replacing or upgrading ventilation systems, installing filtration systems, installing ultraviolet germicidal irradiation devices, or improving airflow.

Federal funding remains available for ventilation upgrades, but none of the ventilation strategies examined were reported by the majority of school districts. Implementation of ventilation improvements vary by school district, U.S. Census Bureau region, geographic locale, and poverty level. High-poverty school districts reported implementation of the highest percentage of strategies.

We also get the article, “Risk Factors and Vectors for SARS-CoV-2 Household Transmission: A Prospective, Longitudinal Cohort Study,” published in *The Lancet Microbe*. Now, the authors start by writing in their introduction, "Despite circumstantial evidence for aerosol and fomite spread of SARS-CoV-2, empirical data linking either pathway with transmission are scarce." Here, they aim to assess whether the presence of SARS-CoV-2 on frequently-touched surfaces and residents' hands was a predictor of SARS-CoV-2 household transmission.

Just a little bit of circumstantial evidence. In this study, contacts' hands, primary cases' hands, and frequently-touched surface samples from communal areas were tested for SARS-CoV-2 RNA. They reported that SARS-CoV-2 detected on primary cases' hands predicted contacts' risk of infection with an adjusted relative risk of 1.7, as did SARS-CoV-2 RNA presence on household surfaces, adjusted relative risk of 1.66, and contacts' hands, adjusted relative risk of 2.06.

I have a few thoughts, but Vincent?

VR: If you're positive, yes, you can have RNA on your hands, and in your household, you're going to have RNA on the surfaces. It doesn't mean that caused your infection, right?

DG: Also, that was a marker for filthy people that don't wash their hands.

VR: Of course, and then we don't know if it's infectious, so there's really no relationship with transmissibility.

DG: Yes. I hope this article does not get much air, but I just felt like it was important to mention it.

All right, COVID active vaccination. We've already talked a little bit here, but we also have the correspondence, “SARS-CoV-2 Neutralizing Antibodies after Bivalent versus Monovalent Booster,” published in *The Lancet Infectious Diseases*. In this study, serum virus-neutralizing titers in 41 participants who received three monovalent mRNA vaccines followed by a bivalent booster, a monovalent booster or a BA.5 post-vaccination infection.

They collected serum samples at nearly a month and approximately three months following the last vaccine dose or post-vaccination infection, and determined their neutralizing antibody titers using a pseudovirus neutralization assay against ancestral D614G and a panel of Omicron subvariants.

Patients who received a monovalent booster were older than those who received a bivalent booster, or even those who had a breakthrough infection. They found that consistent with their previous report, there was no significant difference at nearly one month after the last booster for the two vaccine cohorts. At approximately three months after the last vaccine, last booster, there were, again, no statistically-significant difference between the two groups.

The BA.5 post-vaccination infected cohort exhibited significantly higher neutralizing antibodies at three months against all tested Omicron subvariants when compared for both monovalent and bivalent booster cohorts. Over the approximately two-month follow-up period, meaning neutralizing antibody titers in both vaccine cohorts decreased approximately twofold to 50% against all tested viruses. There was no, as they say, discernible waning of antibody responses in the BA.5 breakthrough infection cases over the same period.

I've got the figure right up here, some comments. I think these can be optimistic as we see here, so I'll say science-based boosters boost, and it looks like we can take comfort in not worrying about needing to get our boosters perfectly matched in the next variant.

Vincent, I think you're looking at the figure. Any comments on the data?

VR: It makes sense that a matched or closely-matched booster will give you good neutralization of those viruses, but as you see, they go down over the two months afterwards, and so there's not an advantage to doing that, at least looking at neutralizing antibodies.

DG: All right. We also have, we're still hitting on these, a letter to the editor, "Durability of Bivalent Boosters Against Omicron Subvariants," was published in *The New England Journal of Medicine*, and in this report, I think this goes with what we've been saying. We read that effectiveness against severe infection resulting in hospitalization or death, remember, this is above a background, reached a level of 67.4% after 2 weeks, decreased to 47.5% after 4 weeks, 44.3% after 10 weeks, 38.4% after 20 weeks. These figures are even more beautiful with lots of colors for you there.

I'm going to have some stuff, just a little teaser. I'm going to have some stuff next week about COVID passive vaccination. Is there a replacement on the way for Evusheld? Stay tuned. That's like a cliffhanger.

COVID, early viral upper respiratory nonhypoxic phase, you get infected. What do you do? We've been saying for a while, number one is Paxlovid. We have the article "Nirmatrelvir and Risk of Hospital Admission or Death in Adults with COVID-19: Emulation of a Randomized Target Trial Using Electronic Health Records, published in *The BMJ*, so using the healthcare database of the U.S. Department of Veterans Affairs.

Man, those guys are just giving us data; 256,288 participants with SARS-CoV-2 positive test result, and at least one risk factor for developing severe COVID-19 disease. Between the third of January and 30th November, 2022, over 31,000 were treated with nirmatrelvir within five days of testing positive; 224,764 received no treatment. Once again, we see that in people with SARS-CoV-2, so folks with COVID-19, were at risk of developing severe disease compared with no treatment.

Nirmatrelvir was associated with a reduced risk of admission to hospital or death at 30 days in people less than 65, older than 65, male, female, black, white, not vaccinated, vaccinated, and even those that received a booster with those with one, two, three, four, or greater than five risk factors, and in those with a primary SARS-CoV-2 infection. Also, the folks with reinfection. The absolute risk reduction varies based upon the pretreatment risk of progression.

Number two, remdesivir, where you can get it. People have been asking for a while, a little more info, "What about that oral remdesivir?" Gilead Sciences unveiled, I like the way they unveiled data from the first human study of its experimental oral COVID-19 antiviral saying the results in healthy volunteers cleared the way for two, large Phase 3 trials of the drug that have begun enrolling patients.

Basically, this is an oral prodrug of remdesivir, and will be taken as one tablet twice a day for five days, theoretically with no drug-drug interactions.

Monoclonal therapy, I think it's important that we learn as we go. The article, “Evolving Real-World Effectiveness of Monoclonal Antibodies for Treatment of COVID-19. A Cohort Study,” was recently published in *Annals of Internal Medicine*. These are the results of hypothetical pragmatic randomized trials from observational data comparing monoclonal antibody-treated patients with a propensity score matched, nontreated control group in a large U.S. healthcare system. They looked at high-risk outpatients eligible for the monoclonals under any EUA.

In this study, they reported risk of hospitalization or death at 28 days was 4.6 in treated and 7.6 in nontreated. They went ahead and did some subgroup analysis. Lots of limitations here, but very much in line with what we've seen so far. Molnupiravir after that, and I will not leave out convalescent plasma and early treatment option for the treatment of immunocompromised COVID-19 patients at high risk for progression of severe disease who have no other treatment options.

We did get a recent ID Society update on convalescent plasma, so I want to clarify or highlight depending upon perspective. As per the latest update, a new recommendation was developed against the routine use of convalescent plasma among immunocompromised patients with COVID-19.

My clarification here. This is about timing. This is about waiting till after you've missed that window. This is patients that are hospitalized with COVID-19. They probably should have said for COVID-19. Folks who have missed that first week, maybe four to five days, and so your timing really matters.

As I've been saying for a while, let's avoid doing harmful things. Let's stop throwing darts at our patients. I do hope there's a lesson here for everyone about just trying stuff with good intentions, and the article, “Effect of Angiotensin-converting Enzyme Inhibitor and Angiotensin Receptor Blocker Initiation on Organ Support-free Days in Patients Hospitalized with COVID-19: A Randomized Clinical Trial, published in *JAMA.* More results from the REMAP-CAP trial. In this randomized clinical trial that included 779 patients, initiation of an ACE inhibitor, ARB did not improve organ support free days. Among critically ill patients, there was a 95% probability that these treatments actually worsened. The outcomes were harmful.

The article, “Efficacy and Safety of Anakinra Plus Standard of Care for Patients with Severe COVID-19 a Randomized Phase 2/3 Clinical Trial,” published in *JAMA*. In this randomized clinical trial, anakinra did not prevent the need for mechanical ventilation or reduce mortality risk compared with standard of care among hospitalized patients with severe COVID-19. In the discussion, the authors comment that their findings that anakinra did not prevent the need for mechanical ventilation or reduced mortality risk compared with standard of care. Agree with those of a Cochrane systematic review which included results from four randomized clinical trials with IL-1 inhibitors that concluded that anakinra probably resulted in the little, or no clinical improvement.

COVID early inflammatory, lower respiratory phase. Remember that's week two, the cytokine storm. No rebound here. Steroids at the right time in the right patient. Here I want to update everyone on the dosing and patient selection. Currently the science supports

dexamethasone six milligrams daily PO or IV for about six days or less. We can do harm by overdosing or indiscriminate use outside these parameters. The recent article published in *The Lancet*, "Higher Dose Corticosteroids in Patients Admitted to Hospital with COVID-19 Who Are Hypoxic but Not Requiring Ventilatory Support (RECOVERY): A Randomized, Controlled, Open-label Platform Trial." People probably remember RECOVERY trial. They found in this study that using higher dose corticosteroids, so dexamethasone 20 milligrams once daily for four days, followed by 10 milligrams once daily for five days or until discharge, if sooner, was not helpful. They observed that 19% of patients in the higher dose versus 12% of patients in the usual care died within 28 days, 7% higher mortality when you overdo it with them steroids.

There was also an excess pneumonia reported to be due, so a 60% increase in mortality by going overboard with those steroids. Remember anticoagulation guidelines from ASH on that pulmonary support immunomodulation, remdesivir if it's not too late.

And we will move right into and wrap it up with the late phase. Let me start with the article, "Risk of Autoimmune Diseases in Patients with COVID-19: A Retrospective Cohort Study, published in *eClinicalMedicine*. I recently attended a WHO meeting expanding our understanding of post-COVID-19 condition, the evolving research landscape. It was actually worth the time. A growing amount of research is helping us to better understand the immune dysfunction involving B-cells, T-cells, vascular system, and other cells. These are the results of a retrospective, test negative cohort study based on the TriNetX U.S. Collaborative Network. They found that COVID-19 is associated with a different degree of risk for various autoimmune diseases. You get COVID, and your risk of rheumatoid arthritis afterwards goes up threefold ankylosing spondylitis 3.2, SLE threefold, dermatomyositis twofold, systemic sclerosis 2.6, Sjogren's 2.6, mixed connective tissue disease over 3, Behcet's 2.3, polymyalgia rheumatica 2.9, almost threefold, vasculitis, psoriasis, inflammatory bowel disease, celiac disease, and type 1 diabetes.

I will say sometimes when we've seen these individuals, they have a slightly atypical presentation of some of these diseases. Also, the article, "Definition of Post-COVID-19 Condition among Published Research Studies," was published in *JAMA Network Open* as a research letter. The authors conducted a descriptive study on post-COVID condition definition following the STROBE reported guideline and performed the literature search using the PRISMA checklist. A total of over 7,000 studies contained information on post-COVID conditions. They reported to have found substantial heterogeneity in defining post-COVID conditions in published studies with the majority, about two-thirds, not complying with definitions from NICE, from CDC or WHO.

I will say, the CDC definition, the term post-COVID conditions, it's an umbrella term for a wide range of physical and mental health conditions experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic infection.

Now, they go on to say, we're already going to disagree because we think four weeks might not be enough, you might want to wait 12, but although standardized case definitions are still being developed, in the broadest sense post-COVID conditions can be considered a lack of return to a usual state of health following acute COVID-19 illness. Post-COVID conditions

might also include development of new or recurrent symptoms, or unmasking of a preexisting condition that occurs after the symptoms of acute COVID-19 have resolved.

I'm going to wrap us up with the last article, “Sleep Disturbance Severity and Correlates, and Post-acute Sequelae of COVID-19 (PASC),” published in the *Journal of General Internal Medicine.* Here we see patients with PASC. We evaluated the Cleveland Clinic, ReCOVer Clinic, clever there, between February, 2021, April, 2022. Sixty percent had sleep disturbances, mostly mild, but 40% had moderate to severe sleep disturbances. I'll wrap us up here saying "No one is safe until everyone is safe." I'd love everyone to pause here. Go to parasiteswithoutborders.com. Click the “Donate” button. Every small amount helps. We are finishing off – this is the last month of our American Society of Tropical Medicine and Hygiene Fundraiser. We'll be doubling those donations up to a potential maximum donation of $30,000 from PWB 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. Daniel on the livestream we just finished, we were saying how most transmission of SARS-CoV-2 comes from the nasal pharynx, very little from the lower tract. Someone said, well, what if a patient is intubated? Does that procedure lead to aerosol generation and transmission? Has that ever been looked at?

DG: It's a great question, and there's two parts, because I've thought a lot about this having spent way too much time in the ICU. One is, most of the time that a person is being intubated, it's going to be in that second week. It's going to be after day 10. It's going to be after that, that peak. The other thing is, usually you're doing this, you're wearing your N95, you're doing in a proper room. The intubation, then they're attached to a closed system. It was really interesting. It was our colleagues in the front lines, the ERs, the urgent cares. I think those were the folks, the primary care doctors who were seeing patients in the first week when we were seeing the highest risk of contagion.

VR: OK, Michele writes, "My 92-year-old mom has not had COVID, told me if she gets it, she doesn't even know if she would take Paxlovid. At 92, she has some underlying health conditions that put her at greater risk. I told her she should take Paxlovid. She said several of her friends have taken it and struggled with side effects. She'd rather have an infusion. I have no idea what infusion she's talking about. Could a 92-year old with COVID present at an ER in New Jersey and receive an infusion of remdesivir? Is there any research which compares the efficacy of Paxlovid with the renal dose of Paxlovid? Trying to come up with a plan for mom.”

DG: One is, love to talk to your mom or have one of my colleagues talk to your mom. That's an ideal thing, is have a medical professional spend the time really going through and explaining risk/benefits of different approaches. We still - thank you, hats off to the Catholic Health system, also Northwell has jumped in on this as well, to provide outpatient access to IV remdesivir, the three-day treatment, which is an infusion. It's not the monoclonals, which some people are thinking about. As we've talked about, those are off the table right now. New Jersey might be a little bit harder to do.

VR: Carol writes, “Our 38-year-old daughter has Type 2 bipolar disorder, ADHD and PTSD. She has alcohol use disorder. Heavy drinker more than 15 years, developed alcoholic fatty

liver disease. Last May, she got COVID, stopped drinking in November, got COVID again. This time worse.

Still not bad enough to require medical attention. Couple of months later, she moved back home, still couldn't work. Persistent cough, fatigue, diarrhea, vomiting. Eventually, jaundice, went to the ER Last month, the original prognosis was worrying. After two weeks in the hospital, several days on prednisone, she's shown a lot of improvement. It's my understanding that alcoholic liver disease is on the rise. One article I read gives the impression that the cause is more people were drinking heavily in the first year of the pandemic.

I don't doubt that, but I'm curious as to how a mild to moderate, non-hypoxic, but miserable week of COVID affects the liver, the mechanisms involved. She also had Hep C several years ago, but it's been inactive. How common is it for mild COVID infections to significantly increase liver damage in patients with compensated steatosis?"

DG: Yes, no, see, great questions. There's a lot here for our listeners as well. In general, I am not sure how much COVID is playing a part. It sounds like there's plenty of other things here that are hepatotoxic, that are toxic for the liver. For a mild case of COVID, I'm going to put this, someone who either doesn't end up in the hospital or someone who ends up in the hospital but doesn't end up septic.

We're not seeing a tremendous amount of liver damage, but we certainly in the severe cases, particularly in people that end up in the ICU, we can see severe liver issues. We don't think it's actually the virus invading the liver cells. The whole impression is this is mediated either through the sepsis process, the poor perfusion. Shock liver is one of the terms we use to sort of group a whole bunch of complicated inflammatory processes together. Yes, we think it's more of an inflammatory impact than any direct viral.

VR: All right. Finally, Rhonda writes, Rhonda is a clinical pharmacist at a clinic in Greenville, South Carolina. "I'm hopeful you can share your insight with me in guiding my 20-year-old nursing student daughter as she prepares for a four-week summer midwife internship in Tanzania in June. She's considering taking PrEP prophylactically due to a much higher rate of HIV exposure during this four-week period and anticipating a high level of exposure to body fluids by nature of this work.

Her primary care provider has not ever prescribed PrEP, but is in agreement with this preventive action. I believe the travel clinic that my daughter has consulted is also advising this step, although they cannot prescribe it. What's your advice? As a pharmacist, the antiretroviral drugs seem intimidating, but so does HIV. In addition to PrEP, the clinic has recommended atovaquone-proguanil for malaria prevention. They also advise TDaP ,polio, yellow fever, and typhoid vaccines, as well as receiving all these in one day.

CDC has confirmed Marburg in Kagera Province. Her internship is in Arusha. No one but me seems to be concerned about this. Would appreciate any guidance you could impart".

DG: Yes, no, I think this is the importance of travel medicine, is specialists in this field, and that's one of my areas. I actually think that this is important thing to bring up, the issue of pre-exposure prophylaxis. A lot of these countries, 10% 20% of the population is HIV

positive. If you're in a situation like this, you're delivering babies, you end up with blood, other fluids, in your face, in your eyes, in broken areas of your skin. You may end up with a cut, might end up even with a needle stick. Hollow bore. These are the things we really worry about.

Pre-exposure prophylaxis, it's a single pill, Truvada, you take it once a day. It's a very reasonable thing. We're still in the world of telehealth, so folks can still reach out. Happy to help with things like that. I think of Marburg as a lower, much, much lower risk. That's something we'll keep an eye on. Yes, these are the complexities of not only your normal vacation travel health, but your higher-risk travel health challenges.

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

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

[music]

[00:54:30] [END OF AUDIO]