This Week in Virology

TWiV 1004 Clinical Update

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

[music]

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology,* Episode 1,004, recorded on May 4, 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: We had a little discussion last time, about 1,000 episodes-plus. Several people wrote in and said "You're not supposed to say 1,000 and 4, you just say 1,004." [chuckles] Did you know that, Dan?

DG: [chuckles] It's nice for the feedback.

VR: Also, I'm not supposed to put a comma in 1,000, which I do, so -

DG: Interesting, I'd like to put the commas in, but I'll investigate. Let us get going. First off, today, I am wearing my coronavirus bow tie. You can see that there.

VR: Which coronavirus is it?

DG: I'm sure it's SARS-CoV-2. Now, this brings up an interesting thing. Now, I had this bow tie from before the pandemic. I actually purchased it, I believe, back in 2016. Here's the question. Is it the same spike protein? [chuckles]

VR: No, it's not. It's probably either. It's just a coronavirus without any - It's a generic, but it's different, clearly.

DG: OK.

VR: It doesn't have three prolines or two prolines either.

DG: [chuckles] All right, we will start with the quotation. "If a child is to keep alive his inborn sense of wonder, he needs the companionship of at least one adult who can share it,

rediscovering with him the joy, excitement, and mystery of the world we live in." That's Rachel Carson. You're my adult, Vince, and I'm the child here.

VR: Got it.

DG: [chuckles] We'll see why I start with this quotation in a minute. Let's get right into RSV. This is very exciting. When I read this first bit of news, I did shout out loud, "Yes. Finally." After 60 years, on May 3, the U.S. Food and Drug Administration approved Arexvy, the first respiratory syncytial virus, RSV, vaccine for use in the United States. This is approved for prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older. We discussed this before, actually discussed it last night with Kathy at our board meeting. [chuckling]

The safety and effectiveness of this vaccine is based on the FDA's analysis of data from an ongoing randomized placebo control clinical study conducted in the U.S. and internationally in individuals 60 years of age and older. The main clinical study of Arexvy was designed to assess the safety and effectiveness of a single dose administered to individuals 60 years of age and older. Participants will remain in this study through three RSV seasons so we will be learning more. This is to assess the duration of effectiveness, the safety, and effectiveness of repeat vaccination. The data for a single dose of the vaccine from the first RSV season of the study was available for the FDA's analysis.

In that study, we've talked about this before, 12,500 participants received the vaccine, 12,500 participants got a placebo. Among the participants who received the vaccine, they saw a significantly reduced risk of developing RSV-associated lower respiratory tract disease by 82.6% and a reduction in developing severe RSV-associated lower respiratory tract disease by 94.1%. This is the GSK vaccine I was checking today.

Maybe we'll hear about another vaccine soon, but the FDA is requiring the company to conduct a post-marketing study to assess the signals of serious risk for Guillain-Barré, acute disseminated encephalomyelitis because there was data from a different study where this vaccine was given concomitantly with the flu shot. We will have more to say as we learn more.

VR: Are you getting this vaccine, Daniel?

DG: I am under 60. [chuckles]

VR: You are? Oh, my God.

DG: Can you imagine that? I'm a young pup. I'm still in my 50s.

VR: I should get it, right?

DG: Yes, you should, actually.

VR: We should point out this is licensed. It's not an EUA. It's fully licensed.

DG: This will be licensed, yes. All right. Influenza, we now have somewhat final numbers on this last year's flu season. We saw a peak, an early peak, actually, similar to 2017, 2018 as far as percent of visits for influenza-like illness as far as where that peak was, but significantly earlier this year. What are the final numbers? I think these are helpful for giving people a sense. An estimated 26 million illnesses, 290,000 hospitalizations, 19,000 deaths, and a total of 145 influenza-associated pediatric deaths. One hundred forty-five kids died from influenza this last season.

VR: Daniel, two things. First of all, it's a very early peak, as you see, earlier than in most recent seasons. I don't know why that is, but that's the way it is. Secondly, it's a lot of hospitalizations and a lot of deaths. I just want to point out people don't usually mask for influenza virus.

DG: Yes, we'll be talking a little bit later. Remember that 19,000 deaths. We'll talk about how many deaths we saw this last year from COVID. All right, COVID update. This is the Rachel Carson thing. I only wish this topic was more science-based and less infused with politics. "Association between SARS-CoV-2 and Metagenomic Content of Samples from the Huanan Seafood Market," was posted by Jesse Bloom from the Fred Hutchinson Cancer Center on *bioRxiv*. He starts with a reference to the Chinese CDC released data from deep sequencing of environmental samples collected from the market after it was closed on January 1, 2020.

He mentions reports from Chinese officials about the outbreak that eventually became the SARS-CoV-2 pandemic that described patients associated with the Huanan Seafood Market in Wuhan. Dr. Bloom reports here that he did implement a fully reproducible computational pipeline that jointly analyzes the number of reads mapping to SARS-CoV-2 and the mitochondrial genomes of chordate species. Those are animals with spinal cords across the full set of samples. He does start by reporting this did validate the presence of genetic material from numerous species, but then reports that the number of SARS-CoV-2 reads is not consistently correlated with reads mapping to any non-human susceptible species.

All right, for instance, 14 samples had greater than 20% of their chordate, those folks with spines, mitochondrial material from raccoon dogs. Only one of these samples contains any SARS-CoV-2 reads and that sample only has one of about 200 million reads mapping to SARS-CoV-2 instead. I feel like they were listening last time and may have picked up on my joke about the frozen fish instead. SARS-CoV-2 reads are most correlated with reads mapping to various fish, such as catfish and largemouth bass.

Dr. Bloom concludes by saying these results suggest that while metagenomic analysis of the environmental samples is useful for identifying animals or animal products sold at the market, commingling of animal and viral genetic material is unlikely to reliably indicate whether any animals were infected by SARS-CoV-2. There's a few takeaways, and then I'm going to get your take on this, Vincent. One of the things that I was really intrigued by is if you go to some of the figures, and I'm going to go to Figure 4, it is amazing how many different animals are here that maybe were not supposed to be there.

The Amur hedgehog, the Chinese cobra, the Chinese salamander, the European hedgehog, the Himalayan marmot, the largemouth bass, the Malayan porcupine, the Malayan field rat,

the Siberian weasel, the bat-eared fox, the brown bush-hen. It goes on and on. There are fennec foxes, that's not cool, masked palm civet. I don't think they're supposed to be there. Snakehead fish, swamp eels, yellow croakers, pigeons, hoary bamboo rats. All right.

VR: Oh, my God. [chuckles]

DG: Interesting. Any comments that [chuckles] you've got there, Vincent?

VR: I do. A number of people have commented that you can change the variables on these algorithms to get different results. They said it's not clear that he did what was supposed to be done. He is actually quoted in a *New York Times* article as saying, "It's an open question of whether that is an informative thing to calculate at all." In other words, he's saying we don't know if this means anything.

Here's my take. The market was the early epicenter of the outbreak. The market sold animals that are known to be susceptible to SARS-CoV-2. They were in a certain area of the market where environmental samples positive for SARS-CoV-2, and perhaps most importantly, there were two lineages of SARS-CoV-2 circulating early in the market, all of which is consistent with that being the origin. Now, it doesn't prove it having these sequences in animals, but I think everything together is all consistent with the market being the origin. That's the way you have to look at this.

DG: I don't think this is just maybe - If you read this, he's suggesting it might be the fish and not the chordates. I don't know.

VR: Basically, he's saying this analysis is useless because it could turn up in fish or palm civet, right?

DG: Yes.

VR: I think it's a matter of how you set the markers on the algorithms too.

DG: It is interesting when you do the pipeline analysis, you're choosing how analysts do this and that. I don't remember those days fondly. I mentioned last [chuckles] week I would be discussing reinfection. Let me discuss the news feature published in *Nature*, "Are Repeat COVID Infections Dangerous?" I like how they put that as a question. Maybe they then plug that into ChatGPT. "What the Science Says," and then a little subtitle, "Researchers Disagree Over How Bad it is to be Reinfected, and Whether COVID-19 Can Cause Lasting Changes to the Immune System." That's interesting when researchers disagree. Of course, researchers disagree. There are a lot of us out there. We're not all on the same page.

Now, the first sentence that caught my eye was, first, reinfections so far seem to be relatively rare in studies that tested people for the virus over time. Really? [chuckles] Then we get some reassuring or suggested to be reassuring bits of information. They mentioned a UK study which looked at 3.8 million first infections and 14,000 reinfections in England. That's a few. Where they found that people were 61% less likely to die in the month following reinfection than in the same period after the first infection.

If you survived that first infections, you still could die that second time, but only about half as likely, despite demonstrating that you can survive COVID once and despite that natural immunity I was so excited about. Then they mentioned another study where they saw that the people who had to be put on a ventilator during the first infection, only about a third of them ended up in the hospital on reinfection. I'm not reassured.

A couple of takeaways. One, cannot die twice of COVID-19, people who survived the first episode of COVID might still end up in the hospital with a new infection or might even die from that second infection, and lastly, people with no Long COVID the first infection might still get Long COVID with a reinfection, but I don't know if you're reassured. These numbers, in general, are a little bit lower with that second infection across the board.

This seems to be getting tweeted out by all different people to support whatever the agenda they are advancing. It, in general, reminded me of that disclaimer. When you invest your money in a stock market, Vincent, past performance is no guarantee of future performance. Don't assume a COVID infection will go well in the future simply because one has done well in the past.

I also wanted to talk about one of the tools. Many of us used during the pandemic telemedicine and the article, “Virtual Care and Emergency Department Use During the COVID-19 Pandemic Among Patients of Family Physicians in Ontario, Canada,” published in *JAMA Network Open*.

First off, I love the lack of spin in the article. You're not really even sure what this article is going to tell you and so they then modestly put in their result as, in this cross-sectional study of 13,820 family physicians with 12,951,063 patients in Ontario, Canada, they found that patients of physicians who provided a high percentage of virtual care during the first years of the COVID-19 pandemic did not have higher ED visits than patients of physicians who provided the lowest levels of virtual care.

Then, you actually look at the results and you see the mean number of ED visits was highest among patients whose physicians provided only in-person care, 470.3 per 1,000, and lowest among patients of physicians who provided more than 80% to less than 100% of care virtually, 242 per 1,000. Basically, the folks that had the opportunity and access to virtual care, about half as many ED visits.

Recently, we had a Columbia morning conference on telemedicine. I quietly listened. Every so often I'll put something in a chat. Rarely will I join in. I had a few thoughts. I personally started doing telehealth a number of years ago. Then, as the pandemic started, our organization, which is now Optum Tri-State, invested in robust telehealth technology so we can conference in family at different locations. We can offer same-day telehealth emergent appointments. We can complement this with having the ability to default down to in-person assessments as needed.

We even have this cool system where a person is like, "I just can't seem to get online," where we can actually send a link right to their phone or computer and all they have to do is click on it, and boom, you're in a telehealth visit. I think a lot of the comments about telehealth and the frustrations that were being expressed at that morning conference have

a lot to do with investing in robust technology, which makes this easy, which makes this accessible. Also, it's not like suddenly you can go from in-person visits to being expert at telehealth. If we're going to start really doing telehealth, this has to be part of training. We should look at incorporating training on how to effectively use this technology.

VR: Daniel, the increased disease in people who go in person, it's not just because you're in the doctor's office but you're traveling and encountering other people on the way, right?

DG: There's also the issue, like if you're not feeling well and you can connect with your doc and they can address your needs, you may not have to go to the ED. You may avoid that ED visit. Also, yes, as you point out, when you go to that ED during a pandemic, that's not the safest thing to do. All right. Children, COVID and other vulnerable populations. This is a special little recap for the pediatricians in the audience, the children and all those young at heart, and everyone baffled by the updated CDC vaccine recommendations. Yes, that actually includes Jay Berger, the head of our pediatrics division.

What did we talk about before? The monovalent vaccine, it's all gone. Everything now, all the shots that we're going to be giving, they're going to be bivalent. As we mentioned last week, CDC recommends that everyone ages 6 years and older receive an updated bivalent mRNA COVID-19 vaccine regardless of whether they previously completed any series. The whole idea is everyone has pretty much been vaccinated or infected. You get one of the bivalents, we call it a day, but then, when you get to the under 6, it gets really complicated. When the head of our pediatric division calls to discuss the updated simplified vaccine recommendations, I'm going to say they're not simplified.

Now, the original primary series for kids six months to 4, I'm going to go through this here. They make this nice and simple. No, they don't. Recommendations for children age six months to 5 years. I'm going to leave links in here. If the children are six months to 4 years, the concept here is they're coming into this naive. If you're going to go ahead with the Pfizer-BioNTech, you're going to give them three shots, three shot vaccine, and if they already finish that, then you go ahead and now we're in the time of the bivalent, you give them a bivalent shot.

What if they've only got two shots so far? Then, boom, you top it off with a bivalent and you call it a day. What if they only had one shot? Then you give the next two shots with the updated bivalent. Two doses, the original, third dose, you get the top off. Think of this as, basically, the Pfizer-BioNTech vaccine is a three-shot vaccine as long as somewhere in there you get the bivalent. If you've gotten three, you never got the bivalent, you top it off Pfizer-BioNTech, you're done for now.

What about Moderna? For Moderna, interesting enough, this is really two doses in the original Moderna vaccine. Here we are six months to 4 years of age. We're going to have this 5-year-old limbo zone here, which I will talk about. Two doses, the original Moderna vaccine, they say go ahead and give that bivalent. What if you only had one dose? You're in the middle of the street. A little subtle twist here. You could just get a bivalent. Here, two shots and you're done as long as it's bivalent.

Now, what if you had two shots in the original? Still got to get a bivalent in there and make it a third shot. They really want everyone at some point in these recommendations to get a bivalent. It's a three-shot series for everyone except for the children six months to 4 who did Moderna, and then it's two shots as long as one of them is bivalent.

If you're not confused yet, now it finally gets simple. Everyone 6 and up, we assume they already have some level of immunity. You get a bivalent at some point. You call it a day. If you're over 65, if you're immunocompromised, maybe some people might get an extra shot in there. A little confusing all the way across the board. What comes up to, Vincent, and this is the question, what if the person got two shots of the Pfizer and now they got an infection. Did they need the bivalent? [chuckles]

VR: I don't think so. Two shots, I think it depends how close they were. If they were close, they should get a third shot or an infection. I think the infection makes the third shot, essentially. Daniel, if you have someone who never got vaccinated, they're 65 and over, what do you give them? Two or three shots?

DG: One shot of bivalent, you call it a day.

VR: That's it?

DG: That's the concept. The concept is, and I think you could go a little bit is, the concept is 99% of people already have some level of immunity. Either they got vaccinated and they didn't know it, they were sleeping through the appointment. That probably didn't happen. Or they got an asymptomatic infection and they just don't know it. They don't want people checking serologies. They want to say, "You know what? At this point, you probably got it, 99% probably, go ahead, get one shot of the bivalent, and then consider yourself vaccinated."

VR: All right. Where did the boosters fit in? Everyone wants you to get a booster now.

DG: [chuckles] Interesting enough, and we'll get to that teaser for next time. June 15, we're going to hear about what's going to happen in the fall. Everyone already thinks they know. We talked a little bit last time. I'm not sure if the current formulation booster even actually boosts at the moment. The only people that we're talking about getting boosters right now is really access to those over 65, those immunocompromised. It's not really even as much a recommendation as, by the way, you got access if that's something you and your doctor want to do.

VR: OK.

DG: If you're not confused, come back next week. If you are confused, come back next week. All right. COVID active vaccination. What is the first, best vaccination to use to prevent COVID? This article that I'm going to discuss reminds me of the early days of the pandemic when I was having a conversation with the now-retired, but at that point, chief of medicine at one of the hospitals. When we were having this whole question about how do you know if someone has COVID? Maybe we could do a procalcitonin. Maybe it had to be a certain presentation. We went back and forth. I was like, I have this brilliant idea. If we want to tell if patients have COVID, we should do a COVID test.

All right, the article, “Vaccination with BCG-Denmark Did Not Result in a Lower Risk of Covid-19 Among Health Care Workers Than Placebo,” was recently published in *The New England Journal of Medicine.* That's nice, right? The surgeons can get that. They read the title. They know what's in there. They can move forward. Here, the investigators are looking at whether the TB vaccine, the bacille Calmette–Guérin vaccine, has immunomodulatory "off-target" effects that might protect against coronavirus disease 2019, COVID-19.

These are the results of a well-designed, I think they themselves called it well designed, a well-designed international double-blind, placebo-controlled trial where the investigators randomly assigned 3,988 healthcare workers to receive the BCG Denmark vaccine or saline placebo and followed them for 12 months. Symptomatic COVID-19 and severe COVID-19 were the primary outcomes that were assessed at six months. They did this modified intent to treat analysis. Basically, they had a negative test at baseline. Recruitment actually ceased before the planned sample size owing to the availability of COVID-19 vaccines.

Interesting enough, a bunch of folks thought it might be a good idea to go with those. The modified intention to treat population included 84.9% of the participants who underwent randomization. We had 1,703 in the BCG group, 1,683 in the placebo group, and the vaccination with BCG Denmark did not result in a lower risk of COVID-19 among healthcare workers.

VR: What's your conclusion from that, Daniel?

DG: That if you want to immunize someone for COVID-19, you should use a COVID-19 vaccine.

VR: Seems reasonable.

DG: [chuckles] What is the best vaccine for COVID-19? On that topic, we have the article, “NVX-CoV2373 Vaccine Efficacy Against Hospitalization: A *post hoc* Analysis of the PREVENT-19 Phase 3, Randomized, Placebo-controlled Trial,” published in *Vaccine*. We don't hear too much about Novavax. I feel like it's the red-headed stepchild. Here is the yes, "the *post hoc* analysis of the PREVENT-19 phase 3, randomized, placebo-controlled trial," as they say in the title, looking at the vaccine efficacy of the Novavax vaccine when the predominant SARS-CoV-2 variant was Alpha, but additional variants were in circulation. There was some Beta, some Gamma, some Epsilon, Iota.

They reported a vaccine efficacy of 90% for the prevention of symptomatic COVID, and a *post hoc* vaccine efficacy of 100% at keeping folks out of the hospitalization. To put this in context, the analysis period was 95 days. They saw zero hospitalizations in vaccine recipients, four among placebo. Very small numbers, very short analysis.

VR: Who can get this vaccine, Daniel? Is it available in the U.S.?

DG: We're having some issues lately because there was a batch that it expired so we're in a little limbo zone at the moment. Not great for those.

VR: The protein in this vaccine is the original SARS-CoV-2 isolate, right? It's not an Omicron, correct?

DG: True. All right, we have the article, “Comparative Effectiveness of the Sars-CoV-2 Vaccines during Delta Dominance*,”* published in *Cell Press* open access journal *Heliyon*. These guys didn't even look at Novavax. They just left it out. This is one of those shared first-author papers and one of those first authors is a statistician, Nazmul Islam. You'll see why we need a statistician here. In this study, they looked at de-identified claims in a research database that included vaccination status and COVID-positivity status. Individuals 18 years of age and older, fully vaccinated with the J&J, Moderna, or Pfizer-BioNTech shots prior to September 30, 2021, were included and compared.

What were the outcomes? They looked at SARS-CoV-2 infection, emergency department visits, outpatient visits, inpatient hospitalizations, ICU transfers, death, and hospice transfers through September 30, 2021. This is very robust data set where we looked at 6,473,000, It's 380 fully vaccinated, non-boosted individuals on or before September 30, 2021. Most of them, 55% received the Pfizer-BioNTech, 38% got the Moderna, and only 7% got the J&J. Yes, I said we because I'm the other first co-author along with our other authors, Megan Jarvis, and Ken Cohen. Now, who did the best? I hope people have their bets in.

Moderna did the best followed closely behind by a nose Pfizer-BioNTech vaccine and J&J was in third by a bit of a margin, about a horse length there. Now, we calculated a number needed to vaccinate to give the comparison some context. The number needed to vaccinate with Moderna to prevent one hospitalization at 90 days was 3,130 compared to J&J and 15,472 compared to Pfizer-BioNTech. The number needed to vaccinate with Moderna vaccine to prevent one ICU transfer at 90 days was 6,358 compared to J&J, 34,279 compared to the Pfizer-BioNTech vaccine. We even did a little bit of a cost estimate here.

For every 1 million individuals vaccinated with the Pfizer-BioNTech vaccine compared to Moderna vaccine, the approximate incremental inpatient costs would be $405,000 and the approximate incremental ICU costs would be $662,000. In summary, right? The reason we put it this way is when you just look at these percentages, you say, "Oh, this is so much better," but you want to put it in real-world context.

In summary, those mRNA vaccines appear significantly superior to J&J. We're really splitting hairs with a slight difference between Moderna and Pfizer. I do think it's important, however, that we keep watching and asking the same questions with different variants. Are our vaccines still working? Also, what can they offer? Not just Omicron. Everyone talks about Omicron. What about XBB, the Gryphon family of variants versus the pre-Omicron XBB variants?

Moving on to COVID, the early viral upper respiratory non-hypoxic phase. I wanted to start this section with the article, “Assessment of Gender-Specific COVID-19 Case Fatality Risk per Malignant Neoplasm Type*,”* published in *JAMA Oncology*. These are results of a cohort study using the Healthcare Cost and Utilization Project’s National Inpatient Sample, they looked at 1,622, 755 patients who are admitted to the hospital from April 1 to December 31, 2020, with a diagnosis of COVID-19. Huge data set again.

The cohort-level COVID-19 in-hospital case fatality rate was 12.9% with a median time to death of 5 days. In a multivariate analysis, malignant neoplasm, here we saw 17.9% versus 12.7%. This was associated with increased COVID-19 in-hospital case fatality rate.

They conclude by saying, "The results of this cohort study confirmed the substantial case fatality rate among patients with COVID-19 in the early pandemic experience in 2020 in the U.S. While COVID-19 in-hospital case fatality risks were lower among women compared with men, the associations of a concurrent malignant neoplasm with the COVID-19 case fatality were overall more substantial for women than for men."

What makes this timely for me was actually a case that I was discussing a little bit with Vincent and Kathy Spindler last night at a poor individual, unfortunate individual who has metastatic breast cancer. She started to develop some symptoms, she was concerned. She went to her oncologist. She was diagnosed with COVID. She asked her oncologist about getting treatment.

The response of the oncologist was, "No, dear, I don't recommend any treatment other than the scheduled Tylenol. You see, the drugs are worse than the disease." Now, I met this woman because she was being admitted to the hospital. I'm not sure if it's the metallic taste that was so upsetting to the oncologist, but no, no, the drugs are not worse than the disease.

We'll talk about this next week, we saw an estimated 0.25 million people die of COVID in 2022. That's about 5,000 people a week. We can drop that number by about 90% with effective early treatment. Who are those people that are dying? It's people just like this woman, metastatic breast cancer, chemotherapy, older, compromised.

Just to hammer home the efficacy of the antivirals if people haven't really gotten it, we have the article, “Clinical Outcomes Following Treatment for COVID-19 With Nirmatrelvir/Ritonavir and Molnupiravir Among Patients Living in Nursing Homes,” published in *JAMA Network Open*. Another retrospective cohort study conducted between February 16 and March 31, 2022, with the last follow-up date on April 25, 2022. Participants were patients with COVID-19 living in nursing homes in Hong Kong.

Of 14, 617 patients, mean age, 84.8, 56.2% women, 8,939, 61.2% did not use oral antivirals, 35.5% used molnupiravir, only 3.3% used Paxlovid, the nirmatrelvir/ritonavir. After propensity score weighting, both molnupiravir and the Paxlovid were associated with a reduced risk of hospitalization. For the molnupiravir, a weighted hazard ratio of 0.46, a 54% reduced risk of ending up in the hospital. Inpatient disease progression also reduced by 54%.

When we looked at the Paxlovid, we actually saw even better, we saw a hazard ratio of 0.35 and 0.17, a 65% reduced risk of hospitalization and an 83% reduction in in-patient disease progression.

VR: Daniel, I've seen some other studies you've talked about where molnupiravir was not this good. Does it really depend on the patient population?

DG: It might be a combination of things. One of the nice things maybe I'll say about, if there are nice things about being in a nursing home, is that maybe a situation where you can get that early diagnosis and treatment.

VR: I see.

DG: A lot of times if you wait too long, I think we miss our window.

VR: Got it.

DG: These data are much more impressive for molnupiravir than we've seen elsewhere. Remember what is our order of recommended treatment? Probably, number one, take it seriously, realize that we had about 460,000 people die of COVID in 2021. We had about 250,000 die in 2022. That's Omicron "mild" during a time when we have access to vaccines, preexisting immunity, effective therapeutics.

We stopped doing harmful things, but we're still seeing 5,000 deaths a week was what we average last year. Still, the top four causes of death. Number one, Paxlovid. Number two, when you can get it, remdesivir. Number three, molnupiravir. Four, convalescent plasma. Remember that's early first week and don't do harmful stuff.

All right, a little bit here in the early inflammatory, lower respiratory, hypoxic phase, the second week, the period of the cytokine storm. As we've talked about steroids at the right time in the right patient. This is after week one in patients with oxygen saturations less than 94% and the data really is settling on a recommendation of a target of about dexamethasone 6 milligrams for about six days.

By the way, maybe you should update those electronic health record order sets so it's in line with this. It's not 10 anymore, a couple of clicks there, please. Anticoagulation guidelines, three, pulmonary support, we have the article, “Timing of Intubation and ICU Mortality in COVID-19 Patients: A Retrospective Analysis of 4198 Critically Ill Patients During the First and Second Waves,” recently published in *BMC Anesthesiology*.

People will probably, our listeners may recall, all the debate are about early intubation, and then this move to try to avoid intubation entirely. Now, here they perform a secondary analysis of prospectively collected data from adult patients with acute respiratory failure due to COVID-19 admitted to 73 ICUs between February 2020 and March 2021. This analysis includes 4,190 patients, intubation was considered very early in 48% of the patients early in 22%, and then late in 10%, and mortality was higher in the late group than the early group, 37% versus 32%.

They comment that the implementation of an early innovation approach was found to be an independent protective risk factor for mortality, hazard ratio of 0.6. They then go on to conclude that early intubation within the first week, 24 hours of ICU admission in patients with COVID-19 pneumonia was found to be an independent protective risk factor of mortality.

I have a comment here, that this is an all-comers coming in, and then just randomly assigning. We're ultimately only looking at folks that ended up getting intubated. How many people avoided getting intubated by waiting? Maybe some of the early intubated folks did not even really need to be intubated. They're going to be fine anyway, pull that tube right back out. By the time you were waiting and it was your last ditch effort - I'm not sure that this is a glowing endorsement for popping those tubes right in within the first 24 hours. Ideally, what we want to do when possible is avoid intubation. I see Vincent nodding his head. He would like to not be intubated.

VR: I want an iron lung, Daniel.

DG: It's interesting, the whole concept of the iron lung and the idea that that might actually have some different physiological impact, right?

VR: Yes.

DG: Remdesivir, as we've been saying, if you're in the first 10 days, if you're not on a ventilator, and a little more today with the article, "Real-life Experience with Remdesivir for Treatment of COVID-19 among Older Adults: A Multicentre Retrospective Study," published in the *Journal of Antimicrobial Chemotherapy*. These are results of a retrospective multinational cohort of individuals aged 65 or older, hospitalized with COVID-19 in six medical centers between January 20 and May 2021. Of 3,010 individuals included, 2,788 individuals required either oxygen supplementation or non-invasive mechanical ventilation, 16% were treated with remdesivir.

Remdesivir was associated with decreased mortality. Remember, we're in the second week, we're in the hospital now. This is when our window is not as wide as it was early on. This is not the 87% reduction we saw in PINETREE. In this second week, we still have the opportunity for here, remdesivir decreasing mortality adjusted odds ratio of 0.49, it's about 51%, but this protective effect was shown for individuals requiring oxygen support and non-invasive mechanical ventilation, but not for the folks that were on ventilators.

Five, remember tocilizumab, some cases baricitinib, and we will close today out with the article, "Long COVID Brain Fog and Muscle Pain are Associated with Longer Time to Clearance of SARS-CoV-2 RNA from the Upper Respiratory Tract during Acute Infection," recently published in *Frontiers in Immunology*. Now, this is interesting, but I will start with the qualification. This is a small study. They only looked at 73 non-hospitalized adult participants that were enrolled within approximately 48 hours of their first positive SARS-CoV-2 RT-PCR test. Mid-turbinate nasal and saliva samples were collected up to nine times within the first 45 days after enrollment. Samples were analyzed for SARS-CoV-2 using RT-PCR and additional SARS-CoV-2 test results were abstracted from the clinical record. Each participant indicated the presence and severity of 49 Long COVID symptoms at one, three, six, 12, and 18 months post-COVID-19 diagnosis.

Time from acute COVID-19 illness onset to SARS-CoV-2 RNA clearance greater or less than 28 days, that's their binary, that was tested for association with the presence or absence of each of 49 Long COVID symptoms at 90-plus days from acute COVID-19 symptom onset. Self-reported brain fog and muscle pain at 90-plus days after acute COVID-19 onset were negatively associated with viral RNA clearance within 28 days of acute COVID-19 onset with adjustment for age, sex, BMI, and COVID vaccination status and we have an adjusted relative risk brain fog 0.46, 54% muscle pain adjusted relative risk 0.28.

Participants reporting higher severity brain fog, or muscle pain at 90-plus days after acute COVID-19 onset, were less likely to have cleared the SARS-CoV-2 RNA within 28 days. The acute viral RNA decay trajectories of participants who did and did not later go on to experience brain fog 90-plus days after acute COVID-19 were distinct. They have a nice figure looking at some of this stuff.

VR: I would really like to see infectious virus here, Daniel, because I don't know what's going on. If this is an infectious virus, it would suggest that Paxlovid might get rid of it, right?

DG: It's actually wondering if the window for preventing Long COVID might be a little more than just that first -

VR: Yes, exactly.

DG: - five days that we start to treat.

VR: No trials are being done with Paxlovid later for this thing. That would be interesting, right?

DG: They're doing it much later. It's 90 days out, the person has already gotten the diagnosis of Long COVID, the virus we think is mostly cleared by then. Again, this is the trial because we're not sure, but it almost would be a trial here. I don't know if Pfizer will ever do this trial, but there's a growing amount of evidence, as we've discussed, that small molecules used to -

The molnupiravir, the Paxlovid used for acute treatment may actually do something to prevent Long COVID and maybe that window isn't just five days. Maybe a person comes, "Oh, it's eight days but we're trying to prevent Long COVID. Maybe the window is a little bigger if this data - I would love more data. I'd also love infectious virus, I'd love to understand a little bit more of what's going on here.

I will close us out by saying continue to think about everyone. No one is safe until everyone is safe. I want to thank everyone. We barely - we squeaked, we met our goal for the American Society of Tropical Medicine and Hygiene fundraiser. We just sent them a check and we now are starting our foundation, International Medical Relief of Children fundraiser.

May, June, and July donations made to PWB will be matched and doubled up to a maximum potential donation of $20,000. We're helping FIMRC with a particular focus on the clinic in Bududa. Actually, one of Paul Offit's mentees is over there right now. We were texting earlier. If you can help us out, go to parasiteswithoutborders.com, click the 'Donate' button, and help us continue to do the work we do and help us support the work that they do.

VR: Before we get to listener questions, Daniel, is it your experience that some people infected with the latest Omicron variant are getting conjunctivitis?

DG: Oh.

[chuckling]

DG: There's this group that I think they must be making fun of, The Vertlantic on Twitter, and they have all these different fun headlines that they make up. I joked about this with one of my colleagues. I see a lot of COVID. This is not an infectious - They see a lot of COVID. Our urgent care docs, we have a huge network, we see lots of COVID. I was like, "I'm not really seeing this and there's really no data to suggest this is true," but the title I was

suggesting for The Vertlantic is, "We Called Our Favorite ID Doc and They Told Us Exactly What We Wanted to Hear."

VR: That's right.

DG: When they call you and they say, "Are you seeing this?" Don't just say what you know is going to get you quoted. Tell the truth.

VR: Please. Oh, my gosh. All right, no conjunctivitis.

DG: Just tell them the truth.

VR: All right, time for your questions for Daniel. You can send them to daniel@microbe.tv. Jared writes, "During *Puscast 27*, you mentioned seeing patients that claim to be allergic to penicillin but are nevertheless able to receive the medication. As someone who has been told since childhood that they are allergic to amoxicillin and CECLOR, I vaguely remember a rash at some point. What sort of conversation should I have with my family practice doctor? Are there any tests that they can order?"

DG: This is huge. We've talked a bit. We've talked even more on the *Puscast* about how folks who end up not getting this group of antibiotics actually have worse outcomes. It's not great to just be like, "Oh, just use something else that's inferior because here you are in the hospital sick." There's testing that they could do. They can even do amoxicillin challenges in a monitored environment, "Here, take some amoxicillin, let's watch it for an hour."

If you're saying I may or may not have had a rash, your chance of having a severe anaphylactic reaction is less than 1 in 10,000, and your chance of not getting optimum therapy is on a whole different level. Talk to your doctor. You may need to get referred to an allergy immunology center to get some testing. It's worth clarifying.

VR: All right, we have two questions, both from MDs, David, and Joe on the same subject. I'll just read David's. "Do you have an explanation of why after turning negative with COVID infection, several days later, antigen tests turn positive, again, with recurrence of symptoms, and sometimes additional symptoms? If this was strictly inflammation, I would expect no change in the antigen test. When I had COVID in February, the test was as quickly positive with the return of symptoms as with the initial onset. This return of test positivity has sparked off-label use of a second course of Paxlovid in some notable celebrities."

DG: Yes, and some notable physicians and scientists. A couple of things to talk about here. We really have a ton of data about the viral replication. That viral replication in just that tiny sample that you might swab. You're not swabbing mucus, you're actually swabbing cells of the inside of the nose. In the first few days, you're getting up into millions and millions of nucleic acid amplification units. Huge amounts.

Now, that by about day four or five really is dropping down. If you're going to be following this trajectory over time, you're going from millions into, 10,000, 20,000, and you're going down into the thousands. You're really getting to a low level, and you're also getting right at the edge of your antigen-positive negative detection. We see this skip positivity off and on. We've talked about this. Forty percent of people who end up with a negative test on day

five, will get a positive test over the next five days. You're still really dropping down to these very low levels of RNA. You're right there at that back and forth.

If you get a better sample with more cells that are now being shed because it's inflammatory, then you get a positive, then you test later in the day, and the next, you might get a negative, but it's right at that level. That second week is not a rebound up into the millions. That is this low level. What are the symptoms you're getting? You're getting the early inflammatory phase. We describe this in a paper in April 2020. I hate to tell you, but Paxlovid was not available back then. That was not Paxlovid rebound.

VR: There you go. Can you say cells shells four times fast, Daniel?

DG: [chuckles] I was having trouble with that.

VR: All right. Martin says, "Some people are saying that people who get mRNA shots, they find that their IgG1 switches to IgG4, and IgG4 doesn't get rid of COVID. Daniel, can you please put this to rest?"

DG: [chuckles] I don't know if I could put it to rest, but I will talk about it. I don't know if you guys ever talked about this under me and Vincent. There was a paper back in December. That was that, "Class Switch Toward Noninflammatory, Spike-specific IgG4 Antibodies after Repeated SARS-CoV-2 mRNA Vaccination." That was published in *Science Immunology*, which took a journal, and this was this interesting study where they actually noted this shift. IgG4, let's talk about it a little so people even know what we're having a conversation about. The IgG subclasses, there are mainly I'm going to say four. IgG1, 2, 3, and 4. There's like A's and B's in there, but we won't go there. Normally, the IgG4 concentration is lower than the other ones. They actually noticed that after this third vaccination that there was this anti-spike IgG4 fraction that was a little bit increased. Is that good or bad? Maybe this is good. Let's talk about IgG4. Is IgG4 a good or bad thing? When they're doing those allergy shots to try to get you to be able to tolerate things, they actually antigen-specific IgG4 correlates with the allergen-specific immunotherapy and may actually help calm down that IgA-mediated effects.

They even discussed in that article which, I thought, I remember because it was an interesting article, where they were looking at beekeepers. You know how beekeepers get stung a lot by the bees? Probably not biting, stinging and they actually don't go into anaphylaxis. I get stung by a bee. I can't breathe. Actually, they think that that mechanism may also be IgG4. Is the increase in IgG4 a good thing? Is it something about that might be helpful decreasing all those allergic-type symptoms that people are reporting after COVID?

Suddenly they're getting hives and itching. Or does this really mean that there might be some slight longer time to viral clearance? Right now, none of us really know what this means. There's no evidence that this is an intrinsically bad thing. Anyone who says that they know what's going on, ask someone else.

VR: It's a very good review article in *Science Immunology* by Shiv Pillai that goes through all of this. He says, the neutralization capacity is fine, it's just the interaction maybe with other cells, NK cells, or macrophages, Fc functions. Maybe that's a little compromised and we just

don't know. I think the fact that these vaccines do work tells you that IgG4 is probably OK, Daniel, right?

DG: Probably just fine. We should leave a link into Shiv's article. I've met Shiv when I used to go to those conferences and he does, there are like poems or songs or something. He's quite a character and a brilliant immunologist so worth reading.

VR: All right, one more from Richard. "I'm a Houston surgeon who has listened to *TWiV* for three years and even enjoyed the barbs at the surgeons occasionally launched. Recently -

DG: Unfortunately, you should have read his email up front because he's not going to still be listening anymore, is he?

VR: Maybe not.

DG: [chuckles] Sorry. That was another barb that the surgeons, but okay.

VR: Yes, that's right. You're right. "Recently toured Italy with a family group, seven out of nine contracted COVID, most recovered in a villa in Umbria. If you got to isolate, this is a great place. Tried hard to get Paxlovid as a tourist, had it sent priority FedEx $130. Never made it through contamination for it required. No pharmacies had it. If they did, it would've been $1,900. Finally, received a call back from the National Infectious Disease hospital in Rome too late to make the zero to five days. Should we consider recommending U.S. tourists to take Paxlovid with them? It's almost impossible to get in or exorbitantly expensive."

DG: I was going to say ask me in a couple of weeks when Pfizer gets full licensure for Paxlovid because I am certain - Right now we're operating under EUA, which is a gray for doing stuff that is not in the EUA. Once this is fully licensed, I think it'll be pretty routine for people to get Paxlovid before they travel. One of the challenges is going to be this issue of - What is it? $800 or $900 for a course. That's not cheap. Who's going to pay that? If you look at people who are high-risk, this is definitely a cost-effective thing to be thinking about doing. I think that you're already touching -

Once Paxlovid is licensed, the data, the licensing, the indication will be to prevent progression to severe disease, hospitalization. We've discussed a lot of the data even outside that. Boy, what happens when you're in Italy and you're a high-risk person and you are having these challenges, it would be great if you could just reach into your pocket and start the therapy. The sooner you start it, as we've talked about, the better. While you're waiting around to get it, that's, you're losing time.

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

DG: Thank you. Everyone, be safe.

[music]