This Week in Virology

TWiV 1102 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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

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From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1102. Now, 1102, recorded on April 3, 2024. 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: On this rainy, stormy night. Is it rainy and stormy where you are?

DG: I usually don't talk about the weather, but the weather is fairly intrusive as of late.

VR: Intrusive. [laughs] I would argue that humans are intrusive.

DG: Yes, thunder claps, the rain will never - seems never to be willing to stop. I live in an old house, Vincent, that was built in the 1800s. Whenever it rains, the water comes in. I wear my shoes to come down to this recording studio as I walk through the water.

VR: Oh, that's terrible. Speaking of wearing, what's on your bow tie today?

DG: What could I possibly have? I don't know if you could Zoom in, but this is a blue bow tie, and it has these little red ribbons. This is the HIV awareness bow tie.

VR: Great, wonderful.

DG: I have a few of them. I have one that's gold with the red on there. It's got a few different ones. All right, well, let's jump right in. I'm glad that you weathered the storm, literally, Vincent, and made it here. Actually, this is perfect. We're talking about nature and the weather because I am going to start off with a Rachel Carson quotation. "I think we're challenged, as mankind has never been challenged before, to prove our maturity and our mastery, not of nature, but of ourselves."

VR: That's from 1962. It's not like today, which would be even more appropriate, right?

DG: It's interesting. I'm rereading *Silent Spring*, and I was talking to my in-laws, and they were thinking about doing it as a town book for Falmouth up in Massachusetts. There was a discussion about, is it timely? It's 62 years ago when that was written. As I'm reading it, I'm realizing it's incredibly timely. It's just amazing as you read through, just realizing, a couple of things.

One is, there's a bit of optimism. We heard this, and we said we need to change. There have been some really positive changes. There are so many other areas we need to work on, and I sort of see a lot of parallels with climate change and other things we're doing to our environment. It is worth the read. We will jump right into measles.

As of March 28, 2024, a total of 97 measles cases were reported. I was sort of waiting, to see when that ticks above 100. A couple - to give some context here. As we've mentioned, this is a considerable number more than last year. Fifty-six percent of the cases have been hospitalized. That's either for isolation or for management of measles complications. Just sort of take that for what it is.

Now, under 5 years, 68%. In that 5 to 19, 27%. In those 20 and older, 56% have ended up hospitalized. Why is this happening? Actually, I'm going to leave - well, we'll leave in the link to a map. It's actually on the same site where you get all the CDC information. You can actually see what is happening with our vaccine coverage for kindergartners. They break it down into where you really want to be, which is this 95% plus. A few states are doing it; California, Nebraska, New York, Massachusetts, Connecticut, Rhode Island, we're doing OK out here on Long Island, Tennessee, Virginia, West Virginia, Alabama. There are a few states -

VR: You can whip off those state names.

DG: [laughs] I spent a lot of time learning the state names as a kid. What's maybe more disturbing is the less than 90%: Arizona. Colorado, what you doing out there? Oklahoma, Idaho, Minnesota, Ohio, Georgia, New Hampshire. I don't understand what's going on there. Also, Washington, DC, in the district, they actually are less than 90%. You sort of understand why we are headed down this road.

Do we need this stark reminder? Do we need hundreds of people to get measles this year before we realize that measles is bad? One of the things that we always sort of say upfront, stop the recording. If you appreciate what we do, how do we turn this around? The way we turn this around, as Paul Offit was saying on one of the recent episodes, is through education.

We have this anti-science misinformation campaign that is funded to the tune of billions of dollars. There's so much money in misinforming people and selling them snake oil. We need that on this side so that we can get this message out. Honest, sober, science-based education so that people are not going to be vulnerable. These 96 people that got measles, I think of them as victims.

All right. Our listeners may remember when Vincent was asking about just adding measles to our multiplex respiratory PCR panel, I think they were listening because we got the *MMWR,* "Implications of Measles Inclusion by Commercial Syndromic Polymerase Chain Reaction Panels - United States, May 2022 through April 2023." A little background, and we get this from the publication. We read here that approximately 5% percent of persons experience a

rash seven to 10 days after the receipt of a measles, mumps, rubella vaccine. My older brother's daughter had this. Oh, was he upset with me for encouraging vaccination of his children? Dare me.

Now, MMR vaccine includes live attenuated, some of us would use this replication-competent measles virus, which is actually detectable by PCR tests. No evidence exists of person-to-person transmission of measles vaccine virus. The child that gets vaccinated, it's not going to spread it to someone else. Illness does not typically result among immunocompetent persons. This self-limited rash is the most of what we see.

Now, here, information was retrospectively collected from a commercial laboratory testing for measles in syndromic multiplex PCR panels. During May 2022 through April 2023, among 1,548 syndromic PCR panels, 1.1% returned positive test results for measles virus. Among 14 persons who received a positive test result, and for whom vaccination and case investigation information were available, all had received the MMR vaccine a median of 12 days before specimen collection, and none had known risk factors for acquiring measles.

To connect this, all positive PCR results were attributed to detection of measles vaccine virus. What they suggest is that increased awareness among healthcare providers about potential measles detection by PCR after vaccination is needed. I also think they might just want to be aware that if you see a child in this context developing a rash and some symptoms after the MMR, you might be thinking about this, not necessarily sending off that test.

Now, the situation that was any detection of measles virus by syndromic PCR tests needs to be immediately reported to public health agencies, which can use measles vaccine history, assessment of risk factors to determine the appropriate public health response. A person recently received MMR vaccine and has no risk factors for acquiring measles, additional public health response is likely unnecessary, and maybe that test was unnecessary.

Just want to discuss a couple of things here that are going to bring me back to my current theme of getting a good history, being cheaper than just ordering tests. Now, while the syndromic PCR that we generally order for respiratory presentations does not include measles, one can order either a PCR for throat, nasopharyngeal swab, or urine if suspecting measles. As we mentioned here, there are multiplex PCR tests that can detect measles.

As we see here, all positive PCR results were attributed to detection of measles vaccine virus. Oh my gosh, if you got a good history, you would've known all had received MMR vaccine a median of 12 days before specimen collection, and none had known risk factors for acquiring measles. Was the clinician just wanting to verify that what they were seeing was that typical 5% post-MMR vaccine rash? Probably not. This does raise the concern that in addition to the cost of adding measles to multiplex PCR panels, one can also start triggering public health investigation of what is just a common post-vaccination phenomenon.

VR: All right. This is very interesting, Daniel. If you saw a child with a rash, you would just take a history and say, "Oh, you got measles vaccine five days ago," and you would leave it at that, is that right?

DG: I think that would be reasonable. In most cases, if the rash was typical, if the presentation was consistent. A lot of parents get upset when a child has a rash, and they might seek medical

attention. In a lot of cases, you stop that. You say, "All right, this is what it looks like." Interesting you bring it up, though, because maybe we'll talk about this. Well, we'll probably talk about it on *ID Puscast*.

There recently was an MMR publication. How good are we as clinicians at, for instance, diagnosing chickenpox. It is interesting. Most of my colleagues have not seen chickenpox because the practice in the U.S. I should say most of my U.S.-based colleagues. I often get the call like, "Hey, would you come and look at so-and-so? They're in the ER, they've got this rash."

Having seen it a lot, I feel in my hubris that I can recognize, well, interesting enough, in this *MMWR* publication, not the MMR publication, they actually had docs say, "Oh, I think this is chickenpox." They had them swab and send off the PCR, really sensitive. Fifty percent of the time, they were wrong, and the PCR was negative. Yes, it does take some experience. Also, I always check myself, too, because, yes, the last thing I want to do is say, "Oh, I think it's chickenpox," and we got to do all this contact tracing and all this isolation when I was wrong.

VR: Can you tell the chickenpox rash from a measles rash?

DG: They tend to be quite different. We talk about measles being morbilliform, as in measles-like, just by the way, that's what that word means. It tends to be on the face, it tends to be on the trunk, it tends to be diffuse and red and not vesicular. You tend not to see little vesicles. Chickenpox, on the other hand, are these little vesicles on little areas of redness. They tend to be in different stages of development. I say tend to because as we're learning more, I think we learned a bit more in the Mpox epic, is that it's not always the case. Yes, there can be - but that's the big - one is a vesicular rash and one is this, yes.

VR: They're both distributed on the face and arms and trunk and legs and so forth.

DG: They can be all over the place, yes. The chickenpox can be all over the place, maybe more so. The measles tend to be more face and trunk. Actually, the measles kids, they're pretty miserable. They're almost like your Kawasaki kids. I've never seen a happy measles case.

VR: Good to know.

DG: All right, the flu. Good news here, we are on the way down. It looks like we're finally starting to drop. It looks like we're getting near the end of our flu season this winter. The data we share, it always takes a little bit to get published. This is data from about a week or so back. It looks like we're really going in the right direction. Now, I don't know if you know this, Vincent, but one of our videos has gone viral on TikTok. Did you know this?

VR: No, which one is that?

DG: It's the one where you ask me about - it's a letter, I think it's a letter, or maybe it was - I think it was our clinical update, but I'm not sure if it was like that office hours thing or a clinical update. Someone asks, is the avian flu, what is circulating, when people are getting flu and we went through, we said, "Actually, it's really - it was the history, H1N1 was that original, flu pandemic early 1900s. H1, H2, H3, think about humans. If it's H5, H7, H9, think about avian, think about zoonotic influenza." Apparently, people like that.

VR: Because of the avian flu case in Texas, people are attuned to this now.

DG: People are, and yes, just to give people a context, what are we seeing, with these human cases of influenza that we're talking about? We're talking about thousands and thousands. We are talking about the influenza A, mostly being H1N1. Then actually at this point in time, 56% are H3N2. Not your H5 or your H9.

Yes, that actually brings us right into our higher number, influenzas. Yes, maybe our listeners have heard about the man in Texas. Actually, very quickly, the CDC, "Technical Update: Summary Analysis of Genetic Sequences of Highly Pathogenic Avian Influenza A(H5N1) Virus in Texas." I am sure the media will get people scared about that. They find this one mutation associated with a change to make it a little bit more fit in a mammalian host. The CDC, very clear, it's not time to sound the alarms for people.

VR: I would agree, yes. They say the genetic analysis shows these are still avian viruses. They have not sufficiently changed to infect mammals.

DG: Yes, and particularly transmission, mammal to mammal transmission. Cows, cats, yes. All right, and I am excited to look at our flu week-by-week map of the United States. Really everyone except for a few places is starting to look green. Wyoming, Nebraska, New Mexico, District of Columbia. I'm not sure what's going on in the District. New York City is also heading in the right way. It's still at the lower level of high, but really coming out of this winter. Dare I say the District is full of unvaccinated Republicans? Oh, you can say that, but now we're going to get comments. [laughs]

VR: Yes, Republicans will write in and say, "I'm vaccinated." The fact is that, as Paul Offit said, in red states, there was more COVID than in blue states.

DG: Yes, no, that was really a shame, the concept of red COVID. A lot of my friends are Republicans. It's just tough that somehow that anti-science message is getting mixed in with maybe some other messages.

All right, moving on to, yes, COVID. I think at some point, I'll probably stop dropping these numbers each time. Maybe it was because finally, this last week, we're down to new deaths last week of 1,202. "Down to," which is really shocking to me, in hospitals still over 10,000 last week. Still a significant thing, but a couple of things I'll say, we started sharing a link to a map.

This is looking at the percentage of deaths due to COVID-19 in the past week by state and territory. They break this down. I put on my glasses for the small print, but what percentage of deaths were due to COVID? There still are a few areas where it's actually 2% to 4% of all deaths. That's Ohio, Maryland, Georgia, South Carolina, North Carolina, other areas where we're in that less than 2%. Really a lot of areas have really gotten down to that less than 1% of the deaths due to COVID.

Moving in the right direction. I think tracking with that also is a nice drop in the wastewater data. Really across the whole country, seeing a really negative trend in a positive spin on that. We want to see that. We want to see those numbers go down.

VR: I want to see, I'm looking forward to see in the next year, whether this becomes a seasonal infection. We had a bump in September, right? Is it going to be predominantly the winter months in this next year? That'll be interesting to look at.

DG: Yes, that'll be interesting to see if it just falls into single peak wastewater, single peak illness, single peak death, and hospitalization. Do we get rid of sort of that late summer bump that we've been seeing for a while here?

All right. I decided to put this next article right up front because I am realizing that this paradigm needs reinforcing over and over again. The fundamental truth that needs repeating that it's not uncontrolled viral replication that is killing people, but rather the triggered immune response that ultimately leads to death. The article, Interplay of Inflammatory Markers and Anti-SARS-CoV-2 Antibodies in COVID-19 Mortality: A Prospective Cohort Study," was recently published in the *International Journal of Infectious Diseases*.

These are results of a prospective multicenter cohort study that included 1,031 hospitalized COVID-19 patients from five hospitals, anti-SARS-CoV-2 spike antibodies, interleukin-6, so IL-6, and C-reactive proteins, CRP, were measured on hospital admission. The pre-specified endpoint was all-cause in-hospital mortality. Patients with high levels of inflammatory markers, so a CRP greater than six milligrams per deciliter or an IL-6 of greater than a hundred, combined with low levels of anti-SARS-CoV-2 spike antibodies, were approximately eight times more likely to die than patients with low inflammatory responses and high antibody levels.

VR: Daniel, I would have liked them to include interferons here.

DG: [laughs] Would you?

VR: Because I think that would be even more correlative with death than having low initial interferon response than antibodies.

DG: Yes. Actually, I like that idea, and I wonder if they're listening and they still have these samples around, if they can run those because that would be nice. Why are you getting this high inflammatory response? Is it because your immune system isn't able to have that proper interferon response upfront and then you end up with this response instead?

Yes, as we pointed out, as we still see, death during the first week is not what we have been seeing. It's not what we are seeing. It's that second and third week with the onset of the cytokine storm that we see, it's when we see people head to the ICU, develop severe disease. That's what makes this tough because it's very human and I understand it, but we've got to sort of move past this.

There's a mentality of, "Well, let's see how I do during that first week." What predicts how you do during that first week is not really how you feel. It's all those risk factors we talk about. We talk about elevated BMI. We talk about diabetes. We talk about age. We talk about comorbidities. It seems to make common sense, well, let's just see how you do. Let's wait and see and then we'll only treat you if you need to. As we see time and time again, if you wait past that fifth, sixth or seventh day, we just can't offer quite as much.

VR: Daniel, remember when I had tested positive for COVID in December '22, I called you and I said, "What should we do? Should we wait and see?" You said, "Of course not."

DG: Thank you. [laughs]

VR: I was just testing you.

DG: OK. All right. I'm not sure why I got this article, this question on one of our last live streams. The article, "Association of Premorbid GLP-1RA and SGLT-2i Prescription Alone and in Combination with COVID-19 Severity," was recently published in *Diabetes Therapy*. We got a question the last time I was on the live stream *Office Hours* about Ozempic.

Here's the context. People with type 2 diabetes are at a heightened risk for severe outcomes related to COVID-19 infection, including hospitalization, intensive care unit admission, mortality. This also applies to diabetes, where having an elevated BMI is strongly associated with higher risk of bad outcomes. This study was designed to examine the impact of use of the glucagon-like peptide-1 receptor agonist, so the GLP-1RA monotherapy, the sodium-glucose co-transporter-2 inhibitor, SGLT-2I monotherapy, and then concomitant therapy on the severity of outcomes in patients with SARS-CoV-2 infection prior to getting an infection.

These are those glucagon-like peptide-1 receptor agonists, so the GLP-1RA drugs like Ozempic, Mounjaro, Zepbound, Wegovy. The sodium-glucose co-transporter-2 inhibitor drugs are perhaps not as well known, but to give this context. Here, these investigators used observational data from the National COVID Cohort Collaborative through September 2022, where they compared outcomes in 78,806 individuals with a prescription of these medicines versus a prescription of an alternate diabetes medication, these dipeptidyl peptidase-4 inhibitors.

Now, the primary outcome was 60-day mortality, and secondary outcomes included ER visits, hospitalizations, mechanical ventilation within 14 days. Now, use of the GLP-1RA drugs, so that's your Ozempic, et cetera, we had an odds ratio of 0.64, so a 36% reduction in this primary outcome of 60-day mortality, and also a lower odds of 60-day mortality seen with the SGLT-2I drugs, that was about 38% for those folks.

If you look just at the ER visits, hospitalizations, similarly reduced. Now my wife asked the question here, which really makes a lot of sense, are we just seeing that they work and you lose weight, and because you lose weight, we're seeing that the weight loss, is there something intrinsic to the drug? Really, I was left with a lot of questions, but I think at the end of the day, we're seeing if you've got an obese patient with diabetes, putting them on Ozempic, still sort of sorting out the details of why, a 36%, 38% reduction, 60-day mortality, a reduction in all these secondary outcomes, that's pretty impressive.

VR: Yes. As you said, the question is whether these are acting as antivirals, or are you treating the diabetes and that's why they do better? I suspect the latter.

DG: I do too, and data to come, I guess, to understand the mechanism here.

VR: If you take a non-diabetic patient, for example -

DG: That would be really interesting.

VR: - and see how they do, yes, I bet it doesn't work, but it would be interesting.

DG: It may be taking away that risk factor, yes, because we've been talking about, you get a BMI above 30, it's like giving someone steroids during the first week, this four-fold risk of progression and Long COVID and all these other things.

All right. For those that don't listen all the time, I hate to say this, Vincent, but there are some longtime listeners who do not catch every episode, so I've got to sort of make sure I pepper in the updates. Recently it came to my attention that people were not aware of the Wednesday, February 28, 2024 recommendation for a booster, so that was the day the vaccine advisors to the CDC and P recommended that people age 65 and older receive an additional dose of the current monovalent vaccine this spring, as long as it's four months after the last shot. Mandy Cohen endorsed the group's recommendation.

We talked about the data that recommendation was based on and then even some more recent data and the fact that we won't really know for sure until another month or two has gone by. Passive vaccination, I actually have started to get patients asking about Pemgarda, the Evusheld replacement, and this is a pre-exposure monoclonal prophylaxis. This is for moderate to severe immune compromise, and we're still waiting to find out about price and access, so, more to come on that.

All right, COVID early viral phase. We will keep in our guidelines, NIH COVID-19 treatment guidelines, so you can share those with folks that are not keeping up to date. Number one, Paxlovid, we also have a number of other medicines that might end up on the market eventually. Number two, remdesivir, remember that's IV, challenges with access. Molnupiravir, that's our third and inferior option. Convalescent plasma in some situations, such as the immunocompromised, and then we have our updated CDC respiratory virus guidance.

Moving into the second week, the cytokine storm week, steroids, right time, right patient, right dose, right duration, anti-coagulation guidelines from American Society of Hematology. I think we've got an update that's going to come out soon, I hope soon.

Three, pulmonary support, and four, remdesivir, if still in the first 10 days from symptom onset, not on a ventilator, and it, just sort of comments here on Remdesivir. If you're within that first seven days, if there's no hypoxemia, PINETREE data, we're doing three days, but if you're past day seven, so if it's day eight, nine, 10, if you've got a drop in that oxygen saturation in room air, then we're doing five days of remdesivir.

Here we have the article, “Cardiac Adverse Events and Remdesivir in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19): A Post Hoc Safety Analysis of the Randomized DisCoVeRy Trial,” it's an interesting little acronym or what do you call that there, recently published in *CID*. And it really fits in here because I have to say, we are still experiencing what I call the impact on expertise.

When it comes to treatment, it used to be you saw the doctor, there was a certain understanding, maybe the years of schooling we had been through, a certain respect for our

opinion, well, OK, why am I bringing this up? It's related to a recent interaction I had. A woman had been in the hospital, she gets discharged, a few days later comes back with COVID, so probably hospital-acquired, unfortunately, we're still seeing that. Get submitted, we're within the first seven days, there's no hypoxemia. I speak to the daughter that I had gotten to know well over the last hospitalization and she says, "Doc, let me stop you before you say anything. My brother is from Florida. Were you thinking of starting remdesivir?" Tell me more. She related that her brother personally knew three people who had got remdesivir and died.

We had this really long discussion and we went through early on when we first started using remdesivir. We were using it week two, week three, not really doing anything to help. We were seeing thousands of people dying a day and yes, some of them had gotten remdesivir at a late stage. We discussed the PINETREE data where there was about this 90% reduction in progression of severe disease and death, but I pointed out 10% of the high-risk individuals who are headed in that direction are still headed in that direction and not going to survive.

Really a long discussion about the fact that we now know how to use remdesivir safely, at the right time, in the right patient, at the right dose, with the right monitoring, et cetera. We still need to have those conversations. I certainly could have seen a provider just sort of being put off saying, "All right, well, if you don't want the remdesivir, moving on." If we don't have those conversations, the other side, I'll brand them that, the other side is very happy to spend as much time as possible disparaging remdesivir and all the other tools that we recommend.

We had that conversation. She spoke to the brother. She spoke to another family member, called me back, "We do want to go ahead with the remdesivir." Three days of remdesivir, and after that, mom returned back home and is doing very well. I wanted to share that story.

In this investigation, the authors performed a post-hoc safety analysis based on data from the multicenter randomized open-labeled controlled DisCoVeRy trial in hospitalized patients with COVID-19. They were specifically looking, as the title suggests, for cardiac adverse events. We read that cardiac adverse events were reported in 11.2% and 11.3% of the remdesivir patients. remdesivir versus control, basically the same, 11.2, 11.3.

Think about this from an anecdotal experience. Someone gets remdesivir, one in nine are going to have some kind of cardiac adverse event. Anecdotally, that's going to add up, "Oh, I know so-and-so, they got remdesivir, they had this cardiac issue." The other side is one in nine people that don't get remdesivir have a serious cardiac issue. Now, the majority of the issues were arrhythmias, 84.8%, 83.3%, so really no difference there. No significant association with remdesivir and any of these different cardiac adverse outcomes. You can really have that science-based, evidence-based discussion with regard to safety concerns, particularly if they bring up cardiac issues.

All right. Moving on to the late phase, and we've got a couple of papers here to talk about. I will recommend that those that missed our deep dive, our Long COVID evidence-based review in *TWiV* 1088 clinical update, I'll leave a link into that. We have the article, “Two-Year Longitudinal Study Reveals that Long COVID Symptoms Peak and Quality of Life Nadirs at 6-12 Months Postinfection,” recently published in *Open Forum Infectious Diseases*.

In this study at one-to-three, six, 12, 18, and 24 months post-COVID, 70 participants had orthostatic vital signs measured, provided blood, and completed surveys characterizing symptoms, quality of life, and return to pre-COVID-19 health and activities using a number of validated tools. I'll let people read all those validated tools. They report that during the study, 33% of participants experienced Long COVID had not returned to pre-COVID-19 health status and reported at least one symptom greater than 90 days post-infection. Eight percent had not returned to their pre-COVID-19 health status 24 months post-infection.

Now this is what I found interesting. Long COVID symptoms peaked six months post-COVID-19, frequently causing activity limitations. They did find here that having Long COVID was significantly associated with decreased quality of life in multiple domains. One of the things people ask when I throw out this number, I say, "Hey, 90% of people with Long COVID are going to get better." They say, "Well, where's that number?" Here we're basically seeing only 8% had not returned to their pre-COVID-19 health status 24 months post-infection. People get post-COVID. There's a peak about six months out. Then part of the natural history of disease is we often see people getting better.

We also have the article, and why is it here? The article, “Paxlovid Use is Associated with Lower Risk of Cardiovascular Diseases in COVID-19 Patients with Autoimmune Rheumatic Diseases: A Retrospective Cohort Study,” published in *BMC Medicine*. Paxlovid up front, how do we do after the fact?

Here the authors are using the TriNetX data from the US Collaborative Network to look at a total of 5,671,395 folks enrolled between January 1, 2010 and December 31, 2021. People diagnosed with COVID-19 were included in the cohort. We've got 238,142. The study population was divided into two groups based on whether or not they got Paxlovid. They did propensity score matching to generate two groups with matched baseline characteristics.

They found that Paxlovid use was associated with lower risk of cardiovascular complications. It has a ratio of 0.65, so about a 35% reduction, arrhythmia reduced by 19%, ischemic heart disease, other cardiac disorders, heart failure, deep vein thrombosis. Really compared with non-Paxlovid groups, the Paxlovid was really reducing the risk of these major adverse cardiac events. We're seeing mortality reduction. We're seeing reduction in admission. We're seeing reduction in ICU admissions, really across the whole board.

All right, I'm going to wrap us up with the - as we've been saying for a while, no one is safe until everyone is safe. As I was going through this quotation perhaps reminded me of, and perhaps others, of Rachel Carson's other famous quotation, “in nature, nothing exists alone.” We do not exist alone.

I want everyone to pause the recording right here. Go to parasiteswithoutborders.com and click on the ‘Donate’ button. We are doing our American Society of Tropical Medicine and Hygiene fundraiser, February, March, and April. We're in our final month. We're going to double those donations up to a maximum donation of $20,000. We are not there. We need your help. A portion of these funds will go to providing travel awards for two female-qualified students or early career investigators.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Bo writes, "I work at a public health lab and a sales rep told us about MeMed BV tests that can differentiate bacterial and viral infections. I'm wondering what you think of this test. Is it widely used clinically? How often does it give a definitive result?"

DG: Yes. BV, bacterial vaginosis, we've actually started having this introduced into clinical practice in our area. There's got to be a learning curve here. Part of the idea is it's going to help make this distinction. You're going to get a diagnosis. You're going to respond to that. Maybe after time, you're going to respond to the bacterial vaginosis and not just start throwing azoles or other unnecessary treatments at folks. I'll say it's in its early days of being introduced into clinical practice. Updates to follow.

VR: Bettina writes, "Hello, I'm a retired pediatrician, pediatric nephrologist, and general medical dilettante. I love immunology infectious disease. My question concerns the use of nasal rinses, normal saline, sodium bicarb, povidone-iodine in preventing/ameliorating COVID-19. I can perhaps understand the rationale in decreasing allergen burden in allergic rhinitis and asthma. I'm less certain about a situation where a virus has already invaded the nasal epithelium. Are you aware of any good-sized randomized clinical trials, controlled trials using nasal irrigation to decrease COVID disease?

Most of the positive reports I found were small and not well-controlled. Aside from the concern about introducing pathogens like Naegleria, I have a fundamental concern about washing away the body's immune cells, antibodies, mediators, and mucus. This is mainly an academic question, but it did come up because of a friend's illness.

DG: OK. No, it's more than academic, so I appreciate this. Yes, as you say, there are a few studies out there. Those get bandied about. The idea here is you're going to use - well, you're not going to use tap water I guess is what I want to point out. That's why this is not academic.

We actually talked about that on the latest *Puscast,* so people want to listen to that, where people use tap water, and tap water is - it's not distilled water. It's not pathogen-free. There have been a number of cases where people have actually introduced amoeba by using tap water and then using the neti pot and putting it up into these areas.

If you're going to go ahead and do this kind of irrigation, you want to use either actual normal saline, not like I added a little salt to some tap water. You want to use distilled water. You want to use clean pathogen-free rinses. It's small studies and I do wonder about the mechanism like how are you going to somehow wash this out of there and putting povidine-iodine up into those areas is also a little questionable.

VR: Lucas writes, "I'm in my mid-30s, generally good health. Every couple of years, I have been getting very strong rotational vertigo. Onset is usually sudden. It stays strong for a few days, then resolves and I'm back to normal. This time after ruling out central cause like stroke, I was diagnosed with a vestibular neuritis, an inflammation of the vestibular nerve likely due to some viral infection. My ENT doctor said it could be a respiratory virus, but often it is believed to be a dormant herpesvirus that gets reactivated.

If this were indeed caused by herpesvirus, which sounds like it, might a course of Shingrix help keep this vertigo at bay in the future. Would Shingrix offer any protection beyond varicella-zoster within the same subfamily?"

DG: This is an interesting question. I don't think I have any great evidence-based response to this. When people have this vertigo, we will try to differentiate it. Is it a central cause? Is it a peripheral cause? Is it an inflammation of the nerve, so a neuritis? Is it an issue with the otoliths? We often do these epilate procedures where we sort of spin a person, twisting the head. There's an interesting maneuver that can help with replacement of those.

If it's actually really a vestibular neuritis, then becomes the issue, are you someone who is just prone to develop this when you get viral infections? I don't know if this could be a dormant herpesvirus. I don't think we have any compelling evidence that would be the case or that something like Shingrix would really offer much.

VR: Marie writes, "I'm confused by my own recent first bout of COVID and my experience with Paxlovid, and I'm wondering if you have any insight. The minute I tested positive, doc gave me the option for Paxlovid." She took it. She is in her late 40s and healthy, completely vaccinated, and boosted.

"While on Paxlovid, my symptoms were very mild, low fever, some fatigue. I started testing negative on day five. After finishing Paxlovid, I remained negative for days five through eight. Days 9, I tested positive again and remained positive up until day 15. My symptoms were worse during the second week. I developed a sore throat with patches of white, which was cultured but not strep, upper respiratory congestion, fatigue, racing heart, high fever. Fortunately, the infection never moved into my lungs.

While I know this was technically a mild case, it was still the sickest I have ever been in my life. I was surprised COVID hit me so hard as I'm youngish with no real risk factors and recently boosted. If I were ever to contract COVID again, I'm wondering what I should do differently. One, was I contagious the entire time I tested positive? Two, was it wise to take Paxlovid?

Can I assume I would've been sicker if I hadn't? Or did taking it as a relatively healthy person give me a different experience? My doc thinks that maybe Paxlovid worked too well at knocking out most of the virus early and that what I experienced in week two was the actual COVID infection versus a cytokine storm. I'm not sure what to think." [chuckles]

DG: OK, well, we will tell you what to think or no, we'll share the science and then based on that science, hopefully you'll think through this. Let's go through a couple of things. You're in your 40s, you're healthy, you're active. It's one of the things we have to be careful about stepping beyond the science. We have good, compelling science that people who are at high risk of progressing to hospitalization, hypoxemia, death, that we reduce that substantially with Paxlovid.

There is this hope and some trends in that direction that maybe early antivirals are associated with symptom reduction. Fever clearing a little bit quicker, feeling better a little bit quicker, probably about the level of what we have with Tamiflu. Then a lot of people, "Can we prevent Long COVID and all these other sort of post-acute sequelae of COVID issues?" Remember, the science is really solid on the higher-risk folks. Someone over the age of 50 or someone with

comorbidities preventing progression from mild to moderate, which can be pretty miserable to severe disease, meaning you end up in the hospital, you need oxygen.

Now, what happened here? One, I'm not sure why you were testing so much, but we'll talk about that. The natural history of COVID is the first week feel like you've got some kind of a viral illness. Then the second week is when you get the cytokine storm. There is no correlation with those symptoms and the levels of virus. You're just as likely to have very low levels of virus, whether you have the symptoms or not.

That second week, just to make it really clear, that is not a viral rebound symptom complex. Symptoms during the second week are driven by an inflammatory response or driven by the cytokine storm. Just to say, it's not that the Paxlovid worked so well that you had the actual COVID infection during the second week. That second week, as you suggest, was the cytokine storm.

Now, it is interesting. Why did you feel so crummy during that second week? What's going to happen the next time? Certainly, people have had COVID now several times and they've had different experiences. I think in the early days, I had a gentleman who weathered his first episode of COVID at home. Six months later, second episode was actually in the hospital. We've had people who've gone the other way, where the first time was pretty bad and then other times have been more mild. Hard to know. Again, that's the science. Did you want any comments here, Vincent? There's just so much here.

VR: I just think it's interesting that the physician decided that there was a little virus left and that's what got her the second time. I don't know why -

DG: [laughs] It rebounded. That viral replication came back. I also want to point out, too, is that, as we've talked about several times, those positive antigen tests, they don't even correlate with the ability to culture virus after day 10. You've got some remnant antigen. The antigen is in cells. You're going to continue to have inflammation and shedding of cells. The antigen is going to be there for you to pick up on a test. There’s really no point to do these repeated tests.

VR: She also wanted to know if she hadn't taken Paxlovid, would she have felt worse? What do you think about that?

DG: On a population level, it seems, yes, we have this 90% reduction in the severity of the cytokine storm during week two. On a case-by-case basis, it's hard to know exactly, but probably, that's thinking of science and mechanism.

VR: All right. Finally, Alan writes, "My wife and I have kept up with all vaccinations. We mask in crowded environments. We have not contracted COVID yet. We have a plan in place with our first personal physician to receive Paxlovid. I have not seen or heard of any studies that determine if the immune response antibody development to COVID infection is muted in some way if Paxlovid is started immediately after testing positive. I would assume some level of immune response would be generated from the initial viral presence, as well as pieces of the virus that might remain following treatment. If so, has it been quantified?"

DG: Yes, this is a great question. I remember early on when we were doing monoclonal antibodies and people are like, "Oh, I don't know if I want to get the monoclonal antibody. Here's my chance to get that survivor immunity." Even where it's interesting, there was an organization Survivor Corps. Their whole goal was they were going to survive. These are people that survived that initial infection and now they're going to be immune and they were going to be around to help take care of everyone else. Then later, a lot of them ended up with Long COVID, needing help themselves.

This idea that, "Oh, here's my chance," and even some people on Twitter are like, "Oh, wait and don't start the Paxlovid for a while so you can get that immune response. You'll have protection the next time." You are going to go ahead and have a fine antibody response, a fine immune response. Go ahead. Start the Paxlovid. What we're really trying to diminish is that cytokine storm, that dysfunction during the second week. Then three months after the infection, if you want to boost, we can do that in a much safer manner with a vaccination rather than an untreated infection.

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

DG: Thank you. Everyone, be safe.

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