This Week in Virology

TWiV 982 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 982, recorded on February 9, 2023. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

DG: Hello, everyone.

VR: Tell me, Daniel, what's more frequent at the moment? Influenza RS or COVID?

DG: None of the above.

[chuckling]

DG: It is important, I would say, to not just, what am I seeing in my own backyard, but what's going on around the country? Because here in New York, we are really doing great when it comes to all of these, actually as a country. The flu, it peaked, it came down. RSV, peaked, came down. COVID, locally peaked and came down, but it's moving across the country. We got the COVID peak a little bit earlier. Still hearing problems across the country, but, boy, flu and RSV are really down everywhere.

VR: That's good.

DG: It is. Let's get right into it with the quotation. "The greatest friend of truth is Time, her greatest enemy is Prejudice, and her constant companion is Humility". This is by Charles Caleb Colton. I don't know Charles Caleb Colton very well, but I just love this quotation about how, it takes time to get the truth, and the more time goes by, the more things become clarified there. Right up front, I want to share the article, “Consistency of COVID-19 Trial Preprints with Published Reports and Impact for Decision Making: Retrospective Review*,”* published in *BMJ Medicine*.

Our listeners are aware that during the pandemic, we often would discuss preprints and even discuss how reviewing preprints should perhaps be part of graduate and medical

education. Well, here in this paper, after reviewing 365 trials, 101 available as preprints, the authors reported that they found no compelling evidence to indicate that preprints provided results that are inconsistent, in general, with published papers. They suggest about 3% of the time they're misleading.

They also pointed out, I think this is important, that preprints remain the only source of findings of many trials for several months. I'm going to agree with the comment, an unsuitable length of time in a health emergency that is not conducive to treating patients with timely evidence. Few of my comments, my editorial, I do worry about preprints. Actually, I had never posted a preprint prior to 2020. I've actually always found that despite the delays, my publications are usually improved by the peer review process. The actual data doesn't change. In a time of emergency, it does seem to make sense to have a faster process.

Here I'll just complain. I currently have two papers out for review and it's been months. [chuckles] The side we often do not discuss is the challenge, actually, of getting reviewers to respond promptly and reasonably so that this process does not take as many months, as many revisions. There's a problem here. This is currently an unpaid process for reviewers and just considered part of our academic duty.

VR: That's the problem, Daniel, because people do it when they can and it can take many weeks. That's a problem and I don't know how to get around it.

DG: I think if it was something where you were given this and we're going to - It wouldn't have to be a lot like, "Here's $20 an hour. If you get this in by tonight, here's a $100." [chuckling] I don't know. This is my paradigm for the future, but it just seems this whole concept of an unpaid process for just a growing number of papers, particularly during the public health emergency, it was a lot of money being thrown around. Maybe some of it could have been focused on timely reviews. Even the recovery trial.

Great data there. How many months between the posting of the preprint before we finally saw something? We'll talk a little bit later about a paper that just came out in *The New England Journal of Medicine* and that data was out for a while.

VR: Most journals are not wanting for money, and so they could do that. I just think if someone's busy, it's not going to make a difference if they get paid or not. What do I know?

DG: I don't know. RSV influenza, as we mentioned, things are better for the moment with RSV and flu. There was an interesting article that addresses the concept of imprinting with flu vaccines. "The Negative Effect of Preexisting Immunity on Influenza Vaccine Responses Transcends the Impact of Vaccine Formulation Type and Vaccination History," published in *JID*.

I had some issues with the article such as when in the first sentence they say, "Sterilizing immunity to influenza virus primarily lies on neutralizing hemagglutinin (HA) specific antibodies that block infection of host cells. The most common strategy to induce this protection for humans is intramuscular vaccination typically involving inactivated influenza vaccines derived from viruses anticipated to match circulating strains."

It's a somewhat complex paper, but the data does seem to support that prior vaccination is associated with a less robust response to the next vaccination in terms of T cells and antibodies. Now, I'm going to talk about another paper when we get to COVID vaccines. I want people to keep in mind this finding as I discuss the importance of prior vaccination enhancing response to infection, which might, I'm going to say, be more important than response to your next vaccine.

The article, "Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in Farmed Minks, Spain, October 2022." I guess this falls under influenza, different type of influenza. This was published as a rapid communication in *Eurosurveillance*. Lots of concern regarding avian flu and it's being found in mammals and a number of mammals that have died recently.

In this report, we hear that during the first week of October 2022, an acute increase in the mortality rate was identified at an American mink farm in Galicia, Spain. The farm clinical veterinarian collected oral pharyngeal swabs initially from two affected animals. The samples analyzed at the central veterinary laboratory actually tested negative for SARS-CoV-2 but positive for H5N1. Post-mortem examination revealed hemorrhagic pneumonia or red hepatization of the lungs as the most notable lesions. The mortality rate increased on a weekly basis until reaching a peak about the mid-end of October.

On the 18th and 26th of October, additional sampling was implemented across distinct areas of the farm. They say, "Prioritizing the barns presenting the highest daily mortality. The presence of H5N1 virus was confirmed with," I fixed this, a little, "High RNA copy number [chuckles] based upon quantification cycle or Cq values in oropharyngeal rectal swabs and lung samples." They went ahead with culling activity, as they say. About 52,000 mink were culled. The mink farm had a staff of 12 workers, 11 of whom had been in contact with the animals and were also involved in the culling activities.

Basically, all those swabs were negative for the avian influenza virus. Dare I say, now it gets interesting. I think it gets interesting. They identified an amino acid change. I corrected this too. T271A. A threonine to alanine at position 271 in the PB2 gene. Same change, they report being present in the avian-like PB2 gene of the 2009 pandemic swine-origin influenza. The concern here is that this may be associated with human tropism.

As I go forward, because, Vincent, I'm going to ask you to jump in on this, by the way. Is H5N1 the next pandemic already giving us notice? Not sure how many of our listeners subscribe to *CIDRAP* out of the University of Minnesota. You can actually go there, click, put in your email, and subscribe. I'm going to encourage you to do that.

February 7, we had the announcement, "Peru Confirms H5N1 Avian Flu in Marine Mammals, Part of Southward Spread." We hear that in Peru they found at least 585 sea lions and 55,000 wild birds dead in several of the country's coastal nature preserves. They say likely due to avian flu. They've confirmed avian flu H5N1 in sea lions, in a dolphin, and then they actually had a lion in a zoo in central Peru with H5N1 identified as likely cause of death.

To expand this, United States so far has reported 110 detections in mammalian species, bears, foxes, skunks, possums, raccoons, seals, and a recent report of three grizzly bears in

Montana. The H5N1 clade circulating in birds, poultry, and an increasing number of mammals has that amino acid change of which we spoke.

Seven human H5N1 infections had been reported all involving people who had close contact with poultry. Some illnesses were mild, but some were severe or fatal. So far, we're not seeing any human-to-human transmission but we did, from that mink report, suggested basically, mink-to-mink, mammal-to-mammal transmission. Comments, thoughts, Vincent, hitting the media hard place lately.

VR: Getting into mammals is a big deal, especially transmitting among the mink. That's concerning. It's also pathogenic. Now, we should point out that this virus has been circulating for over 50 years and has not entered humans in a transmissible way. There have been 400 or 500 human deaths, I think out of 800 documented human infections. Hasn't acquired transmissibility. Now, the past year, we've seen a lot of activity in birds.

More replication than we've seen before. As you know, when a virus replicates, it sustains mutations and so there's always the chance that the right combination could arise to make it transmissible. Who knows? No one can predict but the good news is we do have an H5N1 vaccine that could be used in the case of some human spread.

DG: That's encouraging. The one side which I think is our listeners' call to arms right there, there are a couple of troubling folks who are very worried about us doing research on pathogens such as this. I actually have to say, I think it's really important that we pay attention and do research on pathogens such as this to understand what is it that allows it to get into mammals, what allows it to transmit between mammals. Head in the sand is not a good approach at this moment.

All right, measles, just some closure on the measles outbreak in Central Ohio after a total of 85 cases, with 36 children requiring hospitalization for this vaccine-preventable illness. This has been declared over. There are a few pending tests, but per the CDC, this is officially over with no new cases reported for 42 days. Two incubation periods of the measles virus. By the way, none of these children were fully vaccinated.

COVID. A couple of things right up front. I say two, but actually, it's three. One, how good are we at predicting the future? People may have caught the most recent update of the CDC page *COVID-19 Forecasts: Hospitalizations*. Let me just read, "This week's national ensemble predicts that the number of new daily confirmed COVID-19 hospital admissions will remain stable or have an uncertain trend, with 700 to 6,900 new confirmed COVID-19 hospital admissions likely reported on February 24, 2023."

I love that. It could be stable or it could just do whatever [chuckles] it could do. It's really not much of a prediction. I feel like I'm Yogi Berra here, "If you come to a fork in the road, take it." With this wide range, I'm going to be a bit more optimistic. I anticipate we will see, based on prior years and prior experience with respiratory pathogens, that things actually are going to start to improve and our daily deaths probably dropping from this plateau that's being reported at 500 per day.

There's always this pattern of hospitalizations then deaths. As hospitalizations have started to drop, I'm thinking that deaths will start to drop going into the future. You've got me

quoted here so you'll be able to go back and tell me whether or not I was right. To the variants, I thought this was interesting. I got some emotional correspondence, as of late, and it's this question is the variant, should they have nicknames such as ones like the Kraken, Hydra, et cetera? Where does all this come from? [chuckles]

I thought our listeners might find it interesting to get the perspective on this from T. Ryan Gregory, who is a professor in the Department of Integrative Biology at the University of Guelph, Ontario, Canada. For starters, don't send him or me hate mail, please, but he and a few others feel that the current terminology is too technical and impenetrable for many. He is part of a chat group of genomic researchers. After the first sub-variant monster nickname Centaurus, father of the half-man half-horse race of Centaurus took off on social media, they started proposing similar nicknames whenever they seemed, as they say, useful with no formal process.

Centaurus is also a constellation but monsters became the style, some from Greek myths, some from Norse. Dr. Gregory says that they are not chosen to be scary especially [chuckles] or to cause alarm, but rather to be distinct. Beyond that, it's pretty arbitrary. Others include the famous human-headed winged lion, the Sphinx, that's BA.5.1, the bullheaded human-bodied Minotaur BF.7, Cerberus, that's BQ.1.1, the three-headed dog that guards the gates of hell.

I have to say, I understand the concept that these are just supposed to be a better way for you to remember but naming variants after monsters does suggest to me some degree of menace. [chuckles] Vincent, I see you shaking your head.

VR: I don't understand how alpha and delta and gamma and Omicron are impenetrable. I don't understand that. I understand the sub-variants might be, but since when do they have to be household words? Most people don't know how to deal with all these variants. I just don't think you need to do this. I agree with you, monsters-- Who's going to remember which monster is which one? This is a problem that doesn't need solving.

DG: [chuckles] Just so people understand the background there. Three, excess mortality, are we doing as well with COVID as we think? I know there are growing discussions around this topic. I'm going to leave a link into the COVID data tracker weekly review by the CDC, that links to CDC data, including cases, hospitalization, deaths, wastewater monitoring, other information. Very interesting thing is that excess deaths do track very closely with rises in COVID deaths even when we are not in surge conditions, every time that COVID deaths go up the excess deaths go up.

One of the things that if you go and look at this, you'll notice is early on when excess deaths went up, COVID deaths, they track pretty well. We're now seeing about twice the excess deaths that we would expect this time of year, but only half of them are attributed to COVID. What are those other 50% of these excess deaths? This could be a challenge going forward. How reliable is any of our data about COVID cases, COVID deaths?

VR: Daniel, there could be COVID-related deaths, but it doesn't end up on the death certificate. It could be psychological issues, suicide, people not paying attention and getting

in car accidents, all that sort of thing, all caused by the pandemic stress, but not something you would say is COVID caused.

DG: I think that's important. Not everyone who dies, dies of COVID, even if COVID is circulating, and not everyone necessarily dies acutely of COVID. In some cases, I think we're aware of with other situations, a recent article about people that end up in the hospital with bacteremic pneumococcal pneumonia, chunk of those people will have a myocardial infarction in the hospital and a relationship there so.

Children COVID and other vulnerable populations, I just got to nod my head to this. I know it's pretty difficult this whole idea that 90% of the people that have died of COVID are over 65. They're going to be dying pretty soon anyway. If you're over 65 if you care about people who are over 65, then that's not so reassuring. It moves us right into the have a plan, remember masks, remember ventilation, and other ways of keeping yourself safe.

VR: Are you saying I'm going to die soon? I'm over 65.

DG: You know, Vincent, if you die - [chuckles] I'm not ready to write you off. That's what I just want to say to you, everyone else over 65, everyone out there with a health problem, we're all going to die. What is the greatest risk factor for death? It's being born, but we're all going to die. It's just a question of when and how and let's try to make that when and how something farther off in the distance.

VR: We need to make a plan for MicrobeTV so that keeps going.

[chuckling]

DG: Yes, particularly as we have this conversation. [chuckles] One of the best ways, COVID active vaccination. First, I'm going to plug for the *TWiV* special, *One COVID Vaccine for Them All*. Reminds me of a Tolkien thing with Paul Offit. I think it is much better to give Paul Offit a chance to explain his views and for people to listen to this than just to rely on articles where there are a couple of piecemeal quotes and you're trying to figure out how much of that was Paul Offit and how much of that was the science reporter. Several people, including John Mascola, sent me this next preprint.

Speaking of preprints, “Prior Vaccination Enhances Immune Responses During SARS-COVID-2 Breakthrough Infection with Early Activation of Memory T cells Followed by Production of Potent Neutralizing Antibodies.” Posted as a preprint. That's it. It's all in the title. My thought is that we are actually much more interested, as we talked about before, in how a vaccine prepares us for infection rather than the next vaccination.

In this investigation, the authors share data that show, "Heightened Spike-specific responses during infection of vaccinated compared to unvaccinated individuals. Spike-specific CD4 T cells and plasmablasts expanded and CD8 T cells were robustly activated during the first week. In contrast, memory B cell activation, neutralizing antibody production, and primary responses to non-Spike antigens occurred during the second week." As the authors say, "These data demonstrate the functionality of vaccine-primed immune memory and highlight memory T cells as rapid responders during SARS-CoV-2 infection."

This is an incredibly dense 40-plus pages. I've spent lots of time - I think I'm losing my vision because there's so much packed in these figures. I feel like I need to put them on a big screen and walk through each panel. Figure 6 is really great for pulling it all together. Figure 6, "Rapid memory T cell activation and pre-existing antibodies represent the early systemic adaptive immune responses during SARS-CoV-2 breakthrough infection."

It's really nice. What they've got is all the different responses in different colors, days post-symptom onset. You could see this really rapid Spike-positive CD4 cells, Spike positive CD8 cell activation. You really see the time course of the response. Beautiful paper, by the way.

VR: Preprint.

DG: Yes, beautiful preprint.

[chuckling]

DG: There's a 3.3% chance this is all just nonsense. I don't think so. Now I will go to a paper that reminds me of the early days, right? We didn't have a COVID vaccine, so let's just give them a tuberculosis vaccine. The article, “Bacillus Calmette-Guerin, (BCG) Vaccine for Prevention of COVID-19 and Other Respiratory Tract Infections in Older Adults with Comorbidities: A Randomized Controlled Trial,” published in *CMI*. Very simply, in this trial that looked at over 6,000 participants, BCG vaccination did not protect older adults with comorbidities against COVID-19 hospitalization or clinically relevant respiratory tract infections.

I did want to mention the article about a rare, but it looks like there may be an association here, “Incidence of Chronic Spontaneous Urticaria Following Receipt of the COVID-19 Vaccine Booster in Switzerland,” published in *JAMA Network Open*. These are results of an investigation in Switzerland looking at whether an association exists between COVID-19 vaccines and new-onset chronic spontaneous urticaria. I love the methods section. I'll read, "16 local allergists helped identify eligible patients who were then contacted through the Lausanne University Hospital. Patients were sent an online questionnaire link between April 14 and August 8, 2022.

Then, using this data, the investigators calculated the crude incidence risk ratio of this chronic spontaneous urticaria per 100,000 persons having received a first booster dose, and estimated the relative risk after Moderna versus after Pfizer. The median time between vaccination and onset was about 8 to 12 days in one of the cohorts, about 9 to 13 in the second cohort. Most of the time, actually, this was associated with the Moderna vaccine. They estimated an overall crude incidence rate per 100,000 persons with a booster at 24 and 19 in the two cohorts and actually suggesting this was 20 to 16 full tire after Moderna than it was with the Pfizer. I'll share a case this week.

We have seen a few of these folks with this. You vaccinate billions of people and you're going to see stuff. This was a gentleman in his 30s, had a number of risk factors, went ahead, got his Pfizer shot, developed urticaria probably might have been more likely with Moderna, but this happened. He was very interested in getting protection because he was high risk. His urticaria is something - It is occasionally, he has what we call dermatographia where he scratches himself and you could see the lines, well-controlled antihistamines. Not

a severe case. When ahead, got the J&J vaccine, tolerated that well. Just January, got the Novavax vaccine, tolerated that well without any issues.

The article, “Relationship Between Immune Response to SARS-CoV2 Vaccines and Development of Breakthrough Infection in Solid Organ Transplant Recipients: The CONTRAST Cohort,” published in *CID*. I took this really as a suggestion that if a patient failed to show a robust antibody response to vaccine that correlate with a higher risk of a bad outcome. Not sure we're seeing correlates of immunity here. We're just seeing a group that doesn't always respond well.

This goes along with the line, if you're not seeing much after a third shot, maybe we do a fourth shot trying to get those antibodies elevated. It does seem to add to that, that getting those antibodies elevated or not are associated with differential risks on a group population level.

Good or bad news, depending on how you look on this but an update in the *MMWR*, “COVID-19 Mortality and Progress Toward Vaccinating Older Adults — World Health Organization, Worldwide, 2020–2022.” Here they're actually estimating the percent coverage with a completed COVID-19 vaccination series for the overall population and for older adults from the reporting countries through the WHO electronic Joint Reporting Form.

They're estimating this at about 76%, with it being lower in lower-middle-income countries. They're reporting a low of 21% in the low-income countries, about 50% to 51% in the upper-middle-income, lower-middle-income, and then 74% in high-income countries. Really, unfortunately, corresponding with areas where we were seeing a ratio of excess COVID-19 mortality. [silence]

Moving on. We've got some new stuff here, some interesting stuff in the COVID early viral, upper respiratory non-hypoxic phase, right? This is, you've done everything you could, but now you have tested positive, starting to feel, got some symptoms. You've actually got the disease, not just positive PCR test.

I will start this section with the article, “Early Treatment with Pegylated Interferon Lambda for Covid-19,” published in *The New England Journal of Medicine*. Now, these results have been out there for a while, by the way, speaking of preprints and such, but these are the results of the TOGETHER trial, "A randomized, controlled, adaptive platform trial involving predominantly vaccinated adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brazil and Canada. Outpatients who presented with an acute clinical condition consistent with Covid-19 within seven days after the onset of symptoms received either pegylated interferon lambda -"

It's actually kind of neat. There are these pre-filled single subcutaneous injection, 0.4 milliliters containing 180 micrograms or placebo. The primary composite outcome was hospitalization or transfer to a tertiary hospital or an emergency department visit observation greater than six hours. A real visit due to COVID-19 within 28 days after randomization. A total of 933 patients were assigned to receive the pegylated interferon lambda. Of note, it's lambda, not just any interferon, and 1,018 were assigned to receive placebo.

Overall, I think this is important, 83% of the patients had been vaccinated; 2.7% in the interferon group had a primary outcome event as compared with 5.6% in the placebo group, a reduction in progression of 51%. Incidence of adverse events was similar in the two groups and not really getting an adverse event signal. Among patients who received the interferon within three days after symptom onset, this reduction was actually 65%.

A couple of things to comment for us here in the U.S., this trial was done in Brazil and Canada and was initiated and run by academic researchers rather than the company itself. For this to pass the FDA, a large trial with enrollment in the U.S. would likely be required. What I like here, I actually find this an interesting approach, is this is really just turning on the body's broad antiviral response. This could be a general antiviral boost that looks in the study to be effective and safe. It's like echinacea that actually works. [chuckles] Any comments there, Vincent?

VR: Daniel, it's a single injection so does that get around the side effects of interferon that we see with Hep C patients in the old days when we would treat them for long periods of time?

DG: That's what I was looking here for is, if you get this shot because when we used to treat patients for Hepatitis C with these interferon-containing regimens, you feel like you have the flu for eight weeks. It's miserable, it really was miserable. It's interesting because here, it's I guess it gets into the mix. You've got a viral syndrome. You feel like you've got a viral syndrome. You can't necessarily tell whether you got to interferon or not as far as adverse events, but it is helping boost your immune system to properly target the virus, it seems. I also like the fact that it's just a single shot.

VR: Really, the 51% to 65% reduction in hospitalization, it's not great, it's OK.

DG: It's interesting. I should say, it's not as good as 88% to 89% we saw in the EPIC-HR for the Paxlovid in the unvaccinated. It probably as not quite as good as we're getting with Paxlovid in the vaccinated and that was part of the discussion here, was these are vaccinated individuals. They've already had that 90% reduction, and now this is another 65% reduction on top of that. I don't really see why you couldn't use this with Paxlovid, boost the immune response, and treat with antiviral, thinking, particularly of our elderly folks, elderly-elderly folks, our immunocompromised people, et cetera.

VR: We got letters from some people who don't like elderly-elderly, but we didn't make it up. That was Rochelle Walensky, right?

DG: It's interesting, elderly is different in different countries. I had a partner who came from the UK and they use elderly at a different - You may need to move to the country that considers elderly some older age.

Paxlovid, now, I think this is important, this is our informing. Last week, we mentioned about the updated EUA for Paxlovid, even mused a bit how it might be interpreted.

I just want to comment that EUA was updated to remove the requirement for a positive viral test, but remains as follows. This is really important because, boy, I got a lot of calls this week. The U.S. FDA has issued an EUA for the emergency use of the approved product

Paxlovid for the treatment of adults and pediatric patients 12 years of age and older with a current diagnosis of mild to moderate COVID, who are at high risk of progression.

This really didn't say, "Oh, just start giving it to people to keep around." It just said, "Let's take this scenario, the scenario where the husband has COVID, it's confirmed, now, it's five days later, the wife's coughing, has a fever, doesn't feel well." Tells you she doesn't have any of those rapid tests around. You make the clinical diagnosis of COVID. You could put this person on Paxlovid.

Previous to this, you were really supposed to say, "We got to document this. We got to get a positive antigen. We've got to get a PCR, and I can only start once I get that." Doesn't really say, just give out Paxlovid to anyone who wants it because they should maybe need it in the future, but you're allowed to make that clinical diagnosis without having to confirm it.

Two, remdesivir for those that can get it and then, to say last and least, molnupiravir. When we get to that second week, this is a biphasic disease, the early inflammatory lower respiratory hypoxic phase. This is when our options have really diminished. I do that analogy of if you don't treat during that first week, if you wait and see, this is like waiting to see in a patient with hypertension and then starting the medicine after the stroke.

Let's not start treatment after they have progressed to the early inflammatory phase. We can do a little bit with steroids at the time in the patients, anticoagulation, pulmonary support, maybe remdesivir early enough, maybe some immune modulation with tocilizumab.

Moving to the late phase, PASC Long COVID, we're going to wrap it up here and go to questions. I just want to say this is still very much in the preliminary stage. I thought this was interesting so I wanted to discuss the article, "Long-term High-dose Immunoglobulin Successfully Treats Long COVID Patients with Pulmonary, Neurologic, and Cardiologic Symptoms," published in *Frontiers in Immunology*.

This is a case series. I want to point out, it's not a randomized control trial. Here, the authors describe nine patients suffering from Long COVID for a range of, it could be 101 out to 547 days. Ultimately, six were treated with high-dose IVIG, 0.5 grams per kilogram IVIG, every two weeks for a three-month trial. If clinical benefit was observed at that time, they would continue.

I do want to point out, this was not without risk. Even in the small group of six people, one patient required a port which became infected with Mycobacterium fortuitum. The port was removed, she was admitted to the hospital with an enlarging wound and fever, required IV antibiotics, oral levofloxacin, for an additional eight weeks. They did report improvement, and perhaps this is enough preliminary evidence to warrant an RCT.

VR: Daniel, this is just IVIG. It's not necessarily have SARS-CoV-2 antibodies in it, right?

DG: Yes, it's just IVIG. The idea here is that one of the potential causes of Long COVID are a number of autoantibodies, the number of antibodies that are being generated, maybe they're triggering vasculitis or joint inflammation or cognitive impairment. The idea with

IVIG is you're basically going to target those antibodies, really the FC portion, a plasmapheresis-type approach. so interesting stuff.

I will say, no one is safe until everyone is safe. Like we demonstrated, here we are three years into the pandemic, and a lot of these low-income countries, we have not done well with vaccines. I know folks here in some of the high-income countries are done with the pandemic, but a lot of these folks have not even had access to their vaccines. No one is safe until everyone is safe.

Now's a good time to pause, go to parasiteswithoutborders.com, click on that 'Donate' button. Thank you for everyone. We reached our goal for the MicrobeTV fundraiser there, Vincent. Thank you to all our listeners. We are now in the middle of our ASTMH fundraiser. February, March, and April, donations made to Parasites Without Borders will be matched and doubled up to a potential maximum donation of $30,000 from PWB to ASTMH.

VR: Time for your questions for Daniel. You can send them to daniel@microbe.tv. Justin writes, "In episode 978, you answered the question about stopping other medications as you start Paxlovid. Seems like a better question is when to restart medications that may interact with Paxlovid, as Paxlovid inhibits metabolism of multiple other medications. How long does the effect last? In other words, if a medication is restarted for a patient before the Paxlovid has cleared from their system, could it cause a rise to toxic levels?"

DG: This is a great question. This is an important question and we talked about - Let's say you're taking Lipitor or Atorvastatin and then you find that you have COVID, you start the Paxlovid, and also saying you stopped that statin, don't take any more, you finish your Paxlovid. The current recommendation is, add five more days. You're going to be stopping that Lipitor for a total of 10 days.

It's a little interesting. Why 10? Why not nine? Why not 11? It probably has to do with the number of these things on my hands. The current recommendation is for the five days while you're on the medicine and another five days afterwards, and then physicians, pharmacists, you could think about the potential interactions and use some judgment but that's the current recommendation. Paxlovid is five days, another five days, and then you restart those medicines that you stopped.

VR: Kimona writes, "Hoping you can chime in on guidance about COVID-positive elderly patients with underlying COPD and baseline oxygen Sats 90% to 94% presenting with 'relative' hypoxia. We see a fair share of these patients and our ED providers will often give an initial dose of IV SOLU-MEDROL, 60 mgs to 125 mgs as if treating a COPD exacerbation, despite current guidelines advising lower doses As you recently reviewed, studies using higher dose corticosteroids and COVID illness had worse outcomes than the standard dosing of Dex 6 milligrams daily.

First, it's not always clear what phase of COVID illness they're in. Early, viral versus later inflammatory based on their vague history telling symptoms of maybe just feeling a bit weak for a while and/or lack of home testing. Assuming that you have committed to using some steroid due to their COPD, should we be trying to keep this within the dexa 6 mg dosing range, which my calculations would be prednisone 35 migs to 40 migs maxed.

I feel like recent COPD guidelines have supported lower prednisone dosing regardless." Why don't you take that one first, Daniel?

[chuckling]

DG: There's a lot here. For our listeners, SOLU-MEDROL is often when a patient comes in, they've got chronic obstructive pulmonary disease. Maybe they were a smoker or some other damage to their lungs. A lot of times they'll present to the emergency room they'll be wheezing, they'll be having trouble getting air in and out. A couple of knee-jerk things that will happen in an emergency room, one is these 125-milligram ampules vials of SOLU-MEDROL get pushed in. They might get a nebulizer as well. The challenge here is, what can trigger these exacerbations in someone with COPD viruses? Actually, probably quite common.

When someone is coming in with that being triggered by COVID, all the right points were brought up here, we have found that there's a sweet spot when it comes to the dosing of the steroids. Six milligrams dexamethasone, that's about 35 milligrams, 40 milligrams of prednisone. You're right on with this, 125 milligrams of SOLU-MEDROL. That may not actually be the right dose for some of the COPD exacerbation, as mentioned. That may actually be excessive, as we've learned more. The other you brought, which is really critical is, are we in that first week or are we in that second week?

If you're in that first week, you actually can do harm. Why bother to vaccinate someone if you're going to shut down their immune system when they're trying to fight off the virus? Trying to avoid steroids if possible but this is just the reality. This is an art. This is not a science. We don't have any great rapid test that's going to tell you we're on day four. You get that history, we say that history is the most important but the least reliable. If you're in that first week, if at all possible, do you really need those steroids? Are they really tight? Are they really wheezing? Can you treat that just with bronchodilators and nebulizers?

Once you get into that second week, the sweet spot for the steroids is that about 6 milligrams a day of dexamethasone that 35 milligrams, 40 milligrams a day of prednisone. I think you're bringing up a lot of really good points here. Hopefully, a bunch of ER docs are listening and will start thinking a little bit more about these decisions.

VR: "Second, I do worry that we are also doing harm by even giving corticosteroids, especially if the patient is likely in the early viral phase, despite starting antivirals. I fear that very few providers dare avoid the steroids altogether due to the COPD history. I'm not sure what my question really is, but I appreciate any commentary you can give to this conundrum."

DG: It is a challenge and I think that's my advice. Start with the nebulizer. Start to see if you can get them breathing better. See if you really need those steroids when you're not sure where you are. The other is going to be a change in that oxygen level. Some folks will come in and they're chronically on two or three liters of oxygen. Now, if that then bumps up to four or five, then you're going to say maybe I am getting into that second week. You may want to start with a nebulizer first, try to sort this out.

This is a challenge. This is why we go to medical school. This is why you should take a deep breath and think about and not just be following an algorithm but trying to pick what's the best for that individual patient.

VR: Finally, a commentary about remdesivir IV treatment for those patients for whom Paxlovid may not be appropriate, "I work at a small critical access hospital and have the benefit of reviewing some of the cost analysis of medications and reimbursements. Both Medicare and Medicaid and many commercial insurances reimburse less than what our purchasing price is now that remdesivir is no longer provided by the government state under EUA, et cetera.

Likewise, for tocilizumab, which is ridiculously expensive and we have therefore chosen not to bring on board. In the end, our mission is to do what is best for the patient but there are yet more reasons why rural healthcare institutions are struggling to stay alive."

DG: This is tough. My wife and I were talking about this a little bit earlier about we have so many challenges in our country with regard to healthcare, things like this. I remember in Colorado when I was talking to John Bender, actually one of the other docs in town, about how some of the vaccines, physicians were losing money on vaccines and he was able to set up some system where the state would actually provide the vaccines. Vaccines were financially a loser for some of these family practice in pediatric populations.

This is a huge challenge when the medicine that could make a difference is actually something that your organization is going to lose money trying to provide. A lot of these rural hospitals are struggling financially. The other is actually a lot of these areas, we've talked about 80% of counties in the United States don't have a single infectious disease doctor. For the last few years, a number of us have been reaching out trying to be helpful crossing state lines with telemedicine, but when the public health emergency ends, what happens? These counties no longer have the ability for us to reach out.

I will point out, infectious disease doctors, we're not raking it in. This isn't a huge cost but it is great for people to actually have access to someone who's expert in the area. A lot of challenges. Maybe this is the time to be writing letters to those congressmen, congresswomen. We need to make some changes. Healthcare is here to hopefully help us be healthier, help us do a better job with public and individual health.

VR: Laurie writes three questions. First, "I work in a pediatric office in San Francisco. We're considering moving from the Abbott ID NOW to the Cepheid Xpert Xpress so we don't need to stick so many swabs up the little ones' noses. One concern I have is that the Cepheid literature states it has 100% PPA and 100% NPV. Is that possible? Seems suspect. If we just want to do COVID testing, can we trust the ID NOW in this current viral environment? The studies I've seen seem already out of date by the time they're published. Any advice?"

DG: Nothing is 100%, not even taxes, right? Al Capone taught us that, only death. Both are great approaches. The Cepheid is really nice. I don't know how many people are familiar with this. The Cepheid has these little cartridges and you just pop them in and then you get your result, something we originally were using for tuberculosis. The Abbott ID NOW is also a very sensitive and very good system. Again, this is going to be one of those operational

challenges where you look at the options and try to figure out what's best for you. I think either one is a fine option for making the diagnosis.

VR: Second, "In regards to the question, last week about the perceived punishment for COVID testing, for the little ones who are positive and their parents, it's especially punitive. They can't wear a well-fitting mask so they're home for 10 days. I'm not sure even a 12-year-old can wear a well-fitting mask, especially at lunchtime. If there are multiple little kids in the same house and there's ongoing exposure, the parents may have to stay home for 20 days or more. This seems like this should change. Any advice or comments on this?"

DG: This is obviously a hot-button issue. People can probably guess. You've got a situation like this on one side, and then the other people on the other side who are immunocompromised, who should they get COVID are at high risk of a bad outcome. They're really saying, "Oh, my gosh, really? Is it so inconvenient for your child to miss this educational opportunity? I may die."

This is really tough. This is where public health and politics and all kinds of things meet. I'm glad I'm not going to be the one who has to make this decision but I do understand, in our culture, the current advice where you end up missing 10, 20 days of work to take care of your children, not something that in our culture is necessarily going to continue.

VR: The third is a request, "I'm neither a PhD nor a surgeon, I'm a busy pediatrician. I listen to these podcasts while driving with a dozen things in my head and I would love to see figures, but that would be dangerous. Sometimes I blink and I miss something important. Would you mind giving us the 10-second take-home point at the end of each sub-segment?"

DG: That seems like a good idea. I certainly don't want you to blink look down and then miss the fact that that car in front of you has stopped. It's pretty reasonable. Just do a quick, we'll throw a quick 10, 15-second recap. I will say, listen to the whole episode because the purpose here is not for us just to give you the soundbite but to try to go into the science, to show you why we're suggesting certain things. I never want the clinical update to be my opinions. I want them to be me sharing the science so that everyone can make informed decisions.

VR: One quick one from Evan, "It's been reported that either severe or mild case of COVID can lower IQ. Has this been substantiated? Is there an additive diminishment with repeated infection? Does the patient recover IQ?"

DG: There are certain percent of individuals that actually have cognitive impairment and this can be ongoing. If you include them in the mix, then I'm going to say yes but then becomes really a separate question, what about those folks that had a mild case that didn't develop long COVID which, unfortunately, millions of folks here in the US alone? What about the rest of the folks, do they really lose a couple of IQ points? I'm not sure about that.

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

DG: Thank you, and everyone, be safe.

[music]