This Week in Virology

TWiV 951 Clinical Update

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Guest: Daniel Griffin

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

VR: From ASTM 2022, this is *TWiV*, *This Week in Virology*, Episode 951, recorded on November 2, 2022. I'm Vincent Racaniello and you're listening to the podcast all about viruses. Joining me today here in Seattle, Washington, Daniel Griffin.

Daniel Griffin: Hello everyone, and I was going to say, Vincent, don't forget the H, the ASTM and H, the hygiene, all that hand washing.

VR: Yes, I was going to ask you why is there hygiene still in the name of anything, but it's all about washing your hands, right?

DG: All right.

VR: Hygiene is an old word, right?

DG: Yes, it is. It isn't something we use all the time. We don't say, "Barnaby go in the bathroom and make sure you attend to your hygiene."

VR: Yes, right, right, right. We thought since we were here, we actually had a Parasites Without Borders booth, which was well visited by many people. We thought we'd do some podcasts, and we did a *TWiV* today and now this *TWiV* clinical update, and this is a first for ASTMH meeting, right? Having a podcast?

DG: I think so. James, is it the first? Is this the first time you're doing a podcast at one of the AS-? Yes, it is. We just got verification from James, our A/V guy.

VR: We're being pioneers. We're breaking new ground, and we think that podcasts should be at every science meeting because it's a great way to communicate.

DG: I think so as well. Hopefully, we'll see how well this goes.

VR: All right, with that, let's dive right in.

DG: I will start with my quotation. "It will be enough for me, however, if these words of mine are judged useful by those who want to understand clearly the events which happened in

the past and which human nature being what it is, will at some time or other, and in much the same ways, be repeated in the future. My work is not a piece of writing designed to meet the taste of an immediate public, but was done to last forever," and that's Thucydides, *The History of the Peloponnesian War.*

And right into polio. It's really convenient that, Vincent, you and I are doing this, polio expert here. More on polio. We got the *MMWR* early release, "Wastewater Testing and Detection of Poliovirus Type 2, Genetically Linked to Virus Isolated from a Paralytic Polio Case - New York, March 9 - October 11, 2022." This is going to bring people up to speed on where we are. In July 2022, a case of paralytic poliomyelitis resulting from infection with vaccine-derived VDPV type 2 was confirmed in an unvaccinated adult resident of Rockland County, New York. This report gives more information on what has been reported here and there in the media.

As per this report, we learned that one county, Nassau, that's actually where I hail from, had only a single detection and therefore was not considered to have evidence of a transmission event. However, three counties, Orange, Rockland, and Sullivan had repeated detections over the course of months in one or more, and this is a new word for me, sewer sheds, suggesting some level of community transmission in these areas. Only a single large-volume wastewater sample collected on August 11 from Kings and Queens counties in New York City tested positive for a PV2 genetically linked to virus isolated from the patient.

However, this finding coupled with repeated PV2 positive results from the lower volume samples collected from the broader sewer shed catchment. Areas serving parts of Kings, New York, and Queens counties for which sequencing was not possible, suggested that PV2 could be circulating in Kings and Queens counties as well.

VR: Daniel, I'm not surprised at this, but what I am surprised is that they're not looking elsewhere in the U.S. because I think you would find polio virus in many locations, and so it's not really a good idea to just focus on the New York area, in my opinion.

DG: I'm going to agree with you. I think one of my concerns is if we only look in New York and then we only respond to what we see under the streetlamp, we're not going to come up with great policy. If we're going to be concerned about this, if we want to make decisions and recommendations, we've got to look everywhere. Walk away from that streetlamp, shine some light everywhere, and then hopefully some really measured decisions about what to do.

All right. Influenza, is that flu jab going to work? I think a lot of people are wondering, "Should I get that flu jab? Is it going to work?" Well, a good way to get an idea is to look at the Southern Hemisphere that already had their flu season and say, "Well, how well did it do down there?" The article, "Influenza Incidents and Vaccine Effectiveness During the Southern Hemisphere Influenza Season - Chile 2022," was published. The great thing I like about this is they define vaccine efficacy against what? In its vaccine efficacy against influenza-associated hospitalization, and that was 49%. Hopefully, reminding people of our lesson that vaccines do not prevent all infections, but they do reduce our risk of severe disease. Listeners may recall my question, my insensitive question to all my patients that

complain, "I got the flu and I got the vaccination," and I say, "But did you die?" Remember, here's an opportunity to reduce that risk.

VR: So, 49% seems low.

DG: It is low.

VR: I think that the best you do is about 60%. I'm not even sure if the definition, which is very precise here. I think this is great and people who work on COVID should learn from this that you should define, but it seems to me that there's not a great match, and we might see a similar match up here, but when people say, "Should I get it?" The answer is always yes, because there's no alternative in it, and you might as well get it. It doesn't hurt.

DG: We certainly need a better flu vaccine. I'll give you that. Yes, and a 50% reduction in ending up in the hospital, that's a lot better than not getting the flu vaccine. As I will point out as predicted, my doom and gloom prediction has already come true. Flu-related hospitalizations are already the highest they've been in 10 years. Let's keep people out of the hospital.

RSV, I have some positive things here. After decades of disappointment, four new RSV vaccines may be nearing review by the U.S. FDA, and more than a dozen are in testing.

There's also a quote, "Hope around a promising long-acting injection designed to be given right after birth to protect infants from the virus for as long as six months. A recent clinical trial this antibody shot was 75% effective at heading off RSV infections that required medical attention." I'm going to put in a link to the article. “Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants,” published in *The New England Journal of Medicine*. This is the study looking at monoclonal antibodies as RSV prevention and medically attended RSV-associated lower respiratory tract infection.

Here we saw 1.2% in the MAB group versus 5% in placebo. An efficacy here of 74.5% at preventing medically attended RSV-associated lower respiratory tract infection. All right, and moving on to Ebola as promised, I think that's very appropriate at the ASTMH meeting to be mentioning that. There is a CDC Ebola tracker that people can link to from our show notes. I just checked this tracker last night, and the most recent update post was September 28. We need an update. A few days could be an eternity, but looking through the data, there are already cases reported in seven districts in Uganda, Mubende, Kyegegwa, Kassanda, Kagadi, Bunyangabu, Kampala, that's the capital, and Wakiso.

From the Uganda Ministry of Health, there are 129 confirmed cases and 37 confirmed deaths. I'm going to leave a link here also to the Uganda Ministry of Health, which is updated, I'm going to say a little bit more often there. For starters, what do we need to know about? This is Ebola Sudan rather than Ebola Zaire, and this impacts a number of things. One, testing. Most of the tests that were rolled out in the U.S. during the previous Ebola scare, the West African one that people remember, 2014, that involved Zaire Ebola virus.

Never authorized by FDA administration to be used for diagnosing this Sudan. This is important for us to know. Unlike Zaire Ebola virus, no rapid test kits are available to spot

infections. Doctors must draw blood samples. These have to be sent off to labs that can test. A few weeks ago, only eight members of the publicly funded Laboratory Response Network had the ability, this is now up to 20. We need to keep that ability to test. Critical, and I think this is a critical area for those of us, like myself, who are going to be headed to Uganda next month for Ebola Sudan, we currently do not have a vaccine with proven efficacy, but Merck is donating 100,000 doses of an experimental vaccine for Ebola Zaire that they have in their freezers in Pennsylvania. The WHO and the Ugandan government are discussing whether and how these doses may be incorporated into one or more clinical trials with other candidate Ebola vaccines.

VR: The Zaire vaccine is licensed in the U.S. Are you going to get it before you go, Daniel?

DG: Have to admit, that's a little challenging to access.

VR: Is it?

DG: Yes. Tell a story. I'm sure that the person who will be offended by the story is not a listener. I often am called to consult on issues. This was a case where there were people at JFK who were involved potentially interacting with Ebola suspected folks. They were interested in getting vaccinated, which I thought seemed incredibly reasonable. He went through the process and then the last step was the supervisor needed to sign off on getting these people vaccinated. He did not want to sign off, so all his people quit and had to be replaced. OK, bureaucracy.

Monkeypox, as I keep saying, and I think this is really important. Monkeypox is not a gay disease or an African disease, monkeypox is an infectious disease. Getting an infection is not a moral issue, getting an infection is a tragedy. We have the *MMWR*, early release, "Severe Monkeypox and Hospitalized patients, United States, August 10 - October 10, 2022." We hear that as of October 21, 2022, a total of 27,884 monkeypox cases confirmed and probable had been reported in United States.

This report summarizes findings from CDC clinical consultations provided for 57 patients aged 18 years or older, who are hospitalized with severe manifestations of monkeypox during August 10 through October 10, 2022. Overall, 30% of patients received ICU-level care and 21% died. As of this report, monkeypox was a cause of death or contributing factor in five of these deaths, six deaths remain under investigation to determine whether monkeypox was causal or contributing. One death, they did say monkeypox was not a cause or contributing. That person died with, not from, monkeypox.

Remember, transmission is primarily through contact. Remember testing, if you don't test for it, you're not going to make the diagnosis. As Occam was not a physician, Hickam was a patient and can have as many diagnoses as they please. This is not a diagnosis you make when you've ruled out other things, this is diagnosis you make by testing for it.

For those that end up testing positive, those with patients who test positive, remember the STOMPTPOXX.org trial. This is looking at tecovirimat.

To the COVID, 14 minutes in. I know some people jump right to COVID, but there's other things out there. For the past almost three years, I have talked about the science, but I've

not always mentioned the role I played in creating that science. This is a little bit disclosure and also maybe a little bit of self-PR, self-promotion. Early in the pandemic in my role as a senior infectious disease fellow at UHG, the fifth largest company in the world, I think they make me say that I was involved with many of the advances. I will sprinkle through today's discussion, many of those roles and also the partnerships that made this possible.

Also, I'm going to say this is also perhaps a call to arms for all those in the audience who value science and those that want to advance science. If we are silenced by the often aggressive and threatening attacks of those that have an agenda that is anti-vaccine, anti-science, they win. We have the privilege of recording this at one of the most philanthropic and important meetings in the world, the Annual Meeting of the ASTMH, American Society of Tropical Medicine and Hygiene. I will say one of our dear friends is not here this year. I worry about our bowtie wearing colleague who has done so much and suffered so much abuse.

If you're listening and willing to make money off spreading misinformation or have already made up your mind and just want confirmation bias, this is not the right podcast or video broadcast for you. For those of you listening that understand the power of science and medicine to make this a better world, do not give up the fight and work with those who help us create the tools that we use to change the world.

Now on to the science. Perhaps there's a theme here regarding the different variants and reinfection. The peer-reviewed research letter, "Reinfections with Different SARS CoV-2 Omicron Subvariants, France," was published in *Emerging Infectious Diseases*. Perhaps this will remind our listeners of the article we discussed last week, where the infectious disease specialists up at MGH were incorrect about a third of the time in assessing reinfection versus persistent PCR positivity. Here the authors describe 188 patients in France who were successively infected with different SARS CoV-2 Omicron sub-variants including BA.1, BA.2 and BA.5.

The median time between the primary and secondary infections was 146 days, but a range, and this is crazy, of seven to 214 days. Seven days, that's not fair. The median time between infection with BA.1 and reinfection with BA.2 was only 84 days. Among the patients infected first with Omicron BA.1 or BA.2, the time between primary and secondary infections was one to 29 days, less than a month in 3% of the cases, 30 to 45 in 2% of the cases, and 45 to 59 in 9.6 cases. 60 to 75 days, 5%, 75 to 89, 5.8%. Greater than 90 days that was 73.9.

VR: The vast majority are greater than 90 days, which makes sense.

DG: That's encouraging. I'm hoping that's encouraging. All right. OK. Children, COVID and other vulnerable populations, as I like to say children are at risk of COVID. As we move into this winter, impressive here just how many children have unfortunately already been infected. Now we're seeing reinfections in that population. Let's move to the preexposure transmission testing. Use tests intelligently, and remember there's more out there, not just COVID, have a plan.

I've spent a lot of time over the last two-plus years in this area. Lots of media appearances and publications, testing school and company guidance and even was the Chief of Infectious

Disease for the 'Let's Get Back Program' for Lionsgate, Netflix, and other parts of the entertainment industry to help them safely create content while many were sheltering at home, starting in July of 2020. Hopefully get a little credit for all that content we were able to get out there. People probably remember well, our support of those rapid COVID tests. I will share that there were some very interesting bedfellows I worked with to get those from dream to reality. Lots of partnerships there, Quest, LabCorp, Abbott, etc., etc.

I will mention the early days of New York as an aside, here it was early March, we had just made that first diagnosis of community transmission. Our group had done that in the end of February and then we were left with very limited capacity who actually was partnerships with Quest and then LabCorp that allowed us to do thousands of tests per week in the early days. Not something we could necessarily do on our own without those partnerships.

And masks. What a lightning rod. Starting in the end of March, we were already discussing masks on *TWiV* and Ian Lipkin was even suggesting that people might want to look at the science as there might be something useful there. For a while there I was famous in early April 2020 on NPR, I was quoted recommending masks and saying, "If there's a cloth mask, you should wash your mask as often as you do your underwear. Not what you want to have go viral."

Yes, mask. Where are we with masks? Encouraged by many, a trigger point for others, but where are we with the science? Lots of concerns with the quality of the studies and risk for bias, but just a few important studies that I want to leave links to that are informative. Perhaps people remember the article, "Impact of Community Masking on COVID-19 - A Cluster Randomized Trial in Bangladesh," published in *Science*. I see Vincent nodding there.

VR: I remember we did that on *TWiV*.

DG: Excellent, really ambitious study in villages randomized to surgical masks, and that was 200 villages. The relative reduction was 11.1%. overall, the effective intervention was most concentrated among the elderly population. In surgical mask villages, they observed a 35.3% reduction in symptomatic seroprevalence among individuals over the age or equal to 60, so adjusted prevalence ratio is 0.65. They also, this is if you don't wear the mask, it doesn't work, they reported larger reductions in symptoms and symptomatic positivity in village that experienced larger increases in mask use.

The resource that I want to highlight is the living rapid reviews on masks. You can see the article, "Update Alert 8, Mask for Prevention of Respiratory Virus Infections, Including SARS CoV-2, in Healthcare and Community Settings," published in *Annals of Internal Medicine*. There's a plan for one last update when a large RCT will be published. In general, the science favors mask use and suggests the hierarchy for protection with a 95-mask providing the most protection. There's a lot of complexity in the data regarding indoor versus outdoor, distance, source control versus personal protection. All of science the story is not over yet, and we will share more as it becomes available. Just a word of caution, if your surgeon wants a mask exception so they can breathe that fresh air while operating on you.

All right. COVID active vaccination, never miss an opportunity to vaccinate, and as we keep repeating vaccinated people still get infected. Maybe we'll be discussing an anecdote later.

You are just reducing your risk of a bad outcome. You are less likely to die, less likely to have severe disease. Now what did we do? I should mention full disclosure.

I was involved in the J&J Readiness Cohort Construction and this was a very interesting thing. What we did is, we figured at some point the vaccine people were going to need help getting the phase 3 trials out there. What we actually did we asked who will need help. Moderna seemed like they were doing well. Pfizer they're big guys, they're doing well. J&J actually looked like they could use some help. One of my jobs at UHG was we created a readiness cohort with over a million people who signed up and said, "When there is a vaccine, I'm willing to be in that trial." Then when they got approval, my job was to predict where we thought there would be hot spots where we wanted to enroll, and in a matter of a couple weeks the fastest enrolled vaccine trial in history.

J&J hasn't quite done as well as I would have liked, but great to have that option out there. Let us move to maybe the beginning of the future, the article, “Unadjuvanted Intranasal Spike Vaccine Elicits Protective Mucosal Immunity Against Sarbecoviruses,” published in *Science* and worth a mention. I do like when people come up with catchy names and here, they introduce the prime and spike strategy. They say, "Leveraging existing immunity generated by primary vaccination to elicit mucosal immune memory using an unadjuvanted intranasal spike booster."

Here the authors describe an experiment where they vaccinate mice initially with an mRNA prime IM injection, 14 days later they do an intranasal administration of a recombinant unadjuvanted spike protein. This prime and this is the spike. The mice were euthanized at days 21, 28 and assessed for mucosal humoral immunity. That got us some elevated mucosal antibodies. Then they also find some B resident memory cells. They also found increased levels of CD8+ and CD4+ T-resident memory cells.

They then looked at timing of that spike and at a prime boost and then spike approach. And they even introduced infection into the system. They then move on to these Syrian hamsters and look at the standard prime boost IM vaccination strategy and the prime-spike, and report that cumulative viral shedding assessed by area under the curve revealed that both mRNA-LNP prime boost and P and S vaccinated animals had significantly lower overall viral shedding than naive animals.

Now the exciting part if you're still with me, the vaccinated hamsters were co-housed with naive donor hamsters who have been infected 24 hours prior, to look at impact on transmission. Wait. Isn't that last experiment done backwards? A very complex article with lots of information.

VR: I also want to point out that they did the challenge at 21 or 28 days where we're still having pretty high antibody levels. You're going to get substantial prevention of infection, but when you're farther out months, now you're depending on a memory response which takes a few days you're going to get infection. These are not really informative experiments that tell you if in the long term you're going to prevent infection or not, because they won't. They most likely won't. As we know, we don't keep high antibody levels in any compartment of the body. You're always going to depend on a memory effect.

DG: All right. Contraction. [chuckles]

VR: Contraction. That's right.

DG: All right. The next two articles are important, but I want to put them in perspective. The first preprint, “Antibody Responses to Omicron BA.4, BA.5 Bivalent mRNA Vaccine Booster Shot,” out of David Ho’s lab. They collected a panel of sera here from individuals who had received three doses, the original monovalent mRNA vaccines followed by one dose of a bivalent vaccine targeting BA.4, BA.5. They compared virus neutralization by these sera to panels of sera from individuals who received either three or four monovalent mRNA vaccines as well as to sera from individuals with the BA.4/BA.5 infection followed by mRNA vaccine. A lot of information here.

Using pseudovirus neutralization assays, all sera was tested against an ancestral SARS-CoV-2, that's D614G, and Omicron sub lineages BA.1, BA.2, BA.4/BA.5, BA.4.6, BA.2.75 and BA.2.75.2. To further assess the breadth of antibody responses, they also tested sera for neutralization against several related sarbecoviruses. They did not find in the study any significant difference in neutralization of any SARS-CoV-2 variant tested between those getting the new boost versus a boost with the original vaccine.

The second preprint, I know Vincent is going to jump in, “Immunogenicity of the BA.5 Bivalent mRNA Vaccine Boosters,” out of Dan Barouch’s lab up in Boston. Very similar results with monovalent original shots as well as bivalent boosters increasing antibody levels with only a modest, nonsignificant trend favoring the bivalent boosters by a factor of 1.3. No significant augmenting of the T-cell responses. I'm going to let Vincent jump in, but I know people say, "Oh, they need a bigger study to show definitively that there is a 1.3 factor increase."

VR: I think this emphasizes why people like Paul Offit were wary of the booster because the bivalent booster, we had no evidence that it would make an impact and now we see, at least in terms of antibody, it's no better than the ancestral. It's not likely to have an impact on disease. It's not clear why we're using it instead of just boosting with the ancestral vaccine.

DG: I know this isn't always the most popular stance, [chuckles] but no, I think that that's the silver lining of this information is, I'm not sure that we need to be chasing our tails, chasing every new variant. The original vaccines and we're in a world where we're very lucky that this is the case, continue to provide excellent protection, that third shot, maybe the fourth shot in other individuals, broadens that. It didn't need to happen that way. The science didn't need to work out that way. What we're really seeing here is those original vaccines are great. The bivalent, not really a game changer.

VR: This is really different from influenza, where we have to have a good match between the vaccine and the circulating strain. Here it doesn't seem to matter as much. The ancestral is doing just as good a job.

DG: I think we get into a lot of trouble not realizing that this isn't flu and trying to apply over and over and over again the flu paradigm to what is not an influenza but is a Coronavirus. COVID passive vaccination, Evusheld. Here is a situation where things are not positive. I'm going to discuss here a little bit on engineering of monoclonal antibodies different half-lives,

potentially other monoclonals could step into this space. As we are seeing with the new variants the BA.5 is down to less than 38% of the variants we're seeing in the New York area. We're starting to move into more and more variants which may not be effectively targeted with Evusheld, so a little concern there. I've never actually worked for AstraZeneca, maybe if AstraZeneca is out there listening.

All right. Let's move on to COVID early viral upper respiratory, the non-hypoxic phase , that period of early viral replication. We're recording in front of a live audience. Some of them probably hearing this right now and they can be answering in their heads and those of you listening remotely you can answer as well. How many of the folks out there at home, in your car, out walking the dog? Any people do Twitter out there? Any other social media stuff maybe TikTok, because we're dating ourselves? Not everyone needs or benefits from treatment during the first week, based on the science.

I recently did a tweet series with Pfizer to help educate people about who is at high risk. No one thinks they're at high risk, so this education is much needed. Currently, here in the U.S. we have an average of about 350 people dying every single day from COVID, 2,500 every week, 10,000 a month. This rate is over 100,000 a year with an expected increase per day this winter.

Who are they? I had a conversation with a gentleman yesterday. He said they're all unvaccinated. Vaccinated people don't die of COVID. As a wake-up call, about 40% to 50% of those people dying every day are vaccinated. By January, February 2022, that's from COVID here in the U.S. were no longer overwhelmingly in the unvaccinated. At that point up to 42% of all deaths were in vaccinated, people. There was a nice *Washington Post* article back in April and so, most recently, I created this Twitter campaign to try to raise awareness who is at high-risk, pointing out age, being overweight, multiple medical problems. I'm going to tell you a little bit of a scenario, this hits close to home. Vincent will know about this. Yesterday, I was chatting with a gentleman over the age of 80 who carries a little bit of extra weight, he claimed he didn't.

[laughter]

Has some medical issues going on. I said, "If you get COVID, what are you going to do?" He said, "Well, I will just weather the storm." I said, "You know what, let's run the numbers." We ran the numbers. We said, "You know what, prior to vaccines about 20% of folks were ending up in the hospital. You have a number of risk factors, your baseline risk was probably about 40% but now you got your vaccines so we'll drop that down to 4%. We'll say, about one in 25 risk of ending up in the hospital. That's not so bad, one in 25, we can step in and we can reduce that risk to maybe one in 200. Would you like to do that or do you want to roll the dice?" Well, the punch line is this morning, that gentleman coughing and sniffing tested positive for COVID and what did we recommend?

VR: Paxlovid.

DG: Yes. To this gentleman who is beloved, and we care about and hopefully will be with us for many years, yes, the number one recommended and this is based on the science with an

89% to 88% reduction in progression, in the unvaccinated about a 75% reduction in the vaccinated. This gentleman, this is not his first rodeo with COVID either.

VR: What's interesting, Daniel, is that this gentleman received the bivalent booster two weeks ago.

DG: How is that possible?

[laughter]

VR: He called me early this morning he said, "I can't reach Daniel." I gave him your number and I said, "He's going to tell you to take Paxlovid." Sure enough, you did.

DG: Yes. All right. Remember, the COVID rebound we hear about is the week two. We've been calling this the early inflammatory phase or cytokine storm for over two years. This represents an immune response, it's not a second period of this outrageous viral replication. We have tested antivirals in that second week, in folly, for quite a while now. This is the time when we focus on immune modulation if we need to

All right. I should mention, I've actually never worked with Pfizer on Paxlovid, I would like to. Actually, what I would love to do is PASC studies early treatment with Paxlovid. Are we reducing Long COVID? Even people with Long COVID, is there any therapeutic benefit in any subsets with Paxlovid?

VR: Post-acute, when we're no longer PCR positive would Paxlovid help?

DG: I would love to know that answer. The answer may be no, but we'll see. All right. Remdesivir number two, 87% reduction and progression given in those first five to seven days. We continue to see evidence supporting remdesivir but again the access is not great. Number three, monoclonal antibodies. Now we are down to just bebtelovimab. Some evidence that this is slightly inferior to Paxlovid and we'll leave a link to that. I think that's an important point. A lot of people have their favorites, but the science has its favorites as well.

Paxlovid, most effective. Remdesivir, the monoclonals are not quite as good. A little disclosure on the monoclonals, I've had a lot my fingers in the pie here. Our listeners may not know my background in monoclonal antibodies but from 1999, I don't even know if Vincent knows this, but from 1999 to 2008, I had the title of Medical Director of the Primary Care Osteoporosis Division at Amgen.

VR: I didn't know that.

DG: I was tasked with development of a novel osteoporosis therapy and a group effort, my wife always finds out, there were seven other people in the room, don't take all the credits. We actually targeted the RANK ligand pathway, we developed denosumab, (Prolia, XGEVA), and went on to design the clinical trials for Denosumab. Actually, one of the say widely used osteoporosis MABs. This is actually how I got pulled into COVID early on. I think it was April 4th, got a call from Steven Catani, I think used to be pretty senior at J&J and he's like, "We got to speak to Regeneron."

We got on a phone call, and we asked them the very simple question, "Why are you testing monoclonal antibodies in week two, week three in people in the ICU? It makes no sense." The representative from Regeneron replied, "We agree. We just don't know how to do trials in the first week."

I went on to work with Regeneron, Eli Lilly, GSK, Adagio, and a bunch of other companies. We basically set up those first week. We said we have a network of urgent cares, we need to try these in the first week. I have to say this could have been a disaster if those trials had not been done, those early trials giving monoclonals week two, week three, they were all failures. Not only were they not helpful but there may have even been negative progression. Timing was really critical.

We went ahead and we did trials in the first week in urgent cares, we did infusion sites across the country. Actually, ended up as the PI on the largest bebtelovimab trial in the U.S. with thousands of enrollees. I do have a special place in my heart for the monoclonal antibodies and look forward to their role in other diseases, particularly if they tackle the cost challenges, but the science puts them at number three.

Number four, molnupiravir, last and least may be a 30% reduction in progression. Remember all those things don't do harm to your patients, don't give them steroids during that first week which will increase their risk of progression. Let's avoid those unnecessary antibiotics, let's not feed the antimicrobial resistance demon.

Then early inflammatory lower respiratory hypoxic phase. We had this discussion this morning, Vincent and I, about our dear friend who just got diagnosed, should we treat him right away, take advantage of this window of opportunity or just see how well he does? If he does poorly, we'll say we missed our opportunity.

VR: Well, that's a good way to put it. It exemplifies why you just have to act. You can't wait. There's no benefit in waiting.

DG: If you wait, you miss your window of opportunity. I will start here with the story of an elderly-elderly woman, who has a daughter, who is a clinician. This elderly-elderly woman got COVID. During the first week, her daughter was a clinician, did not recommend or steer her toward any therapy. This woman progressed, ended up in the hospital on day nine. I started the remdesivir and then the daughter, who I know, reached out and said, "Are you sure she really needs treatment?" I very gently pointed out that we had already missed our first opportunity, she's already in the hospital, maybe it's about time we started doing something.

Remember, steroids at the right time, in the right patient, at the right dose. This is after that first week and only in patients with oxygen saturations less than 94%. We're only getting about a 17% mortality reduction, not quite as impressive as first week. Number two, anticoagulation, pulmonary support, maybe remdesivir if we're in the first 10 days, immune modulation. Again, avoid those unnecessary antibiotics and unproven therapies.

All right. We're wrapping up, we're now in the late phase. I'm just going to put in a link as I always do to the *BMJ* paper, “Long COVID - An Update for Primary Care.” I also want to mention a few new articles here. The “Long-term Gastrointestinal Sequelae Following

COVID-19: A Prospective Follow-up Cohort Study," published in *Clinical Gastroenterology and Hepatology*. The authors start the article with the sentence, "COVID-19 is associated with long-term gastrointestinal sequelae, however, prospective longitudinal data are sparse."

I wonder how many people realize this and that there is a subset of PASC or people with Long COVID with gastrointestinal issues. To do this study, they had 320 cases with COVID-19, two control groups, 320 healthy spouses, family controls and a group B of 280 healthy COVID serology negative controls prospectively followed at one, three, and six months. We learned that of the 320 cases at one month, 11% developed functional gastrointestinal disorders. Persistent symptoms were noted in 8.4% at three months, and 6.6% in six months. Three months 2.5 had IBS, 2.2 had functional diarrhea, 2% had functional dyspnea, about 1% had constipation and less than 1% had overlap.

Among symptomatic individuals at three months 29.6, almost 30%, were positive for isolated carbohydrate malabsorption, 4% post-infection malabsorption syndrome, and about 4% intestinal methanogen overgrowth. None of the healthy controls developed any of these functional disorders. Really interesting knowledge. We are moving forward here and I want that to be a word of encouragement.

VR: What do you think is the mechanism here? You don't think it's virus reproduction? Some cytokine imbalance, perhaps?

DG: I don't think at this point we have major viral replication, I would love to do a Paxlovid trial in this group just to rule that out, but no, I'm worried about ongoing inflammatory issues, I'm worried about a dysbiosis.

VR: Is it we're seeing in patients that already have intestinal disorders, IBD and so forth, IBS?

DG: Not necessarily, but what is seen is if you have gastrointestinal issues symptomatic in the acute COVID, those individuals are more likely to have chronic.

VR: Got it, which is actually an argument against extended viral reproduction.

DG: Yes. I also want to mention the article, "Evaluation of an Automated Text Message-Based Programs to Reduce Use of Acute Healthcare Resources after Hospital Discharge." The study published in *JAMA Network Open*, patients received automated check-in text messages from their primary care practice on a tapering schedule during the 30 days after discharge. Any needs identified by the automated messaging platform were escalated to practice staff for follow up via an electronic medical record inbox. This resulted in a 41% reduction in 30-day readmission.

Just my plea not to clap people out the door, the day of hospital discharge is the first day of hopefully a long period outside the hospital. We need to stay engaged and provide these people with the resources they need to keep them from ending up back in the ER.

We are winding down. The, "Review: In Adults with COVID-19, Melatonin Was Assessed for Effects on Inflammatory Markers, Clinical Signs and Symptoms and Mortality," published in *Heliyon*, actually published in *Heliyon*. This is interesting, it's a review of 10 articles, and I will say there is some support for the idea that melatonin might reduce levels of a number of

inflammatory cytokines, and the expression of some genes, including the signal transducer and activator of transcription, STAT4, STAT6, T-box expressed in T-cells, or T-bet, GATA binding protein 3, GATA3, apoptosis-associated speck-like protein containing a caspase recruitment domain, ASC, some of these names. In addition, melatonin may actually alleviate some of the clinical signs and symptoms and accelerate recovery. Just a little more information, the 10 included articles classified into two observational retrospective, five RCTs, three clinical trials, six of these studies in Iran, one in the United States, one in Mexico, one in Italy, and one in Iraq, total number of patients involved was 665, so not a lot.

The dosing many are using is lower dose, so in the two to five milligram range. There was one study that suggested that if you went above five, so you went to the six to nine, they might actually be harmful. A little surprise because I usually think of this as a fairly benign medication. The authors conclude so far, there have been no high-quality large-scale studies to establish or reject the effectiveness of melatonin in the treatment of COVID-19 and more high quality randomized clinical trials are needed. Many are using melatonin in PASC in long COVID folks.

There is a subset, where we think there is benefit, we think I qualify that, but optimum duration, optimum dose, optimum timing, still much to learn here. A lot of these studies, I will come and have publication bias. An update on recovery program looking at PASC now greater than 10,000 study participants enrolled. These trials are now going to look at five specific clusters of symptoms and their potential causes. I like to close here and this is perfect being at ASTM and H, no one is safe until everyone is safe. I've been saying for a while, the most selfish thing we can do is reach out, vaccinate, work with the world, there are no borders.

Parasites represent no borders, viruses represent no borders, illnesses represent no borders, so no one is safe until everyone is safe. Those of you listening while you're driving, those of you here in the audience, go to parasiteswithoutborders.com, click on the ‘Donate’ button, every small amount helps, the big amounts help even more. Thanks for all of you. We reached our goal of support for Floating Doctors. We were just a little under, so I rounded upward, but we will be sending them out $40,000 in support. During the months of November, December, and January, donations made to Parasites Without Borders will be matched and doubled up to a total maximum donation of $40,000 for MicrobeTV.

VR: That's my favorite time of the year, that MicrobeTV fundraiser at PWB. It is time for your questions for Daniel, you can send them to daniel@microbe.tv. Terry writes, "Even though I am fully vaccinated and boosted, I recently had COVID. I took Paxlovid within two days of symptoms and did well. I'm 70 years old with mild asthma. I know I should be fairly immune to reinfection for about 120 days, but if I get COVID again in two, three or four months, should I take Paxlovid again? What is your advice regarding recurrent COVID, and how often high-risk patients can take Paxlovid?"

DG: There's really no limit. If you get reinfected, you take Paxlovid. You don't take it during week two for the rebound, you take it for the reinfection. As we've discussed repeatedly, people get COVID more than once, more than twice, more than three times. The question our colleague asked me this morning, "How many times can I get this?" I said, "There's no limit."

VR: OK. Lindsay writes, "I have two questions. First, has the been any change in the recommendations for monkeypox vaccines for the general public? My local health department is still restricting them to limited high-risk populations, even though it seems that the spread is under control, it doesn't seem like it's going anywhere."

DG: The guidance is still the same, I'm a little surprised. I think it would be nice to update that and a little broader vaccination, but now the update hasn't really been updated.

VR: Second, "What is the name of the quad rapid antigen tests, and is it available outside of a doctor's office or hospital setting? Unfortunately, I've run into more than one person that thinks as long as they test negative for COVID, they don't need to stay home, even when they're showing obvious signs of a respiratory infection."

DG: I think that's a bit of a shame and hopefully, we've been sending the message out there. There's more out there than just COVID, so all the tri-state urgent cares are using a quad test, and it's a doctor's office quad test, and there's a lot out there by a lot of different manufacturers. The recent story I had was an older gentleman went in, his COVID was negative, they sent him home, he's now in the hospital with severe influenza A, so there's more out there.

There is no home test the way we have with COVID, but I do know at least LabCorp has the ability, and the timing kills me. This is where your doctor orders it, it is FedExed to your house, you do the swab, you FedEx it back, and then one or two days later, when it's no longer relevant, you can get that result.

VR: When it's no longer relevant, those are the key words there, I like that. This is Em: "You've emphasized in many *TWiV* episodes how treatment with steroids early on is associated with significantly worse outcomes. I'm curious how this applies to patients who are already taking steroids for another condition. If you have a patient taking steroids, you can have them take a break, or is the disruption in their existing treatment a greater risk?"

DG: This is a challenge, but unfortunately, people who are on steroids are to some degree, and the dose of steroids has impact to what degree, immunocompromised. People who go into a COVID infection on steroids are at higher risk of a bad outcome. This is going to have to be an individual decision made with your clinician, what are the risk/benefits of stopping that steroids, but this is certainly going to put someone in a situation where we would recommend early antiviral treatments.

VR: Tom writes, "Hello, Dr. Griffin. I'm a private pediatrician in New Jersey. I've been enjoying listening to *TWiV* podcast for close to a year. I have two patients who are freshmen at a private university in New York City." We could probably figure out which one.

DG: I wonder what school that is.

VR: "Both of their parents have reached out to me concerned that the school is requiring them to receive the fourth dose, aka, the bivalent booster, prior to December 1. They're both healthy and have received two primary and one original booster dose. Do you understand why this university is requiring the fourth dose? Both parents are asking me to give them a note exempting them from the vaccine."

DG: Oh, and it was going so well. I think this is tough. My assumption is those decisions are made by administrators, not necessarily with the advice of up-to-date clinicians. We've talked a lot of times about what vaccines can and can't do, what boosters can and can't do. I'm not sure that the science would support such a broad mandate. One of the challenges in a situation like this at a private institution, at a private business, you've got to look at their policy and you've got to ask, what would be the criteria for an exception should one be granted?

VR: At Columbia, we don't require it, it's just recommended, and I think maybe these schools are taking the CDC recommendations too literally.

DG: Yes. It's a recommendation, it's not a mandate, and I think we need to be careful. We've eroded confidence in vaccines. If you mandate too much, we're in this for the long haul. We're not just in it for this winter.

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

DG: Oh, thank you and everyone be safe.

[music]

[00:50:10] [END OF AUDIO]