This Week in Virology

TWiV 1132 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.

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From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1132, recorded on July 18, 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: I think I recognize that bow tie. I've seen it before, Daniel, but I can't remember what it is.

DG: It is apparently plague, Yersinia pestis, which apparently got a little debut in the news not too far back, but yes, some interesting science about plague. I think we talked about it on *Puscast*, about maybe it's been with Western Europe for much longer than people had thought before. Some interesting science there. Let's get into it today because we have a bunch of things happening.

Start off with our quotation, and this is back to Winston Churchill, who I quoted quite often during the dark days. "Courage is what it takes to stand up and speak. Courage is also what it takes to sit down and listen." Just sort of like that. I was tossing over a couple of different quotations for this week. It's been a difficult week for a number of individuals, a number of prominent individuals. Among them, we heard that President Joe Biden tested positive and has COVID. They said tested positive for COVID. I said, "Well, he really tested positive for SARS-CoV-2. He has COVID." We heard that the president promptly started, what did he start? Paxlovid.

VR: Paxlovid.

DG: Yes. There was an article in *USA Today* and it was titled, “Biden's age makes COVID risky. Is his health in danger?” There are a few quotations from apparently this Dr. Daniel Griffin fellow. I'll go through them. Let's just talk a little bit about this. I always hate when you talk about a politician because people tend to think about the political aspects of this. I just want to, as I talk about these things, I want to point out we're talking about a human being who is sick at the moment, what's going to happen for this individual, and just thinking about all the other individuals who might get this disease.

There was this comment, Biden's multiple vaccinations and quick receipt of medication will reduce his risk of severe disease down to about 1%. I may have even said less than 1%, said Dr. Daniel Griffin, but the risk isn't zero. We've talked about that. It's a mixed picture here. There's a history of atrial fibrillation, maybe some heart disease. That is sort of a negative. Also, he leads an active life. We've always talked about how important it is to take care of yourself, stay active.

Now, encouraging, I point out that this is not a debilitated person in nursing home. Unfortunately, the deaths we're largely seeing are happening in immune-compromised, debilitated individuals. Then I put out another thing, and this was something we will keep hitting on over and over again, is that with COVID, it's not just what happens in the first or second week. Then I say here, “Griffin said his real concern is two weeks or a month from now when Biden or really anyone his age might not fully bounce back from an infection. Each episode of Covid-19 doesn't predict the next one. Aging has an impact on the body's ability to fight off infection.” After a month or two after COVID infection, many older people find themselves short of breath after climbing a flight of stairs, a little more forgetful perhaps than they were before. Then, running for president involves a lot of crowded rooms, handshaking, and all three of the leading candidates are over 70. Just making a note of that.

VR: Daniel, I think it's interesting that he immediately got Paxlovid. So many physicians in this country just wait. I'm glad that the White House physicians are on top of things.

DG: I think that's great and hopefully that's a learning lesson, because, every time something like this happens, you really have to ask, what can we learn from it? What did an individual who has access to the top science-based, evidence-based clinicians do? What we've been talking about over and over again, you start the Paxlovid right away. You don't wait and see. We want this individual to do well. We don't want him to have acute issues. We don't want him to have issues down the road.

VR: I presume he had some symptoms and he was tested right away.

DG: That was what I heard is that was some upper respiratory type symptoms, prompted testing, and he was at this crowded event. A lot of folks are on the campaign trail at the moment. That is tough because, right now there's a lot of SARS-CoV-2, so a lot of folks with COVID-19 out there. When you get in these crowded rooms, all that interaction, this is a risk.

All right, moving to COVID, big picture, what are we seeing across the country? Unfortunately, we're still seeing this really high percent of all the deaths in Puerto Rico being due to COVID. Then if we look at our wastewater viral activity, it really has gone up since we last talked. It's really rising across the country. It, in a lot of these areas, is reaching those peaks that we reached last summer. Actually, last summer, we reached them in sort of late August-September. We seem already at those levels at this point.

VR: Epidemiologically, Daniel, what is going on here? Do you think this is associated with travel, mainly summer travel?

DG: I wonder, it'd be great to really break stuff down, like, how much of it is travel, how much is it people getting indoors? Because there's always a weather effect, right? When it's really hot and people are gathered indoors, these poorly ventilated areas. I think you guys did a good job of talking about some of the outdated views about how transmission occurs. You get in a poorly ventilated suburban environment with limited air exchanges, and it's just a recipe. You have gatherings. July Fourth is always a nice trigger. We have holidays. Then, yes, people are traveling. They tend to have their summer vacation plans.

VR: I always associate the summer with people being outside. That's why it's a little bit surprising to me.

DG: Yes, it would be interesting, over a long enough period of time, let's say when the weather is milder, less people are indoors, hiding in the air conditioning, because, boy, I would like to be outdoors, but it's been really hot lately.

VR: Daniel, we don't see outbreaks of influenza at the same time. It's really interesting, right?

DG: Yes, there's something here that I certainly don't have the full answer to. All right, so we're moving into the vulnerable population section, and we have the article, "Post–Acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) After Infection During Pregnancy," published in the journal *Obstetrics* & *Gynecology.*

These are the results from a multi-center cohort study. Individuals who are pregnant during their first SARS-CoV-2 infection were enrolled across the United States from December 2021 to September 2023, either within 30 days of their infection or at a different time point. The primary outcome was PASC, post-acute sequelae of COVID, defined here as a score of 12 or higher based on symptoms and severity, as previously published in the NIH RECOVER Adult Cohort. Risk factors for PASC were evaluated, including socio-demographic characteristics, clinical characteristics before SARS-CoV-2 infection, baseline comorbidities, trimester of infection, vaccination status, really doing a lot of these and doing a whole regression analysis.

What do we see? Of the 1,502 participants, 61.1% had their first SARS-CoV-2 infection on or after December 1, 2021, so during Omicron variant dominance; 51.4% were fully vaccinated before infection, and 12% were enrolled within 30 days of their acute infection. The prevalence of PASC was 9.3%, measured at a median of 10.3 months after the first infection.

What were the most common symptoms? Post-exertional malaise, 77.7%. Fatigue, 76.3%. GI symptoms, 61%. In this multivariable model, they look at the proportion of PASC positive with versus without a history of obesity, 14.9 versus 7.9. Almost twice as much with obesity. Depression or anxiety disorder, we see 14.4 versus 6, so about 2.6 increased odds ratio, adjusted odds ratio there. Economic hardship, 12.5 versus 6.9. Then we actually get some severity of acute infection, so treatment with oxygen during acute SARS-CoV-2, 18.1 versus 8.7. They go on to just sort of remind us that the most common Long COVID symptoms reported were, as we just went through, post-exertional malaise, fatigue, and GI symptoms.

VR: They have obesity here as a comorbidity but it would be really interesting to look at more things and see if they also track with it, right?

DG: Yes, it would be interesting because people always, and I'm working on that review, are like, if I get COVID and, you almost want to do a calculator on, what's my risk? Because we're going to get to an article where we see that right now, vaccinated Omicron, it's about 3.5% of people end up with Long COVID, but people want to know, well, yes, but what about me? Because we're all 18 years old and healthy and immortal. Yes, it'd be nice to be able to individualize that more.

All right, moving into transmission, this is actually a nice update. Unfortunately, not giving us the data we would like, but the article, "Oral Nirmatrelvir–Ritonavir as Postexposure Prophylaxis for COVID-19," published in *The New England Journal of Medicine*. Basically, if I'm exposed, can I just take a whole bunch of Paxlovid? Will that keep me from getting the COVID?

Well, here are the results of a Phase 2-3 double-blind trial to assess the efficacy and safety of Nirmatrelvir–Ritonavir in asymptomatic rapid antigen test-negative adults who have been exposed to a household contact with COVID-19 within 96 hours before randomization. The participants were randomly assigned one to one to one. Either they're going to get Paxlovid for five days, Paxlovid for 10 days or placebo. The primary endpoint was the development of symptomatic SARS-CoV-2 infection confirmed by testing. A total of 2,736 participants were randomly assigned, end up with about 900 in each group.

What do the numbers show? In the five-day Nirmatrelvir group, 2.6%. In the 10-day, 2.4%. In the placebo group, 3.9%. A little bit of a trend in the right direction, but really minimal potential benefit, not reaching statistical significance. They give us reductions relative to placebo, maybe 29.8%, but this huge confidence interval, p-value of 0.17. When we do the other 10-day group, 35.5, p-value 0.12.

Even if you take that, oh, I can get this 1.5% reduced absolute risk, we're talking about 66 people unnecessarily taking a medicine to prevent one person from getting COVID-19. Thought was interesting, you had almost 1% dysgeusian people in the placebo group, so people are sort of expecting a bad taste and getting it from the sugar pill, which I find very entertaining. So don't take it before, take it if you turn positive.

We have PEMGARDA out there. I'm happy to say we started to get some folks at Columbia getting their prophylactic monoclonal treatment, that's Q3 month, and COVID early phase. What have we got here? Well, we've been talking about the NIH treatment guidelines, the IDSA guidelines, and we'll start with an interesting article making me think a little. It is the article, "Combined Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 Reduces Molnupiravir-Induced Mutagenicity and Prevents Selection for Nirmatrelvir/Ritonavir Resistance Mutations," published in *JID*.

For background, the present treatment approaches for SARS-CoV-2 primarily relies on these direct-acting antivirals, with Paxlovid being the most frequently prescribed in the U.S. Now, the combination of the oral direct-acting antivirals and molnupiravir, there's this idea it might provide some additional benefit, but has anyone tested it? Well, in a previous study, this research group compared the antiviral effects of molnupiravir and Paxlovid and the co-administration in a SARS-CoV-2 macaque model, and the macaques received the oral treatment of molnupiravir, Paxlovid, combination therapy, or vehicle control 12 hours after

exposure to SARS-CoV-2, and then were followed for four days before necropsy. The combination therapy resulted in milder disease progression, a greater reduction in virus titer, and reduced lung pathology compared to either single-agent treatment.

Sounds great, but what about any downsides, such as the development of resistance to nirmatrelvir due to the mutagenic effects? This group here shares data generated by using what they tell us is a highly accurate viral RNA sequencing approach, multiplexed primer ID-next-generation sequencing, MPID-NGS, that they tell us has an error rate as low as 0.01% to look at the SARS-CoV-2 mutation profiles for the different treatment groups, and they found that the Paxlovid reduced the molnupiravir-induced mutagenicity of SARS-CoV-2 when co-administered while still contributing benefit to dual therapy. Mutagenic property of molnupiravir increased several mutations related to 3CLpro resistance, but these mutations were not further enriched in the combination therapy. Any thoughts on that, Vincent?

VR: It's interesting because the mutagenesis is how molnupiravir works. They're saying that the combination works better, but it reduces the mutagenicity. I don't know, does that make sense to you?

DG: I guess it tells us maybe it's additive, but it's not necessarily synergistic. You're getting all the benefit of Paxlovid, maybe getting a little bit of extra benefit from molnupiravir, but not as much as you might get because--

VR: What's the mechanism of the reduced mutagenicity, right?

DG: I guess if you have less viral replication, that would be sort of my thoughts.

VR: Well, it depends on if they just report number of mutations, but if they do it as a percentage of the genome, then that should be normalized for that.

DG: That's actually interesting. Yes, because you think like number of, yes. [crosstalk]

VR: But it must be something like that reduced replication because there's - Paxlovid is a protease inhibitor, so there's no way it's going to impact mutagenesis.

DG: Yes, interesting.

VR: Based on this, would you ever give people both- [crosstalk]

DG: I don't think I would at this point. I feel like we're getting enough benefit with the Paxlovid. We're getting this 80%, 90% reduction. You'd have to really show me that you're getting more that would justify the co-administration. The article, “Real-World Effectiveness of Ensitrelvir in Reducing Severe Outcomes in Outpatients at High Risk for COVID-19,” was published in the journal *Infectious Diseases and Therap*y.

This is that other medicine out there, the Japanese medicine, and these results come from a retrospective study that used a large Japanese health insurance claims database. It included high-risk outpatients for severe symptoms who received their first COVID-19 diagnosis between November 2022 and July 2023. The study included outpatients aged 18 or older.

The primary endpoint was all-cause hospitalization during the four-week period from the date of outpatient diagnosis and medication. Comparing the ensitrelvir group, we have an *n* of 5,177, and the no antiviral treatment group, that is a huge *n* of 162,133.

Remember, the thing here is that when ensitrelvir was first being studied, they said, you know what? There's not enough mortality. We're not going to see it. Let's focus on basically how quickly people feel better, but we see here that the risk ratio for all-cause hospitalization between the ensitrelvir group and the no antiviral treatment group was 0.629 with a good confidence interval. About a 30% reduction for all-cause hospitalization and the incidence of both respiratory and heart rate monitoring and oxygen therapy were lower in the ensitrelvir group.

VR: This is another 3CL protease inhibitor, but it does not require ritonavir, correct?

DG: Correct. Yes.

VR: This trial is done - well, it's a Japanese health insurance claims database, so this data would not be used to license it in the U.S., right?

DG: Yes, it wouldn't, which is tough. Xocova has the advantage is you take - it's the XPAK, I call it, because you take three pills on day one and then just one pill a day for the next four days. It's a little bit easier. It does have similar P450 interactions, so not a complete walk in the park.

Then we've got another one here. This is the article, "Comparative Effectiveness of Combination Therapy with Nirmatrelvir-ritonavir and Remdesivir versus Monotherapy with Remdesivir or Nirmatrelvir-ritonavir in Patients Hospitalized with COVID-19: A Target Trial Emulation Study," published in *The Lancet Infectious Diseases*. I guess I should put this in context. The normal thing is people are, in the outpatient setting, maybe we put them on Paxlovid, they end up in the hospital, pretty much their routine is to put them on remdesivir. What about rethinking that paradigm?

These are the results of a target trial emulation study where they used electronic health records of patients aged 18 years or older who received either combination treatment with Paxlovid and remdesivir or monotherapy of either drug between March 16 and December 31, 2024, within five days of hospitalization for COVID-19 in Hong Kong. The primary outcome was all-cause mortality. They compared the risk of all-cause mortality, intensive care unit, ICU admission, or ventilatory support for 90 days of follow-up between groups.

Now between March 16 and December 31, 2022, 18,196 participants were identified from electronic health records and assigned to receive remdesivir, we've got 4,232. Paxlovid, we've got 13,656, or combination Paxlovid and remdesivir. After a median follow-up of 84 days, the risk of mortality was lower in participants who received nirmatrelivir, Paxlovid monotherapy, we see an absolute risk reduction there, or remdesivir and Paxlovid combination therapy than in patients who received remdesivir monotherapy. Similar results for ICU admission or ventilatory support. Compared with combination therapy, the Paxlovid monotherapy was associated with a lower risk of mortality though in ICU admission or ventilatory support. Some sort of mixed things we're seeing in here.

VR: The absolute risk reduction, 16% with the monotherapy and 6.5% with the combined therapy. Correct?

DG: Yes.

VR: OK. So it's a bit better.

DG: Yes. All right. That sort of brings us back to the paradigm that we're seeing played out in real life with our president getting COVID-19. Number one, what do we recommend? Not waiting, but starting as soon as possible on Paxlovid. Don't give it those three to four days to let the immune system fire up. Don't wait and see how they're going to do. The data is very clear. The sooner you start, the better.

Number two, we have remdesivir. Number three, molnupiravir, convalescent plasma in some situations. Remember isolation guidance. You are contagious, as annoying and inconvenient as that might be. The second, the early inflammatory week, I hate the fact that people are still calling this something differently, including some of those commentators. During that second week, when we get that inflammatory, that cytokine storm, in the right patient at the right time we might use steroids, hospitalize patients, anticoagulation guidelines, pulmonary support, remdesivir, and immune modulation.

VR: Daniel, going back to the president, what is he going to do now? Is he going to stay in the White House and not wander outside, I presume, right?

DG: I think he's going to go to Delaware, to his home in Delaware, and rest up for a number of days.

VR: When would he be free to go again?

DG: The science hasn't changed, even though people wish it would. For the first five days is when he's the most contagious. For the next five days, he wants to, and other people want to not be basically in a situation where they're going to end up with COVID-19. You look at, when did symptoms start? That's day zero, one, two, three, four, five. As we've talked about, after day five, if you can do things with masking and good ventilation, there is some transmission that occurs after day five. We've talked about how testing out is not a science, not an evidence-based approach. Then after that extra five days of precautions, then he's good to go.

VR: OK.

DG: All right. Long COVID. For starters, on July 11, the CDC updated their Long COVID basics page. It's actually, they changed the definition a little bit. Long COVID is defined as a chronic condition that occurs after SARS-CoV-2 infection and is present for at least three months. Long COVID includes a wide range of symptoms or conditions that may improve, worsen, or be ongoing. This definition links to the National Academies' *A Long COVID Definition* with the robust PDF there.

There are five key points that we get. Long COVID is a serious illness that can result in chronic conditions requiring comprehensive care. Long COVID can include a wide range of

ongoing symptoms and conditions that can last weeks, months, or even years after COVID-19 illness. Anyone who had a SARS-CoV-2 infection, the virus that causes COVID-19, can experience Long COVID, including children. I think it's important to point out. There may be different things that increase your risk, but we see this even in children. COVID-19 vaccination is the best available tool to prevent Long COVID. Living with Long COVID can be difficult and isolating, especially when there are no immediate answers or solutions.

Then this article is published in *The New England Journal of Medicine*. It made a bit of a media splash after its embargo ended and it was printed. The "Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras*."* Here the authors used health records of the Department of Veterans Affairs to build a study population of 441,583 veterans with SARS-CoV-2 infection between March 1, 2020, going all the way back, and January 31, 2022, and 4,748,504 non-infected contemporaneous controls. They estimated the cumulative incidence of PASC at one year after SARS-CoV-2 infection during the pre-Delta, Delta, and Omicron eras of the COVID-19 pandemic.

I want to point out, that's one year after infection. That's really giving a lot of people a chance to get better. Among unvaccinated persons infected with SARS-CoV-2, the cumulative incidence of PASC during the first year after infection was 10.42 events per 100 persons. Initially, when we started, the pre-Delta pre-vaccine, we're talking about 10% using their criteria. Not much of a change, 9.5% in the Delta era, 7.76% when you move past the Delta era. Not a huge change. Among vaccinated persons, the cumulative incidence of PASC at one year was 5.3% during the Delta, 3.5% during the Omicron. That really gets us where we are right now. Vaccinated persons, Omicron period, we're about 3.5% of folks.

VR: It looks like vaccination cuts that roughly in half, right?

DG: Yes. When they do the math, we get about 72% of the reduction that we're seeing is attributed. We get that reduction. There's also some other things playing in.

VR: Of course, these are veterans. You have to remember, it's not a general population.

DG: Yes, these are older men, aren't they, in general?

VR: That's right.

DG: In general, because there are some veterans who are women. There are some veterans who actually are younger. No, in a large way, this is skewed towards an older male population. So, yes, 3.5%, that is a non-zero.

There was a CNN article by Brenda Goodman, "Long COVID Risk has Dropped over Time but Remains Substantial, Study Shows." Experts who were not involved in the study agree that 3.5% means the risk of Long COVID is still substantial and serious. Then they're quoting this guy again, "Large numbers of new infections and reinfections are still translating into a huge number of persons with Long COVID," Dr. Daniel Griffin, an infectious disease specialist at Columbia University who treats people with Long COVID said, "While numbers have dropped from the early days of the pandemic, we are still seeing new patients with Long COVID that developed after a recent infection."

Then I think we're going to close it off with a couple here. The article, “The Efficacy of Antivirals, Corticosteroids, and mAbs as Acute COVID Treatments in Reducing the Incidence of Long COVID: A Systematic Review and Meta-analysis,” was published in *CMI.* The investigators did a search for articles that reported Long COVID incidence post-acute COVID. A follow-up of at least 30 days, they identified 2,363 records, effect size from 14 papers. Investigating acute Covid-19 antiviral therapy concluded its protective efficacy against Long COVID odds ratio of about 0.61. That acute antiviral looks like it's going to reduce your risk of going on to get Long COVID.

Corticosteroids, not helpful, actually odds ratio 1.57, so folks getting those too early may be increasing your risk. The monoclonal antibody treatments just did not generate much of an effect. They looked through subsequent subgroup analysis revealed that antivirals provided stronger protection in the aged, males, unvaccinated, interesting enough, non-diabetic populations. Furthermore, antivirals effectively reduced eight out of the 22 analyzed Long COVID symptoms. Get those antivirals in early. They reduce your risk of acute as well as longer-term issues.

VR: Get vaccinated and if you get infected, take an antiviral.

DG: You got it. Excellent. This is, I think, where we wrap it up before we get to our emails. I think it's a fun, interesting paper here. With all we have talked about regarding the relationship between the gut microbiome and Long COVID, I just want to take a moment to share the article, “The Interplay between Diet and the Gut Microbiome: Implications for Health and Disease,” published in *Nature Reviews.*

In this review, unfortunately, behind a paywall, the authors explore how geographical location affects the gut microbiome and how different diets shape its composition and function. They examine the mechanisms by which whole dietary regimens such as, they've got the Mediterranean diet, high-fiber, plant-based, high-protein, ketogenic, and Western diet. Then they look at all the different impacts it has on the gut microbiome.

I think that our listeners will be interested in the usual suspects, for instance, what's going on with bifidobacteria. The high-fiber diet and the plant-based diet are actually going to increase our bifidobacterium species. What about those Bacteroides and the Clostridium and the Firmicutes? We're going to actually see that the Clostridium and the Bacteroides are going to go up with that high-protein diet. Bacteroides are going to go up with that Western diet. It's really interesting to look through all the different effects that we can have just with diet alone.

VR: The article is on Long COVID, right?

DG: No. Actually, the article is just on how we can use the diet to affect our gut microbiome.

VR: It would be interesting to know if these different diets have a different impact on Long COVID incidence, right?

DG: Exactly. Because we have the data, that when you get acute COVID, you get a disruption of the microbiome. We have the other data that if you can take bifidobacterium

supplements, that can help with certain - maybe instead of supplements, you just do a plant-based or high-fiber diet and then you adjust your microbiome.

VR: A lot of people are not going to like that, Daniel.

DG: [laughs] Some people will. All right. I'll wrap it up here with, as we've been saying for a while, no one is safe until everyone is safe. I'm hoping folks will pause the recording right here, go to parasiteswithoutborders.com and click on Donate. We're doing our Foundation International Medical Relief of Children fundraiser, May, June, and July. We double your donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Martin wishes Daniel a happy birthday. What was that, Monday, the 15th of July, Daniel?

DG: Yes. It was just this past Monday.

VR: What, you're 50 years old?

DG: Maybe older, 57. I turned 57.

VR: You're never going to catch up to me, Daniel.

[laughter]

DG: That's the way it works.

VR: I don't know how Martin knows this, because he recently wished Rich Condit a happy birthday. His birthday wasn't too long ago, and now you. I don't know where he gets this from.

DG: Wow. People can now put all this in their calendars, and be reminded each year.

VR: Well, I have you in my calendar now. I have all the MicrobeTV people in my calendar. Betsy writes, "My four-year-old nephew has severe asthma, which gets worse when he has a viral respiratory illness, which is often as he attends daycare. He was recently diagnosed with IgA deficiency. His doctor is recommending a year of prophylactic antibiotics since respiratory infections trigger his asthma so badly. Is there any data to support this recommendation? He doesn't frequently get bacterial infections, so it just doesn't make sense to me that this will help with the mostly viral-triggered asthma symptoms."

DG: Yes, Betsy, I like the way you're thinking it through, and I also like the way you're asking, is this an evidence-based recommendation? This is actually a standard evidence-based recommendation in this context of severe IgA deficiency with recurrent respiratory infections. It is interesting, because the idea is, oh, but these are being triggered by viruses, the antibiotics are not going to help with viruses, just want to sort of double down on that.

No, there is some data that when you get into the situation where a person has these recurrent infections, how exactly does it work? Are there some certain bacterial infections in the mix here? No, this is actually a standard and evidence-based recommendation. I think

the studies were usually done with about six months, so you could always discuss how long you're going to do the prophylactic antibiotics.

VR: Matthew writes, "What is your current vaccination guidance for adults not in the high-risk age groups or categories? For example, are yearly boosters necessary? I'm 33, no known immunodeficiencies. I've had four mRNA shots. Most recently, December 22. One bout of COVID. Last year I thought I had good protection from severe disease, so didn't get any booster for '23. Catching up with recent clinical updates, it seems that the understanding of the longevity of the mRNA vaccines may have changed. Wondering if yearly boosters should be the norm after all for those in my age group." So, 33 years old.

DG: Yes, Matthew. Nice that you're listening because I think you're bringing all the points to bear here. When we talk about the benefits of the vaccines, we're really talking about reducing your baseline risk. If your baseline risk is 20%, you drop that in half to 10, that's huge. Your baseline risk is one, you drop that in half, the absolute risk reduction is small.

We've been musing a little bit about what's going on with the longevity of these vaccines. Why do we have to keep recommending these shots every year? Most of the compelling science is in older populations where you have a big enough risk that you can see that reduction. You can imagine if you're turning 1% and 0.5%, just the sample size you're going to need. Yes, we're still learning more. In general, the recommendation is yearly boosters as the norm for folks in your age group.

VR: Linda writes, "I'm a generally healthy 68-year-old, have had all recommended mRNA COVID vaccines. My last were October 23, April 24, a few weeks ahead of events that would likely and did have COVID exposures. Though I would normally wait for the full, I would like to have another shot around August 9th, two weeks before flying to a wedding. Then I would get the updated vaccine in December, four months later, maybe trying the protein-based vaccine.

I haven't had COVID yet and have compelling reasons for avoiding infection. I live with my developmentally disabled adult daughter, and no one will come in the house to care for her if I'm sick, and I will still have to take care of her no matter how sick I am. I mask in public, haven't traveled since 2019. I would like to enjoy myself with less worry and sometimes not wear a mask at the wedding festivities. I appreciate *TWiV,* listen to the clinical update most weeks. I'd appreciate your thoughts on whether this sounds like a reasonable course of action. PS. My doctor is happy to prescribe Paxlovid for me to take on the trip. Yay."

DG: All right. Now, Linda, this all sounds like a very reasonable course of action.

VR: Brent writes, "I wanted to ask Dr. Daniel if he has read *The Lancet* article regarding Novavax, which suggests that three doses of Novavax vaccine spaced two months apart is potentially equivalent to a sterilizing vaccine. My primary care physician read it, and after consulting the FDA's guidance, approved three spaced doses of Novavax for myself and my family," and he gives links to *The Lancet* article and to the FDA guidance. "Immuno-compromised individuals, an additional dose of Novavax vaccine may be administered at least two months following the last dose. Additional doses may be administered at the

discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. I'd love to hear Dr. Daniel's opinion."

DG: This all makes sense, as we've learned over time, that initial vaccine, think of that as your prime, and then a boost. Then what we've seen, a growing amount of evidence that a third shot gives us this broadening. Maybe with Novavax, we'll see over time, is it even more durable than what we got with the mRNA vaccines? No, this seems, again, like a very reasonable approach. We're only going to have this incredibly high-quality randomized control trial data for so many things. There will be points like this where you're getting a little to the, does this make sense based upon the preponderance of data? Is this a reasonable and advisable course of action? In this case, I'm going to say yes.

VR: Terry writes, "Would you please talk about the safety of blood transfusions from COVID-vaccinated donors? I'm a blood banker. I've seen a marked increase in people requesting autologous or directed donations so they can ensure they don't get blood from a vaccinated donor. Some seem to think that blood is no longer human. Others think that since the vaccine causes so many health issues, the blood from vaccinated donors will also cause health issues, but they may not show up for years. I obviously know that's nonsense, but haven't had any luck convincing people that there's no evidence that blood from vaccinated donors is any less safe or effective than blood from unvaccinated donors. I don't even know where they're getting this particular brand of misinformation. You have any insight on this?"

DG: Yes, Terry. Unfortunately, this is out there. This is a real thing. I've run into it with patients where they require a blood transfusion and they're all focused on this. This is going to be a hard lift because this is entrenched in a cultural-tribe worldview and surrounding yourself with other people that share these similar misinformed views. This is one of the challenges in science. It's, you can prove something is true, but it's really hard to prove something is not true. I just don't know where we're going to be able to come up with science to get rid of these fears. It makes no sense. There's no evidence here that this would be the case.

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

DG: Oh, thank you. Everyone, be safe.

[music]

[00:41:46] [END OF AUDIO]