**This Week in Virology**

**TWiV 1002 Clinical Update**

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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

**VR:** From MicrobeTV, this is *TWiV*, *This Week in Virology,* Episode 1,002, recorded on April 26, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

**Daniel Griffin:** Hello, everyone.

**VR:** It still feels weird to say 1,000, Daniel.

**DG:** 1,002.

**VR:** It's hard and it's like when we went into the 2000s, remember? 2001 you had, but now we're used to "20." We say, twenty twenty-three." I guess I could say, "Ten, one," no, that doesn't work.

**DG:** No, it doesn't work.

**VR:** Forget it. We'll get used to it. Just like we're in the 900. All right, Daniel.

**DG:** We will. Well, a little bit of a change because I got a lot of feedback at *TWiV* 1,000. People always want to know what bow tie I'm wearing. Now I'm going to have to keep track and go through and also, not only will I have quotations but try to have my bow tie appropriate for the episode. I hope that my antibody or immunoglobulin bow tie is appropriate for some of the things we're talking about tonight. In the future, it'll be pretty much viral motifs but let me start with that quotation.

**VR:** What do you got on for socks? Do you have something interesting?

**DG:** They always match the bow ties.

**VR:** Wow. Good for you.

**DG: "**Our society must make it right and possible for old people not to fear the young or be deserted by them, for the test of a civilization is the way that it cares for its helpless members," and that's Pearl Buck, actually, one of our listeners sent me that quotation. Feel

free to send quotation suggestions. It's actually rather similar to another quotation I talked about before. Just about how we can really measure ourselves by how we treat the most vulnerable among us.

**VR:** I wouldn't say I'm helpless, Daniel.

[laughter]

**DG:** I like that. I don't think of you as an old person there, Vincent. Nobody thinks of themselves as an old person and maybe that's part of our challenge here. I'm going to jump right into COVID this time. I'm going to try to keep this focused. Just a reminder, and I think this is really important. We are still seeing thousands of people being hospitalized each day here in the U.S. because of COVID. Not just with COVID. About 60% are 70 or over. Sixty percent, meaning about 40% are under the age of 70.

We're still seeing over 1,000 deaths each week, narrowly defined as due to COVID within the first 28 days after being infected. We're still seeing excess deaths above that 1 million we've already accumulated. Now a common denominator, I'm going to comment about these hospitalizations, I think it's really important. At this point, 99% of the people here in the U.S. have either been vaccinated, infected, or both. The common denominator here, these people are vaccinated, they're previously infected, but they're not being offered antiviral treatment in the first week.

People are just saying, "I hope you do well." I actually share a story that I had to take a deep breath at this. I'm at the nursing station in one of the hospitals and one of the physicians, "I don't even understand why people are giving out this Paxlovid, no one really gets sick from COVID anymore. No one dies or ends up in the hospital from COVID." I looked at him, I said, "Well, if he would like, you can walk 10 feet and look in the window of the gentleman who just got COVID who is now on a non-rebreather.

We're having goals of care discussions because I don't think he's going to survive. You could explain that to his wife and then you could even talk to the doctor who did not offer him treatment in the first week." OK. Take a deep breath there. Another deep breath. Right. Right up front, we talk a lot about preprints. I wanted to mention the research letter, “Completeness and Spin of medRxiv Preprint and Associated Published Abstracts of COVID-19 Randomized Clinical Trials,” published in *JAMA*.

In this investigation, the researchers examined publication timelines, completeness, and spin in the abstracts of all randomized clinical trials, RCTs, related to COVID-19 posted to *medRxiv* during the first two years of the pandemic and compared with their published counterparts. They found that 1 in 5 of the *medRxiv* preprint abstracts remained unpublished for at least 12 months after posting. Interesting. It ends up there, 12 months later, it's still not published, which tells us something about it.

The most interesting was that these preprints that remained unpublished were less complete, more highly spun than preprints that actually went on to be published. They also commented that adoption of COVID-19 treatment protocols based on erroneous preprints suggests they say potential problems associated with less complete more highly spun preprint abstracts. I don't think suggests - We clearly saw that people with an agenda were

putting stuff up there as a preprint. Some of those studies, as we later learned, never even happened.

They weren't even studies. They were fabrications and they influenced patient care. They actually had some pretty significantly negative impacts. All right. I'm going to move on to testing because we started off pretty rough there and now I want to - let's move on to some cute puppies. Maybe its time has passed for this one, but I'm still thinking we can learn a lot for the next time. Here's an article, "Lessons Learned From a COVID-19 Dog Screening Pilot in California K-12 Schools," published in *JAMA Pediatrics*.

I've got some great photos from the article here. I know you're probably enjoying those Vincent and we will leave in a link so people can go in and enjoy this as well. Here's the cool part, I have to say. No swabbing armpits and sticking gauze and sniffing cones at some off-site. Here, the dogs just directly sniffed the people, and they actually have this picture. You've got these little kids and they're facing forward. Apparently, this is for, I don't know, healthcare privacy. They say it's for privacy. The kids are looking forward and the dogs are walking behind them.

If the dog suggests or senses that the child might have COVID, they sit down. The dogs alert their handlers, the people are looking away, those that are actually - A dog sits down behind, they go ahead and they do a confirmatory test. They ultimately are going to test a lot of folks so that they can get a sensitivity specificity. Just having a dog, you're ready for this? Just walk by, sniff the ankles and feet of the people, sensitivity, 83% and a specificity of 90%. Now, you can imagine I want to know about CT values and the ones they missed, but we're just using antigen tests in this study. What a wonderful way to screen.

**VR:** It's great.

**DG:** All right. Hopefully, we'll have that in the next pandemic. All right. Maybe we'll even have it in the future. Moving into COVID, active vaccination immunity, and we're going to be sprinkling in a bit about reinfections, talking a bit about antibodies today. Actually, we're going to even hit on reinfections and associated risks next time as a *Nature* paper out there that I want to spend a little time discussing next time. That's like the Marvel preview of what's coming ahead, but the article, "SARS-CoV-2 Reinfection and Severity of the Disease: A Systematic Review and Meta-analysis," was published in *Viruses*.

This is a systematic review summarizing the results of 23 studies addressing SARS-CoV-2 reinfections. A total of 23,231 reinfected patients were included with pooled estimated reinfection rates ranging from 0.1% to 6.8%. Re-infections were more prevalent during the Omicron variant period. The mean age of reinfected patients in these studies was about 38 plus or minus 6 years. The most common symptoms during first and second infection were fever, cough, myalgia, fatigue, headaches. This is interesting because every new variant, there's a news article about how you can tell it apart by clinical pattern.

No significant differences of clinical pattern were observed between primary infection and reinfection. Right? You're getting one, later on, new variant, you get reinfected. Oh my gosh, you can't tell them apart. If you read the newspapers, you can. No significant differences in the severity of infection were observed between primary infection and reinfection. That

seems a little surprising to me. Now, being female, being a patient with comorbidities, lacking anti-nuclear capsid IgG after the first infection, being infected during the Delta and Omicron wave, and being unvaccinated, were all associated with a higher risk of reinfection.

Interesting. I think it's worth looking a little bit more closely, a couple things that people might be asking about. Weren't we told that in new variants we're less virulent? In these reinfection studies, the most frequent variants, SARS-CoV-2 circulating at the time of reinfection in countries where studies were conducted were Alpha in four studies, Delta in four studies, Omicron in two studies, other variants in five studies. What I really like, they've got a nice far spot where you can actually look as far as hospitalizations, ICU transfer.

Prevalence of hospitalization during the first infection, 12.8%, and the second infection was 10.3%. Now, transfer to the ICU tended to be lower during the first infection than the second infection, so about twice as high with the second infection. That was a little bit surprising to me as well. We'll be revisiting this with some more data next week. I want to give a little background with a preprint and then we're going to be talking about boosters again. I just want to say don't shoot the messenger. I am sharing the science, but let's start with this preprint, “Effectiveness of the Coronavirus Disease 2019 (COVID-19) Bivalent Vaccine.”

This was posted as a preprint, so all the qualifications but important is that we are not just looking at antibody levels here. We're asking that simple question, did the vaccines provide protection? Our sophisticated listeners are certainly asking what type of protection, Dr. Griffin, what do you mean protecting us against what? Here it is protection against infection. This is interesting because we've talked about the first you complete that series, you've got maybe three shots, or you've had a couple infections, and then a shot, maybe you've got that hybrid immunity.

We have that reassuring message that the science supports that durable protection against severe disease hospitalization, Long COVID is durable. What about getting a boost? What about three to four months of just reducing your risk of getting infected, that's what we're talking about. Among 51,017 employees, COVID-19 occurred in 8.7% during the study, so 4,424. Now, the bivalent vaccinated state was associated with a lower risk of COVID-19, but now this is the really important part to focus on. It was associated with that during the BA 4.5 dominant period, so about 29% lower.

We see BQ dominant about a 20% lower, but decreased risk was not found during the XBB dominant phase. Estimated vaccine efficacy was maybe 4% for all these XBB or Gryphon variants. Maybe but this was not statistically significant, so maybe it helped a tiny bit or not at all. With this context, last week we discussed the FDA EUA modification for the bivalent vaccine. Today I want to touch on the CDC's response. We hear that the CDC simplifies COVID-19 vaccine recommendation, allows older adults and immunocompromised adults to get second dose of the updated vaccine.

Very much just sign off on the FDA modifications, but - and I'm going to go through this slowly and kind of hammer on it a little. These changes CDC include, CDC's new recommendations allow an additional updated bivalent vaccine dose for adults aged 65 years and older and additional doses for people who are immunocompromised. This allows

more flexibility for healthcare providers to administer additional doses to immunocompromised patients as needed. You'll notice they're commenting that this allows access. We don't see here anywhere an encouragement.

Let's move on. Monovalent vaccines no longer here. Now the CDC recommends that everyone ages 6 years and older receive an updated bivalent mRNA COVID-19 vaccine regardless of whether they previously completed their monovalent primary series. OK. Now remember, this isn't an additional one, this is basically, finish that series with a bivalent at the end of it. Individual ages 6 years and older who have already received an updated mRNA vaccine do not need to take any action unless they are 65 years or older or immunocompromised.

For young children, multiple doses continue to be recommended and will vary by age, vaccine and which vaccine was previously received. I will make a comment here**,** which they make, alternatives to mRNA COVID-19 vaccines remain available for people who cannot or will not receive an mRNA vaccine. CDC's recommendations for use of the monovalent Novavax or the J&J were not affected by these changes. Here we are. It's during the time we're living in the day of XBB.

The fact that a bivalent shot may have been in the past given us a bit of a boost and a small window of protection against infection, it's not clear actually that bivalent boosters actually even boost. Or that they even provide any protection against infection for XBB. Protection against disease, it is durable and I mean all disease. I mean ending up in the hospital, I mean dying, I mean developing Long COVID but it's not so compelling that boosting actually boosts.

**VR:** Do we need a boost to protect against disease or is the previous course sufficient for that?

**DG:** It does look like the previous course is, is durable. It looks like it's still holding strong. I think that's because that T-cell memory is still there.

**VR:** If the boost does not actually boost, then why are we recommending it even in older - I can see immunocompromised maybe, but 65 and up blanket, why that?

**DG:** I don't think we're actually recommending it and I think that's the point here. It's not so much recommended as -

**VR:** They're allowed to.

**DG:** Yes, we've just said, you know what? If there's certain contexts when a physician-to-patient want to go down this road, you have this access, you have this option.

**VR:** That's tough because how are they going to - from our view on this program, Dan, you get e-mails from physicians who don't know what to do. [laughs] How are they going to make a decision?

**DG:** I think at this point and we just had an urgent care call and I'm not recommending it, actually, I'm saying, you know what? We'll see, maybe in the fall, maybe we'll have a - and

this does raise, maybe we will have a new formulation because it doesn't look like the current one is really doing it. It will be interesting if some people go ahead and if we get some new data. That's science. We're always waiting, is there any information that informs us in a different direction? Right now we're not seeing any compelling data.

Small percentage of people got the last boost. I don't expect there to be a huge uptake here.

**VR:** What's the percentage? Do you know offhand?

**DG:** It's like less than 20% I think of folks got that boost. Yes, not a huge amount, but I do have some good news and I think this is important. That was the end of don't shoot the messenger. I'm just sharing the science. I would've loved if we had some great data that boosting really boosted, but COVID passive vaccination, and this has been a tough area for those folks who are immunocompromised, those folks who could not get that response. AZD3152, I teased about this last time. It is a new antibody from AstraZeneca that may be able to neutralize, they say all known viral variants.

This is envisioned as the Evusheld substitute. The data was actually presented as a poster at the 33rd European Congress of Clinical Microbiology and Infectious Diseases. They've got a six-letter acronym, I'm not going to bother, Copenhagen, Denmark. That was April 17. There's actually the "Francica J et al. The SARS-CoV-2 monoclonal antibody, AZD3152 potentially neutralizes historical and currently circulating variants." I think that is honest. AZD3152 was derived from B-cells donated by convalescent patients after SARS-CoV-2 infection.

AZD3152 was optimized with the same half-life extension and reduced FC effector function and complement C1q binding as Evusheld. The extended half-life is expected to confer protection from COVID-19 for six months. That's just something, it is interesting. We have the ability or people have the ability to really modify the half-life of these agents to really almost whatever we want. There is an ongoing SUPERNOVA Phase 13 trial. This is a new one, evaluating the safety and neutralizing activity of AZD3152 for the prevention of symptomatic COVID-19 in adults and adolescents 12 years of age and older.

Participants have conditions that cause immune impairment may and may not mount an adequate protective response after COVID-19 vaccination and therefore are at high risk of developing severe COVID-19 if they become infected. Actually, they're anticipating to have results in the second half of 2023. One of the things I'm hoping is done here is a real focus on efficacy, not just on neutralization because as we've learned, we may have thrown some stuff away while it still had some efficacy, just not neutralizing efficacy.

**VR:** Generally, this is a single monoclonal, correct?

**DG:** Yes, which has me a little worried. This is great, but I almost would've liked to see it as part of a cocktail with maybe another or maybe even three in there.

**VR:** Do you know where the epitope is? Is it at the interface of ACE2 and spike, or is it somewhere else? Do you know?

**DG:** I don't actually. It's neutralizing, right?

**VR:** Yes.

**DG:** I'm assuming it's going to be in that receptor-binding domain, but I don't know exactly where it binds.

**VR:** OK. Some antibodies against the N-terminal domain can also neutralize, but they're rare and less potent, I understand. Probably that's not here, but we don't have that data. They haven't published this yet. It's opposed to -

**DG:** I have very limited information, just I've got poster presentation shared and some links that people can look at. A lot less data than I would like, and we will get more before this gets approved. All right, so let's move into that situation, that window of opportunity that for, unfortunately, the gentleman that I described right up front, he tests positive. What do you do? Listen, I agree. Most people are going to be OK, but still, an individual gets diagnosed, if they're high-risk, we have the ability to reduce that risk further.

We have the ability to keep that individual out of the hospital, to significantly reduce their chance of dying. We're going to talk even a little more and reduce their chance of Long COVID, probably. Number one, Paxlovid. Number two, remdesivir. Number three, molnupiravir. Let's talk a little bit more about that today. I will say an exciting article more from a mechanism standpoint. The article, “Molnupiravir and Risk of Post-acute Sequelae,” the *BMJ*.

More data out of the *VA* and here we have a cohort study, 229,286 participants who tested positive for SARS-CoV-2 between 5th of January, 2022, 15th of January, 2023. It's about a year, and had at least one risk factor for progression to severe COVID-19 and survived the first 30 days after testing positive were enrolled. We're forgetting about any potential benefit here to mortality because we're going to look at something else. 11,472 participants received a prescription for molnupiravir within five days of the positive test and 217,814 received no COVID-19 treatment.

Now PASC, post-acute sequelae, of COVID was defined based on a pre-specified set of 13 post-acute sequelae. They reported that compared with no treatment, the people that survived, the folks that got molnupiravir use within five days of a positive SARS-CoV-2 test result was associated with a reduced risk of PASC, relative risk 0.86. About a 14% reduction and absolute - and I think this is important. Absolute risk reduction at 180 days was about 3%. Post-acute death, they actually give us a hazard ratio there, post-acute hospitalization.

I want to point these out. The post-acute death, we've narrowed, defined. I talked upfront about dying from COVID is dying within those first 28 days, but people then die in the next 180 at a significantly higher rate. If you follow the folks that got molnupiravir out to 180 days, the hazard ratio is 0.68. 38% reduction in that post-acute death, and we're also seeing a 14% reduction in that post-acute hospital admission. Molnupiravir was associated with reduced risk of eight of the 13 post-acute sequelae.

So less dysrhythmias, less pulmonary emboli, less deep vein thrombosis and less of that fatigue and malaise, less liver disease, less acute kidney injury, less muscle pain, and less neurocognitive impairment. This was across the board, molnupiravir was associated with reduced risk in folks that had not received a COVID vaccine, still out there. Folks that had

gotten one dose, two doses, people that were boosted, people that were getting it the first time, people that were reinfected. All the way across the board.

All right. Number 4, convalescent plasma .An early treatment option for the treatment of immunosuppressed COVID-19 patients at high risk for progression of severe disease who have no other treatment options. Remember, this is first week the IDSA has recommended against the routine use of convalescent plasma among immunocompromised patients hospitalized with COVID-19.

**VR:** It's too late at that point.

**DG:** It's too late. It's about timing. This is not saying bad stuff. They're just saying you've missed your window. Then week two, the early inflammatory, the cytokine storm, Number 1, we have steroids. That looks like a target dose of about dexamethasone, 6 milligrams a day times six days , so six times six**.** Our anticoagulation guidelines, pulmonary support, remdesivir maybe if we're early enough, immunomodulation, tocilizumab, maybe baricitinib, avoiding those unnecessary antibiotics and unproven therapies.

Sometimes people have infections, probably about 10% of the time. There might be a secondary bacterial or fungal process that you want to consider. Then we will wrap ourselves up with a few, I think, interesting articles and preprints. The preprint, "Risk of New-onset Long COVID Following Reinfection with SARS-CoV-2: A Community-based Cohort Study," was posted on *medRxiv*. This is a UK study looking at self-reported Long COVID, 12 to 20 weeks after each infection. Separate analyses were performed for those less than 16, those 16 or older.

In this preprint, Long COVID was reported by those 16 or older, 4% and 2.4% after the first and second infections respectively. Lots of limitations, but there is some consistency here with what we're seeing. We are seeing less new cases of Long COVID, but we're seeing less. We're still seeing them. I want to point about that. Are we still talking about vitamin D? I still have that jar. I should actually take some vitamin D. The article, "Low Vitamin D Levels are Associated with Long COVID Syndrome in COVID-19 Survivors," was published in *JCEM*.

Long COVID was defined according to the NICE guidelines. Just let me pause here and explain. National Institute for Health and Care Excellence, they left the "h" out of there, but I'll leave in a link. [laughter] What is that NICE definition? N-I-C-E definition. Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body.

Post-COVID-19 syndrome may be considered before 12 weeks, while the possibility of an alternative underlying disease is also being assessed. Then, in addition to the clinical case definitions, the term Long COVID is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 from four to 12 weeks, and post-COVID-19 syndrome 12 weeks or more. Now we got our definition. Fifty Long COVID and 50 non-Long COVID subjects were matched on a one-on-

one basis, enrolled from an outpatient, post-COVID clinic cohort seen from August to November 2020.

Therapies, comorbidities affecting calcium, vitamin D, bone metabolism, and or admission to ICU during hospitalization were exclusion criteria. They measured the vitamin D at hospital admission and six months after discharge. They observed lower vitamin D levels at follow-up in subjects with Long COVID than those without. Not a huge difference, 20.1 versus 23.2, p-value 0.03. Regarding the affected health areas evaluated in the entire cohort, they observed that lower vitamin D levels were found in those with neurocognitive symptoms compared to those without.

There was a bigger spread, 14.6 in those with neurocognitive symptoms. All right, and I'm going to wrap it up with a last article with a bunch of comments. This article must have gotten tweeted or something because I've been getting a lot of questions specifically about it. The article, “Clinical Experience with the Alpha-2 adrenoceptor agonist, guanfacine,” that's guanfacine, G-U-A-N-F-A-C-I-N-E. Not to be confused with something else, with a bunch of similar letters, “and N-acetylcysteine (NAC) for the Treatment of Cognitive Deficits in Long COVID-19.”

This was published back in November, but as I mentioned recently, seems to have gotten a bit of attention, a couple patients just this last week asking about it. This is really a series of case reports and it is not in any way a placebo-controlled trial. Twelve patients with brain fog, including difficulties that executive function were treated with guanfacine. It's a medicine often used in ADHD, one milligram, PO at bedtime for the first month, increase to two milligrams after one month if well tolerated. They also were getting 600 milligrams of the NAC daily.

I must say the NAC at a 500 or 600 once or twice a day is being used quite often by a lot of folks with Long COVID. This combination of guanfacine and NAC improved cognitive abilities at eight of the 12 patients, four patients discontinued therapy, two for unspecified reasons, two due to hypotension and/or dizziness, which actually are common side effects of guanfacine. This isn't something you just give out, you need to actually pay attention. Those who stayed on the guanfacine and NAC reported improved working memory, concentration, executive functions, including a resumption of normal workloads.

One patient briefly stopped due to a hypotension episode, and then actually reported a return of cognitive deficits that abated, then resumed guanfacine treatment. A couple comments here, this is a case series, and that was worry, people put out case series. One of the couple comments I'll make, one is, the natural history of Long COVID, of post-acute sequelae of COVID, in most cases, is gradual recovery. You always worry when you give people something. Did they get better, you get to take credit because you did something.

These are things where we really need randomized control trials. I really find this an incredibly challenging area to practice, and not only are people suffering, but I do not like the lack of evidence-based guidance in this area. We really need to change that.

**VR:** Do we have any idea of the mechanisms of guanfacine and acetylcysteine for Long COVID?

**DG:** We have ideas. The guanfacine, I think we're thinking of it similar to ADHD, so having that neurological benefit. The NAC is purported to be an anti-inflammatory medicine, antioxidant, et cetera. I actually have several patients who swear by it, anecdotal evidence, ouch, I can't believe I'm actually saying that. Low-middle-income countries, the rest of the world, let's just remember, no one is safe until everyone is safe. I am hoping people, more than one or two, will pause the recording, go to parasiteswithoutborders.com and click Donate, because we're finishing up actually our ASTMH fundraiser.

This is our last show that will drop. February, March, and now just for the last little bit of April, donations made to Parasites Without Borders will be matched and doubled up to a potential maximum donation of $30,000 to ASTMH. Not only we're going to support them now, but in October we're going to be headed to Chicago to do another live recording there.

**VR:** That's fun, I look forward to that, and hopefully this time we don't get COVID, me and Dickson, right?

**DG:** [laughs] Yes.

**VR:** Time for your questions. For Daniel, you can send them to daniel@microbe.tv. Efthemis writes, "What an enjoyable 1,000th episode. This is so exciting that *TWiV* has been this successful. Congratulations on this huge milestone. Dr. Griffin, during this episode, you mentioned you got infected with Dengue virus twice before you became extremely curious about virology. I'm fascinated with Dengue virus above all other viruses. I would love to learn more.

Could you go into more depth about your experiences during both infections? Which serotypes did you get infected with, what symptoms do you expect to get if you get a third infection, and how deadly is Dengue for every subsequent infection? Is the third much deadlier than the second? The data for this seems to be inconsistent. I'm not sure what to believe."

**DG:** These are great questions. The first part which I'll talk a little bit about my experience as I shared on *TWiV 1,000*. The first time I got sick, I had no clue. It was really in retrospect the second time that I figured out what the story was. So, we'll start with the second time. It's the second time I spent a couple of weeks. I've been in Zambia, Zimbabwe, canoeing down a river, I'm camping out in pop tents, hiking through the bush. I really had this silly idea, was explained to me, that if you stay inside a pop tent, the elephants, the lions, hyenas, they won't come in, you're perfectly safe, seem to work.

It was interesting, you'd wake up in the morning and there would be elephant footprints, they would just step over the lines that were holding the pop tents. You just basically held it in if you had to go until sunlight. On my way back from that, I started to feel sick. It really was this classic of getting fever, horrible headache, pain behind the eyes, then I had this characteristic rash, and it was later that the platelets dropped. That was when the history was pulled together, that for me, this was probably a second infection with Dengue, probably with a second serotype, particularly with the gap of time.

An interesting thing about that, I think this is important, just to use this as a forum to comment on, is the majority of cases of severe Dengue are actually in children, and for

them, it may actually be their first infection. We always think of it as reinfection and we just talked about the antibody-dependent cellular cytotoxicity, this enhancement. This fact that because it's a little bit off, it's actually improving viral entry into cells as opposed to neutralizing. Really, I was actually listening to one of the first three episodes of *TWiV*, where Dengue was discussed it.

We really think at this point, not DENV-3 but DENV-2 is probably associated with most of the severe cases. Interesting thing, back when I got Dengue in Sub-Saharan Africa, no one believed Dengue existed there. We now know it does, by the way, it's one of the things you don't test for it, it's not there. Now that we test for it, particularly in returning travelers, yes, it's there. It's really fascinating. Not only is a fascinating disease, but because of that issue with one type of Dengue infection really precipitated potentially a severe second infection.

That's why vaccines are so tricky here, because you've got to maintain high levels of protection against all the different serotypes.

**VR:** Matthew writes, "I'm a healthy 45-year-old man who received the second dose of Pfizer COVID vaccine in 2021, three weeks after the first dose. I have not tested positive for COVID at any time, I have not had any symptomatic respiratory infection for at least five years. I lead a normal life and don't usually wear a mask, so it strikes me as unlikely, although not impossible, that I have not had an asymptomatic infection. I eat a healthy plant-based diet, exercise 30 minutes a day, of healthy weight, no medical conditions.

I've heard you mention several times that the three-week gap was too short, and the vaccine should really be considered a three-dose vaccine. However, isn't it likely that as almost two years have passed since my second dose, the memory B-cells have already matured in this time, with or without asymptomatic infection? I don't really see much value in a booster, and in some countries like the UK would not even be entitled to one. The bivalent booster is available to me, but I'm not inclined to get it as the risk of serious disease seems so low. Do you see any flaws in my analysis?"

**DG:** I think this is reasonable. Let's go through as you did. You say healthy 45-year-old man, it's really at 50, we start to see, 65 is really when the risks start to go up. I'm thinking in my head as I say without ending up in the hospital of dying of this. I'm not sure I can say the same about Long COVID. That seems to a roll of the dice. There is age-associated risk there. We've talked about this several times. The three weeks apart made sense in the pandemic, it made sense because that was what science was.

From an immune standpoint, it probably makes more sense if you're not under those pressures to have a larger gap between those doses. I'm not even sure if that third dose at six months is just properly timed, or if you really need three doses. I don't know if we'll ever get the data, but it would have been wonderful to have a comparison of people that get up front, people that get a shot three weeks later, people that get a shot six months later, but didn't get or did get that shot at three weeks later. You also make another thing, which I think is, there is a lot of SARS-CoV-2 virus out there.

Have you been infected since, may or may not notice, do you have hybrid immunity? A lot of your logic here is reasonable.

**VR:** I think he's probably been infected asymptomatically, I would guess.

**DG:** Yes, I would suspect.

**VR:** The real point is that, that second dose too close interrupts the affinity maturation, and it doesn't go back again. It's not like, because it's been a year, Matthew, that it's caught up, no, it never does because it's interrupted.

**DG:** It was interesting that comparison of the UK that did it at three months for other reasons, not necessarily, may have actually been worked out well.

**VR:** Louise writes, "I'm a family physician in suburban Pennsylvania, and in March, my nephew brought home a cold. His 8-month-old daughter ended up having a seizure and was diagnosed with human metapneumovirus. I have not taken care of adults or children with this. I'm curious if Daniel has seen much of this in his adult population in addition to the RSV, which you've discussed."

**DG:** Yes, so human metapneumovirus, I used to joke, was one of my favorite viruses. The reason I said that is it had a clear seasonality. It would for me be like, "Oh, the sun's coming out." We would have flu, we'd have RSV and then in about early April is usually when the human metapneumovirus season would start in the Northeast, which reminded me spring is coming, time to start thinking about getting the sailboat ready. It is interesting because human metapneumovirus often causes a lot of bronchospasms.

Sometimes clinically you get a little bit of a hint. Yes, I don't have a good reference on that. We have actually seen quite a lot of human metapneumovirus in the whole spectrum. It's quite contagious, right? Mom, Dad, Grandpa, kids, it's enough actually that it'll put folks in the hospital. Still a little bit out of seasonality. It's lost that charm for me at the moment. Many viruses have, but yes, it's actually quite common. It's a virus, we don't have any specific antivirals. If you recognize it, it's good to keep your hands in your pocket with those antibiotics.

**VR:** JB writes, "I am a primary care physician actively caring for COVID patients who recently contracted COVID for the first time. Fully vaccinated, but based on risk factors. Took Paxlovid on the day tested positive, initially felt good. Day three, felt extremely fatigued; by day five, felt better. An antigen test negative returned to work while masking. Day 10 started feeling URI symptoms again, tested positive for the next five days. An antigen test SaO2, totally normal, through the second week.

Mike Osterholm said he took a second course of Paxlovid for folks that get ill again after Paxlovid treatment that clearly aren't hypoxic. Is there a role for retreating with an antiviral? As a follow-up, is it possible that we may be treating too early with antivirals, as in my case, where I could test ad lib and initiate antiviral immediately and not allowing the immune system to get fully engaged leading to recrudescence of symptoms?

**DG:** Dr. Ketner, for everyone out there, I'm glad you're asking this and I'm going to go through this because I think that this is a huge misconception. Sorry, Mike, sorry Anthony, sorry Joe, Kamala, everyone else who went down this road, listen. We really now understand what we thought we understood early on. Now it's really, we have a lot of

science behind this. It's during the first five days that you have the significant viral replication, it goes up. When you do one of those swabs, you're talking millions, you do a PCR 12, 13, 14, it comes up hot positive.

The first five days is the period of active viral replication. That is your window of opportunity for antivirals. Whether they be small molecule like Paxlovid, molnupiravir, remdesivir. Whether they be antibody therapies like the cocktails we used early on. You do not wait, and I'm going to comment why you do not wait. You'll lose time. This is like waiting to treat a stroke. If you start that antiviral within the first three days, you have better outcomes than if you wait to day five. I know there were some people out there saying, give your immune system a chance to respond.

That is not helpful. That is what we were trying to prevent. We were trying to prevent your immune system from that dysfunctional response. First week, that's the window for antivirals. We have studied antivirals after that first-week ad nauseam, they are not helpful. Paxlovid is five days, that's the deal the second week. Then you say on day 10, started feeling URI symptoms again. I'm going to rephrase, I'm going to say on day 10 you started to experience the cytokine storm, the early inflammatory phase.

In most cases, hands in your pockets, antivirals, convalescent plasma, some more Paxlovid, not helpful. I'm glad you were checking your oxygen saturation because a subset of individuals, if the oxygen drops below 90%, a short course of the right dose of steroids makes sense. If you stay in the 90s, you're better off doing nothing. I think people really have to realize this, starting that Paxlovid, it's to keep you from having that dysfunctional immune response that ends up getting you into the hospital, ends up triggering something that might lead to your death, ends up maybe leading to Long COVID.

**VR:** This is the problem, Daniel, guys like Mike Osterholm who have a lot of listeners, he does something, and then everyone thinks they should do the same thing, right?

**DG:** It was tough, though. I hate to be, Anthony Fauci did this. Mike Osterholm did this, Joe Biden did this, Kamala Harris. A lot of prominent people did this. You got to realize like if you could do something not so - just don't tell anyone about it if you're going to do it. If you tell everyone, they're going to do it too. The science not only doesn't support this, but we've looked. It's not that there's an absence of science. There's plenty of science. This is not helpful.

**VR:** They're not doing trials, they're just one-off. That's not how we do medicine as you know. Science-based medicine, that's *TWiV*, weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

**DG:** Oh, thank you so much. Everyone be safe.

**Vincent:** Hey, we're getting like the news programs. [laughter] We're going back. All we need is a big desk with a glass top and we'll be all set.

[music]

**[00:46:20] [END OF AUDIO]**