This Week in Virology

TWiV 1126 Clinical Update

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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 1126, recorded on June 27, 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 see some viruses on that bow tie, don't I?

DG: You do, and they've got these spikes sticking out all over. I wonder what it could be.

VR: I think it's the SARS-CoV-2.

DG: It's definitely SARS-CoV. It's hard for me to tell whether it's the One or the Two. Considering this was made prior to 2019. Probably the -

VR: SARS-CoV-1, right?

DG: - Version One.

VR: I haven't seen that one before. That's a new one. Very good.

DG: All right. Not sure how many Kurt Vonnegut fans we have, but perhaps to lighten the mood before we get into things. “True terror is to wake up one morning and discover that your high school class is running the country.“ Barnaby just graduated. My youngest, my 19-year-old, just graduated from high school, so I'm looking out at his class. Maybe not as terrifying if that class runs the country compared to my high school class, because I was a member of that high school class, so what could be more frightening? Lots going on with RSV.

It's actually my cousin, Peter Gates, texts me the other morning, "Dan, what do you think?" We've covered the durability of some of the RSV vaccines, so the GSK's vaccine, Arexvy, about 68% effective over 23.3 months in a clinical trial. Pfizer's Abrysvo was 78% effective after 16.4 months. Really good, holding steady. Then, everyone's, of course, thinking, oh, those mRNA vaccines, those are just going to knock everyone down. Moderna's mRNA vaccine for RSV

showed an efficacy at 3.7 months. First season, 78.7 or 80.9. This is when they define it as RSV lower respiratory tract disease, with either two or more or three or more symptoms, but only about a 50% efficacy in preventing the illness after 11 months.

VR: Eighteen months.

DG: Eighteen months, sorry about that. Yes, so 18 months.

VR: The Arexvy and Abrysvo, they're both protein-based vaccines, right?

DG: Yes. This is mRNA.

VR: This is very interesting. We're starting to see a picture formulating here, aren't we?

DG: That's what I'm a little bit concerned about. We all got all excited about mRNA has saved the day. I'm really curious, and we're going to talk about a study coming up where it looks like with the mRNA vaccines you got to get a booster every single year. It doesn't seem like you get the durability that we were used to with our traditional vaccines. Is it an issue with the mRNA technology and how that triggers the immune system? I'm curious. Novavax, right?

VR: What's the durability of Novavax? Do we have any studies on that?

DG: I would love to see those. I was looking for those. If I can dig some up or get some data, I'm going to talk a little bit. That is a very interesting thing to be thinking about.

VR: Just anecdotal information, when I was at the Karolinska a few weeks ago, one of the immunologists, she said protein is going to be more durable overall than mRNA.

DG: Let's hope Novavax as a company survives, and we can find out. I don't know if you remember, last year, I was trying to get my Novavax vaccine before one of those conferences, and I ended up getting an mRNA vaccine. It was just the timing issue. Still ended up with COVID. I got an mRNA vaccine. Who knows? We'll see. We also got news as of Wednesday, the 26th, the CDC updates RSV vaccination recommendation for adults. CDC updated its recommendations for the use of respiratory syncytial virus vaccines, RSV vaccines in people ages 60 and older.

It's interesting, *The New York Times* headline, they pull back. They're actually recommending less broad. Everyone aged 75 and older should receive the RSV vaccine. People ages 60 to 74, previously this was just go ahead, shared decision-making, they say people ages 60 to 74 who are at increased risk of severe RSV, meaning they have certain chronic medical conditions such as lung or heart disease, or they live in nursing homes, receive the RSV vaccine. This recommendation is for adults who did not get an RSV vaccine last year. Because last year, people got those two non-mRNA.

We still think there's durability there. The RSV vaccine is not currently an annual vaccine. Who knows, for the mRNA, maybe it needs to be. People currently do not need to get a dose every RSV season. Now, eligible adults can get an RSV vaccine at any time. People who've been listening might think about this and follow the CDC that says, the CDC Advisory Committee, says the best time to get vaccinated is probably late summer, early fall, because that's about

when RSV usually starts to spread in communities. Remember, it starts a little earlier down in Florida, down in the South.

Those are probably late summer. Here in the Northeast, we get a little bit later. Mandy Cohen, what does she have to say? The CDC has updated its RSV vaccination recommendations for older adults to prioritize those at highest risk for serious illness from RSV. Then just reiterates people 75 and older, 60 to 74 with certain chronic medical conditions or living in a nursing home should get one dose of the RSV vaccine to provide an extra layer of protection. What's going on here? Why did they step back a little? Couple things.

One is the suggestion that the committee viewed the potential elevated risk of the neuroinflammatory condition, Guillain-Barre syndrome, as a reason for hesitation. Despite evidence suggesting that GSK's Arexvy does not statistically increase the risk, the signal's all coming from Pfizer's Abrysvo. The other point is that the advisory group acknowledged that this whole concept of shared decision-making, it's really just not easy to do in clinical practice.

You end up with this unclear messaging regarding who really should be vaccinated. I think the acknowledgement that patients and their providers could use a recommendation, not just you guys sort it out, shared decision-making. Now, the group also postponed a recommendation for use of GSK's Arexvy in people ages 50 to 59 due to a lack of data, and again, this Guillain-Barre lingering concerns.

VR: As you just pointed out above, the durability of a single shot is very good, so this is OK.

DG: Yes, it's great. It looks like it's great for the traditional GSK-Pfizer RSV vaccines, maybe not so good with the mRNA. Of course this was not head-to-head. Maybe there was something special about the mRNA vaccine trial. I have to tell you, if it went the other way, they wouldn't be throwing any caveats. Anyway. This is really disturbing, moving into COVID. I put up the map and there's a link. I'm recommending everyone click on this link and look at our map. What is going on in Puerto Rico? It went from this hash-tagged, what is like, a teal color to green to yellow.

Now we're up at orange. We're up at 6% to 8% of deaths in Puerto Rico are due to COVID. That's a lot. We're really seeing a rise there. That's a hard endpoint. We're basically seeing for the wastewater, that pattern that we saw last year, a year before, we see this summer rise, and then a little bit of a drop, and then the winter peak. We're seeing that summer rise. We'll see what happens there. I have to say locally, yes, we're starting to see admissions. Really a downer this week. I had a 33-year-old gentleman die from COVID in the ICU. Just, we're seeing admissions. We're seeing people end up in the ICU. Maybe we'll talk a little bit upcoming, like what is going on? Why are we losing ground here?

VR: Puerto Rico is a vacation destination. That could be part of it.

DG: Interesting. I wanted to discuss what I thought was a really interesting article. There's every so often, hopefully, an episode, Vincent, where they're going to have a little soundbite because we're teaching something important. Doesn't happen very often. I had dinner with the whole ID group at Columbia. Magda, the head of the division was talking about how I am valued for the wisdom that I bring to the group. I was a little embarrassed. Maybe this is some

of that wisdom, Vincent. It's really borrowed wisdom. This is the article, "Human SARS-CoV-2 Challenge Uncovers Local and Systemic Response Dynamics," published in *Nature*.

I suspect most of our listeners remember when the Brits exposed a bunch of healthy people to pre-alpha cells SARS-CoV-2 to see what would happen, a bunch of crazy scientists over there. Here are the investigators' report on results from single-cell multi-omic profiling of nasopharyngeal swabs and blood looking at, we're going to go more into depth, these abortive, transient, and sustained infections in seronegative individuals challenged with SARS-CoV-2. First off, I want to walk slowly through what I think is really important language. The first concept, the first term, is abortive infection.

As we're going to learn in this article, some people get exposed to the pathogen. They remain PCR negative, they remain seronegative, they're asymptomatic, but they have a detectable innate immune response. That's abortive infection. Transient infection, you get a positive PCR, but not more than one quantifiable detection of viral RNA over time. You can pick it up, there seems to be some replication going on, high enough to be detected and then that's the end of it. Then this is like what we usually talk about, sustained infection, at least two quantifiable detections of viral RNA over time.

You can see that this is different from asymptomatic versus symptomatic, and perhaps opens a discussion about what is going on with those abortive infections that seems ideal. Would we even call it an abortive infection versus an abortive exposure? I think as we learn here, there must be some degree of limited viral replication and limited infection as we're seeing an immune response, not just an adaptive response. This is a complex 38-page *Nature* research article that deserves a few hours of time. There is a brief discussion, and I do encourage -

This is a brief discussion, I do encourage a deeper dive, just the brief discussion. The investigators report detecting activation of MAIT cells and certain monocyte responses that occur during early and abortive infections. MAIT cells, who's heard of those? These are mucosal-associated invariant T cells, so MAIT, "mate" cells. They're a subset of T cells that you can find in the blood, but they're also enriched in many tissues. The mate cells, MAIT cells, express a semi-invariant T cell receptor restricted by the MHC class 1-related MR1 molecule.

During sustained infections that lead to disease, symptomatic COVID-19, they observed an immediate and new APR in ciliated cells at the site of infection. In addition, they described a distinct cell state for activated conventional T cells that harbor SARS-CoV-2-specific T cell receptors and showed that this signature could be projected onto patient cohort data to identify disease-specific T cell responses. In sustained infections, they saw global activation of interferon signaling that affected all circulating immune cells. Interesting in that the activation of interferon signaling in blood preceded widespread activation at the site of inoculation.

Odd, right? We're seeing this widespread before we see a lot going on locally. The activation of interferon signaling at days five to seven after inoculation coincided with global immune infiltration and a peak of detectable virally infected cells. This relatively slow immune infiltration at the site of inoculation is in contrast to the immediate immune infiltration that we observed in individuals that were only transiently detectable. This data suggests that

individuals with HLA-DQA2, so this is MHC class 2 expression, seem to be better at preventing the onset of this sustained viral infection.

Very complicated stuff here. I don't expect everyone to take this all in. Really the takeaway I wanted was this concept of abortive infection, transient infection, and then sustained infection that might be symptomatic or asymptomatic. This is fun, Vincent. Remember when we discussed that study where it appeared that coffee can inhibit multiple variants of SARS-CoV-2 infection by restraining the binding of the SARS-CoV-2 spike protein to ACE-2 and reducing TMPRSS2 and cathepsin L activity, and they suggested that we should all be drinking and perhaps inhaling a little bit of coffee each day?

[chuckling]

VR: Right.

DG: You were the one who suggested that we needed to be actually aspirating or inhaling those two cups, not just drinking them down. This week, more fun or less fun, “Cannabis, Tobacco Use, and COVID-19 Outcomes,” where they tell us that smoking on the weed may not be the best idea. This is a *JAMA* publication. In this study of over 72,000 patients, they reported that current tobacco smoking was significantly associated with increased risk of hospitalization, so odds ratio 1.7, ICU admission 1.2, all-cause mortality 1.37.

What about smoking on the weed cannabis use? Also significantly associated with increased risk of hospitalization, almost doubling it, odds ratio 1.8, ICU admission 1.27. Not all-cause mortality. They did adjust for a number of factors, including vaccination, comorbidity, diagnosis date, demographics. Apparently, Vincent, you can inhale your coffee, but don't inhale the cannabis.

VR: Cannabis, tobacco, they are plants. You burn it. You inhale the smoke. There's just no way this is going to be good for you. Didn't someone say at one point a while ago that weed was good for COVID?

DG: Oh yes. I won't mention which family member, but if my family is listening, they know who we're talking about. He was smoking weed to keep himself. He was like, oh, don't you worry, Dan. I'm not going to get the COVID because I'm surrounding myself in a cloud of the weed smoke. I'm like, what are you doing? His wife was quite unhappy with his approach. Here's some science saying his smoking on the weed is not a good idea. He ended up with COVID. Then when he called, I'm like, oh, that must have been a mistake because you're smoking on the weed. Doesn't that protect you? [laughs]

This is an interesting article. The article, "Estimated Effectiveness of the BNT162b2 XBB Vaccine against COVID-19," published in *JAMA Internal Medicine*. These are the results of a test-negative case control study performed to estimate the effectiveness of the BNT162b2 XBB vaccine against COVID-19-associated hospitalization and emergency department or urgent care encounters among adults in the Kaiser Permanente Southern California health system between October 10, 2023 and December 10, 2023. Cases were those presenting with an acute respiratory illness.

Then you have your cases had a positive PCR for SARS-CoV-2. Then the controls had the acute respiratory illness but they tested negative. Among 2,854 cases, 15,345 controls, you end up with this median of 34 days prior versus not having received the XBB vaccine of any kind, 62% against COVID-19 hospitalization, 58% for ED urgent care visits. This is the caveat that I want to point out.

Compared with being unvaccinated, those who had received older versions of the COVID-19 vaccines, they said, oh, I've been getting enough of them shots, I'm done with that, I don't need a shot of that XBB this last fall. They did not get their yearly shot as recommended, did not show statistically significant reduced risk of COVID-19 outcomes including hospital admission. It seemed to be no durability past that year.

VR: I think that's the key. It's not really a strain-specific issue, it's durability. Because I think T cells should be - we've seen a number of studies where T cells help moderate disease severity, but I think they're just not lasting here because of the mRNA vaccination.

DG: I think this is the theme that I'm concerned about is, yes, the mRNAs, you make them quick, they're great, you get them out of the gate, you protect people but then now you've got some time. Do you just keep giving an mRNA vaccine every single year? We see that people just really are not up for that. Or, once you've got a little bit of time, do we move over to a protein-based, what people still refer to as the traditional platform approach? We're starting to see that story and we'll see, is this an mRNA vaccine thing? Is it a COVID thing? With the RSV data, it's starting to suggest it might be an mRNA vaccine thing.

VR: I think we need to have some studies to confirm that with the protein-based vaccines.

DG: Early viral phase, you test positive. Unfortunately we're getting a bunch of these folks now as we're seeing numbers come up. We have guidelines. We have NIH COVID-19 treatment guidelines, we'll leave a link. We have ID Society of America, IDSA guidelines, we'll leave some links. We'll leave in that COVID-19 drug interaction checker. I still get people texting me, calling me, like, what about this interaction? Go to covid19-druginteractions.org/checker. Look them up. They're great. They guide you. They let you know exactly what to do.

Keep checking those interactions. It's not hard to do. You just need a computer and access to the internet, maybe your phone, which is really a computer in your pocket. This week, I will mention the article, "Adjunctive Statin Therapy in Patients with COVID-19: A Systematic Review and Meta-analysis of Randomized Controlled Trials," published in the *American Journal of Medicine*. Make sure you go a little bit into this. Don't just read the headlines. I read the headline, I was like, wow, that's surprising. Then I read the article.

Here the authors systematically searched Medline, Embrace, Cochrane, and ClinicalTrial.gov databases from March 2020 to late April 2024 for randomized controlled trials, RCTs, comparing statin versus no statin use in patients hospitalized with COVID-19. What about the dark and the gray web, Vincent? I love when they do that. They pooled risk ratios and hazard ratios, applied this random effects model, and they ended up with seven RCTs, 4,262 patients, of whom 2,645 or 62% were randomized to get a statin.

They do point out that although individual studies included in this meta-analysis have not found any statistically significant difference in overall death, when they piled the cowpies seven high, they turned into gold. They reported that they performed this meta-analysis, compare with no statin, statin use significantly reduced case fatality rate. Give us a relative risk of 0.88. You can see the confidence interval, 0.80 to 0.98. They just make it. Maybe a 12% reduction. There are, however, no statistically significant differences between the two groups in length of hospital stay, elevation of liver enzymes, C-reactive protein levels.

A bit less impressive when you actually look at the figure. If you look at Figure 2, I'm going to say, before you start quoting this, go ahead, look at Figure 2, this is really a study of REMAP-CAP that has a weight of 63.1% and is really just getting pushed over the line. By adding these other studies. In even closer inspection, you see that they're really only adding four studies, as the Davoodi and the RESIST study contribute a weight of 0% each. Then the Ghafoori and Hejazi, really they're contributing 0.4% each. Unfortunately, this is behind a paywall. It's hard for you to see more than the headline, but not sure how many people will get a chance to move past the headline, see these actual forest plots.

VR: Daniel, is 12% worth doing?

DG: If it was true, then - the only problem is I don't know if it's true when you have to do all this to make it true. The REM-CAP, which is 1,835 statin folks, you have 504 events, not reaching statistical significance. Maybe a little bit of a trend. Now you're introducing a new drug, statin. I'd love to get a 20%. You start off adding up all we can get, but you want to know if it's really true. Don't forget all the negative data, all the studies that don't - there's always a bias towards positive data. When it's this hard to build the story from what's published, it makes me worry.

Paxlovid. Another article, "Nirmatrelvir and Ritonavir for Inpatients with Severe or Critical COVID-19 Beyond Five Days of Symptom Onset: A Propensity Score-matched, Multi-center, Retrospective Cohort Study," published in *BMC Infectious Diseases*. For this study, a prospective score-matched cohort was constructed by using multi-center data from 6,695 adult inpatients with COVID-19. These are inpatients. More than five days have gone by. We're in China, December 2022 to February 2023. This is after the epidemic control measures were lifted.

The symptom onset of 1,870 enrolled severe or critical inpatients was beyond five days. Then they either end up getting Paxlovid plus standard treatment, or just standard treatment, no Paxlovid. In the Paxlovid group on day seven, the number of patients with an improve in the SOFA, that's a sequential organ failure assessment score greater than equal to two, was much greater than in the standard treatment group. You're not seeing any impact on COVID-19. They're doing better looking at their SOFA score. Additionally, the rate of new intubation was lower, the p-value of 0.004.

Basically, the clinical benefits were seen here even when you were missing those first five days, even when they're in hospital. This is really preliminary. The authors point this out, that we need some more randomized control trials to really validate the Paxlovid. This is really preliminary. The authors point this out, that we need some more randomized control trials to really validate, when does that window close? Number two, we do have remdesivir. This is

going into week two, the article above. We also have to ask the question, is this any better than - Why don't we just put people on remdesivir where we do have the data?

Number three, molnupiravir, convalescent plasma in some situations. Remember the isolation guidance, you're still contagious. You could still give it to other people. I think people seem to forget this as I walk down the hospital hallways with their open doors and people coughing away. Number two, where we are, the early inflammatory week. This is week number two, steroids at the right time in the right patient, at the right dose. This is after that first week. This is in folks with oxygen saturations less than 94%.

This is in the hospital. I had a patient today where one of the attendings and I were talking about, they got one reading. Do we trust it? Put them on a continuous pulse oximeter. We're going to see how they do over the next few weeks, make that call. Number two, anticoagulation. Three, pulmonary support. As mentioned, remdesivir if we're still in the first 10 days. Then immune modulation with things like tocilizumab.

Couple exciting, I'm going to say two, but mainly this first one is what has me the most excited in the late-phase PASC/Long COVID section.

This is the article, "Fecal Microbiota Transplantation for Sleep Disturbance in Post-acute COVID-19 Syndrome," published in *Clinical Gastroenterology and Hepatology*. Between September 22, 2022, lots of twos here, and May 22, 2023, they recruited 60 PACS patients with insomnia defined as they have this ISI, which is the insomnia severity index. I'm going to change that to PASC. It autocorrects to PACS. They're going to either assign them to getting a fecal microbiota transplant or control. Basically they're not. You're going to have 30 get the transplant, 30 don't get the transplant.

The primary outcome is going to be impact on insomnia. You're going to see clinical remission defined by this insomnia severity index. You can have some secondary outcomes where you look at this sleep quality index. We're going to look at anxiety disorder scale. We're going to look at the, I love this, the Epworth Sleepiness Scale. I'm going to start incorporating that into daily life. How are you doing? You look sleepy. How are you on the Epworth Sleepiness Scale? They also have a multi-dimensional fatigue inventory. I like that too. Then they're going to check blood cortisol.

They're going to check melatonin. They're going to do this gut microbiome analysis using metagenomic sequencing. Let's see, did it work? At week 12, more patients in the fecal microbial transplant, let's call it the FMT group, than control group had insomnia remission. We had 38% had remission versus only 10%. The transplant group showed a decrease in that score, that insomnia severity score. They either had remission or they were getting better. They did better on the Pittsburgh Sleep Quality Index. They were having less issues. They were getting better quality sleep. They did better on their anxiety disorder, generalized anxiety disorder.

This is crazy. You get a fecal transplant and you feel less anxious. You sleep better. Your blood cortisol gets better. There was enrichment of certain bacteria, such as the, there will be a test on this, the *Gemmiger formicilis*. You got that? *Gemmiger formicilis*, and depletion of microbial pathways producing the menaquinol derivatives after the transplant. The gut

microbiome profile resembled that of the donor in the responders, but not in the non-responders. If you gave the transplant and you ended up seeing it really, I'm going to say engraft, and you saw this change in the gut microbiome, those are the people that responded. You do it, you don't see a change, those are your non-responders.

VR: What's the source of the fecal transplant? Healthy volunteers, I presume?

DG: Yes. It's now pretty involved. They screen the potential donor. Lots of blood tests, questionnaires, any high-risk things. They screen, do you have any multi drug-resistant organisms in your biome, any other infections? Then those people then donate their poo. Then it moved along. Initially, we used to put a tube up from below and spray it in, other techniques they put a tube from above. Now a lot of times they're actually taking the poo. They're mixing it with glycerol, they're freezing it, making actually what we call affectionately "crapsules". Then you're swallowing those.

VR: Wonderful.

DG: Can you imagine? If it's going to cure your insomnia, your anxiety.

VR: Sure.

DG: Another study, "Precision Symptom Phenotyping Identifies Early Clinical and Proteomic Predictors of Distinctive COVID-19 Sequelae," published in *JID*. This is always this thing. You're trying to make a diagnosis. Does this person have Long COVID? Do they have PASC? Then the next step is OK. Then trying to group that. What type of PASC do you have? Because maybe that's going to help us. Here, they're going to identify three symptom-based clusters; a sensory cluster, a fatigue, difficulty thinking cluster, and a difficulty breathing, exercise intolerance cluster.

Cluster one, this is the sensory, characterized by a higher frequency of sensory symptoms such as a loss of smell or taste. Cluster two, this is fatigue, difficulty thinking, characterized by a higher frequency of fatigue, including mental and physical. Want to point that out, mental and physical fatigue, that difficulty thinking, the brain fog. Then you have cluster three, difficulty breathing, exercise intolerance. Here you have a higher frequency of the difficult breathing symptoms, the shortness of breath, the exercise intolerance, the difficulty exercising.

That's helpful for our clinicians to start thinking about this. I will point out other studies have shown that over time people can shift from one phenotype to another. I will close as we have for a while. No one is safe until everyone is safe. We're nearing the end of June. I do want everyone to pause the recording right here, go to parasiteswithoutborders.com and click Donate. Even a small amount helps us keep doing our work. We are doing our Floating Doctors fundraiser for May, June, and July. We will double your donations up to potential maximum donation of $20,000. We're going slow, we need you to step up. Everyone who's done so far, thank you. The rest of you come on, click on that Donate button.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Michelle writes, "My mother-in-law passed away about a year and a half ago. At the time she had a staph infection that had spread to her blood. Though she was being treated for it, it was

implicated in her death. After she passed, my husband had packed up several of her items and furniture when he cleared out her room. He was gloved and masked at the time as I am immunosuppressed and we didn't want to have me get staph from handling her items.

These items have been in our garage for about 17 months now and my husband wants to bring them in the house. I've read that staff can last on surfaces and objects or furniture for months. Is it safe to bring these back after 17 months? These are items she had in her room while she was sick. Will the staph still be infectious? I can have him wipe down some of the items with disinfectant wipes, but not all, as several are paper products such as photos and documents, as well as clothing. Disinfecting is not an option for everything."

DG: Michelle, this is a good question. It raises an important issue. There are certain pathogens that I'll say are rare. When this happens, like in the hospital and other environments, we really do this big push to put precautions in place. Other pathogens are really just ubiquitous in the environment. Staph is notorious. We have our MRSA staph. We have our MSSA, which is a methicillin-sensitive *Staph aureus*. A large number of people have *Staph aureus* living in the nares, living on other parts of the body. People have staph living in their gut tract. Staph is all over the place. The first thing I was looking at is you say mother-in-law.

People always, when they get a family history and they want to find out what we're susceptible for, like oh, does cancer run in your family? Does heart disease run in your family? Interesting. If you have a family member that dies of a specific infection, your risk of dying of that specific infection is much more significant than the transmission of heart disease or cancer. Just interesting little factoid that people are not aware of. If you said, my mom died, you start building a different story. I think at this point, recommendation, nothing special that really needs to happen here. Certainly if it's been in the garage for 17 months, have your husband clean everything up. I don't think there's any undue risk here.

VR: Ella writes, "My niece, who is 33 weeks pregnant, has a positive COVID test with mild symptoms. Her doctor said not to worry, consider it just as a flu. Is this a valid statement? What would be your advice?"

DG: Ella, we've covered this a bit. Happy to hit it again. This doctor is certainly not following the guidance of the professional societies. During pregnancy, though the risk is low to begin with, there's about a 20-fold risk that a pregnant individual end up hospitalized. We see this happen. It's not during those first seven days. It's not based on oh, my symptoms were mild. It's what happens as far as the immune response during the second week. We also see an increased risk of miscarriage, other things. Flu is not what COVID is during pregnancy. The general recommendation is that the benefit of early treatment with Paxlovid during that first week is better than just ignoring it and letting things progress till things end up too late.

VR: Alina writes, "I've depended on you for reliable information since the start of this pandemic. I've been glad that I did. I felt reassured by your support of mRNA vaccines. I've now had seven of them. One AstraZeneca first, the others all Moderna or Pfizer, and was preparing to have the latest update this coming autumn. The attached research article, however, now makes me worried about all this.

Is reliable data emerging that vaccines are riskier than was thought? I hope you will discuss and comment on the article. Should I and others like me be worried? I'll turn 70 this year, generally healthy and fit. Please comment on the study." This is a link to a paper in *Biomedicines* called, " 'Spikeopathy': COVID-19 Spike Protein is Pathogenic from Both Virus and Vaccine mRNA."

DG: Let's set the record straight, Alina. We talked a little bit about our concerns that, with the mRNA platform, really critical that you keep getting vaccines every fall. There's certainly a lot of people out there that would rather you get COVID and send them your millions of dollars each month to either pay for their Substack or buy their herbal remedies instead. No, the science is very clear: 60%, 70% reduction in progressing and having issues. You say, I'll turn 70 this year. Yes, you're one of the people. These are the people we're seeing.

They forgo that vaccination either because they feel like they've got vaccine fatigue or some of these anti-science charlatans are trying to misinform and get you to send your money to them instead of staying healthy. They didn't take an oath like some of us did. Ignore this study. Ignore this bit of misinformation and misguidance. There's no spiky apathy that you need to worry about.

VR: Lisa writes, "I'm traveling to France in mid-September. Could you comment on receiving flu and COVID vaccination in late August? I know that the updated COVID and flu vaccines for fall 2024 most likely won't be available."

DG: We're hearing murmurs that they might be by late August actually. Even Novavax was saying, by August, we're going to have the shots ready for you. I expect them to be ready by late August. If so, yes, this might be a time for you to go ahead and get that COVID, get that flu vaccine. The interesting thing we're still waiting is the durability. You get it in August, four months go by. September, October, November, December. Still we're seeing that the durability was still there at four and five months. It may have been a variant issue in the past, we're not sure. Now I think that the current guidance for you would be to go ahead with that vaccination, flu and COVID.

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

DG: No, thank you. Everyone, be safe.

[music]