This Week in Virology

TWiV 1012 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 3 June 2023

pdf of this transcript available (link)

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

[music]

From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1012, recorded on June 1, 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: Daniel, in the old days, I used to ask you, "How are the COVID numbers?" But not really a reliable question any longer since there's not a lot of testing. Right?

DG: It's really gotten to be tough. As we've talked about, a lot of the deaths are now silent. People are dying in facilities. Decisions are being made just to make them comfortable. Yes. It's tough. It'll be interesting to see what happens this summer. It'll be interesting to see what happens next fall going into the winter.

VR: I guess you'll keep us informed. Right?

DG: I will. I certainly will.

VR: OK.

DG: All right. Oh, my bowtie, this is my plague, Yersinia pestis bowtie -

VR: Nice. Very good.

DG: - and we'll be talking about the modern plague. Let me start with my quotation and this was by Marcus Aurelius from his *Meditations*. "Never let the future disturb you. You will meet it, if you have to, with the same weapons of reason which today arm you against the present." We're going to be talking a bit about Long COVID, so I just thought this would be a nice quotation, sort of an encouraging quotation for clinicians, and those still suffering.

I actually have a bunch of, I think, really, interesting, important news this week, I'm actually going to think this is, Vincent, I'm telling you ahead of time, it's going to be one of our best episodes ever, if you can believe that.

VR: All right. [chuckles]

DG: [chuckles] All right. We'll start with a couple. Right off the bat, RSV, we just learned, Wednesday, May 31, 2023, that as their advisors had recommended, the U.S. FDA approved ABRYSVO, this is Pfizer's vaccine for the prevention of respiratory syncytial virus in older adults.

As we've discussed before, this is the bivalent RSV prefusion F vaccine for the prevention of lower respiratory tract disease caused by RSV in individuals of 60 years and older. This is an adjuvanted vaccine composed of two pre-F proteins selected to optimize protection against RSV-A and B strains. This was based on the results of the Phase III clinical trial RENOIR, kind of a cool acronym. We'll give it five points. That's Sara's style of rating acronyms, published in *New England Journal of Medicine*.

I'm also going to mention briefly, unfortunately, I think I may be talking about this more in the future based upon the *MMWR, "*Potential for Recurrent Mpox Outbreaks among Gay, Bisexual, and Other Men Who Have Sex with Men in United States, 2023."

First off, I don't like the title. There are a number of women, a number of children that ended up with mpox, seemingly our Optum Tri-state networks, are the only people testing and diagnosing it outside of the "high-risk population." Let's not keep the blinders on. Let's not have them on going forward, but we read that in this study, with mathematical modeling, they're suggesting that the risk for future outbreaks depends linearly on the level of immunity in the population at risk. Cumulative incidence, on the other hand, has multiple thresholds.

In recent months, diagnoses have declined. We've heard about a couple of outbreaks, but the mpox vaccination coverage varies regionally, suggesting a variable potential for mpox outbreak recurrence. The biggest factor that they suggest that will impact outbreak risk, and then, size, is vaccination. In this modeling study, they used conservative estimates for one- and two-dose efficacy of 37% and 67% respectively. I'm going to just keep moving on there, [chuckles] some comments, but OK.

The big thing is they have a nice table where you can look through at the differential risks of future outbreaks. For instance, you can look up Suffolk County, which is eastern Long Island. You can look at Massachusetts. You can look at a bunch of different places. I'll just mention a few. Let's take Harris County, Texas, where there's only about 17% immunity in the target population. They're estimating it's about a 50/50 chance that we're going to see an outbreak.

Actually, there are lots of counties in this model with greater than 50% risk for another outbreak. Based on this model, just how good are models, Cook County, Illinois, only had an estimated 22% risk for a sustained impacts recurrence. However, the city of Chicago, which is part of Cook County, actually, has a cluster of mpox cases that just emerged in April 2023. We can do a better job rolling out these vaccines or we could just wait and see where the next outbreaks will happen. I will say 70% of the top 10 most likely counties for outbreaks are in Texas and Florida.

VR: Daniel, one thing I want to clarify. You said one in two dose efficacy of 37% and 67%, those are the reduction in risk with one in two dose, in case people don't understand that because you didn't mention reduction in risk. It's not the likelihood of a risk, because that wouldn't make sense to have it higher for two doses.

DG: Yes, two doses in your higher risk. It is interesting. I was going to talk a little bit, so maybe I will there. These are the conservative estimates of what kind of efficacy. I was asked that. When someone says, "Yes. What kind of efficacy are you talking about?" Are you talking about an infection, which then leads to spread to the next individual? Are you talking about staying PCR negative? It's really tough. What exact vaccine efficacy are they talking here.

Here, they seem to be talking about the conservative estimates for reducing 37%, a 67% reduction in you getting an infection, which will then spread to another person. Clinically relevant, either personally having symptoms or signs or you being part of a chain of transmissions.

VR: It's worth pointing out that the original outbreak, which started in Europe, was really based on a chance introduction into a very specific group, which is a low-probability event, because we've never seen it before, and this virus has been around for a long time. These models assume introduction of virus, but that might not happen depending on who has it and who's passing it on.

DG: Yes. This will be interesting. As I mentioned, we may or may not be talking more about this in the future. We will see what time will tell. All right. I'm going to - jump ahead here. We've got a couple exciting things to talk about today. One is this idea that keeps coming up. We're talking about COVID early viral upper respiratory, non-hypoxic phrase. This is that acute, very acute first week of COVID.

I'm going to start with a topic that has lots of staying power. When that patient walks in the door or when you yourself getting infection, can you tell which variant you have? If you read the popular media, you can tell. The article, “Association Between SARS-CoV-2 Variants and Frequency of Acute Symptoms: Analysis of a Multi-institutional Prospective Cohort Study - December 20, 2020 through June 20, 2022, was published in *Open Forum Infectious Diseases*.

This gives us information on the prevalence of acute symptoms. Here's how they're going to lay this out. You're going to have pre-Delta, you're going to have Delta, and you're going to have Omicron. We're going to look at the incidence of about seven different symptoms based upon those three time periods, those basically three variants.

They enrolled 4,113 participants. Let us start with sore throat. Apparently, if you read the popular media, early-on sore throat was not a thing. Well, if you look here, it was a thing 41% of the time. Once you got it to Delta, it was a thing 55% at the time. It's currently a thing 71% at the time, so it's been a thing.

What about cough? This is this new variant. Well, cough has been a thing 51%, 63%, and 67%. What about runny nose? Everyone's saying that, "Oh, now it's just a runny nose." Well, we were seeing that 49% upfront. Once we got into Delta, it was 71%, Omicron 73%, so not really big change there. Chest pain, 31%, 24%, 21%, shortness of breath, we should never see that

with Omicron, if you listen, 43%, 30%, and 28%. Really, pretty similar Delta to Omicron, 30% and 28% there.

Now, this is one thing where there's been a little bit of a change, I'll say a movement, but not like you can just use this, loss of taste or smell 47%, 48%, dropping to 56% to 62%, and then, still say it's about 20% of the time in Omicron folks.

VR: I think you have to remember that these are not taking into consideration anything about the population differences. Early on, very little immunity, it grows as we get later, the ages of the people involved. I think all of that can affect this. Of course, this is self-reporting, add that to the mix, and it probably all these numbers are the same. [chuckles]

DG: [chuckles] I think, basically, yes. That's my point. [chuckles] This is another thing. This comes up a lot. I think people muse on this or maybe that's just reflecting my household, but if someone gets COVID, can we predict for others that they live with who's going to get it? What are the risk factors?

The article, “A Prospective Study of Key Correlates for Household Transmission of SARS-CoV-2,” was published also in *Open Forum Infectious Diseases*. This is a post-hoc analysis. Actually, it was a separate study, but they did a post-hoc analysis on this. They actually found two potential correlates to have a statistically significant association with transmission risk. One was a log increase, so a tenfold increase in viral load was associated with a 40% increase in odds of transmission, and sharing a bedroom with the index participant was associated with about a 200% increase in odds of transmission.

VR: Daniel, again, the caveat that viral load is measured by PCR. We don't know what that means because nobody looks at infectious virus. Right?

DG: Do you think they should have said RNA copy number? [laughs] Actually, I had a friend of mine that he was actually at the big Optum Conference. When he started reading the Reviewer #2, he was like, "I knew it was you because [chuckles] every time I said viral load, there's a diatribe about RNA copy number." It is amazing that the reviewers just let that slip through. We're doing PCR. We are not doing viral load here. All right.

VR: Daniel, in the AIDS field, don't they use viral loads to report PCR?

DG: I think that may be where we got in this bad habit. I think we really - Yes. We need to talk about nucleic acid amplification copy numbers or- Yes. Let's improve our verbiage. All right. Here's big news. Pfizer's Paxlovid received FDA approval for adult patients at high-risk of progression to severe COVID-19. The person's got COVID, they've got whatever symptoms they've got, you're not going to know what variant other than, "Hey, it's all XBB."

As we've talked about multiple times, number one recommendation is Paxlovid. This is now fully licensed. Physicians can use their clinical judgment. I will read, "Based on the relative risk reduction seen across both clinical and real-world data, the FDA provided an estimate in March 2023 that more than 1,500 lives could be saved and 13,000 hospitals avoided each week." You can do the numbers on those with Paxlovid use in eligible patients.

This isn't giving it to everyone. This is based upon that narrow definition of high-risk people. We are talking 1,500 lives per week. You do the math on that, 75,000, 13,000 hospitalizations each week. We're getting up into the hundreds of thousands of hospitalizations. This is a medicine that can really make a difference. I'm hoping now that we have full licensure we'll get better education going. Hopefully, we will move past all the barriers.

Number two, remdesivir, that three-day early IV, but limited access for most folks. Molnupiravir, convalescent plasma as that early treatment option in the immunocompromised, and let's avoid doing harmful things.

Moving into folks that end up in the hospital, I'm going to talk about an article here that could have ended up here or in the first week as well, but remember, these are the folks that progress, become hypoxic, might require hospitalization. We're talking about second week because some people end up in hospital in the first week, older folks having a tough time, but in those individuals that are hypoxic, this is that dexamethasone, six milligrams a day times six days, anticoagulation, pulmonary support, maybe remdesivir, maybe further immune modulation, but I will say repetition may have some benefits.

Again, the article "Efficacy and Safety of Antimicrobial Stewardship Prospective Audit and Feedback in Patients Hospitalized with COVID-19 (COVASP): A Pragmatic, Cluster-Randomized, Non-Inferiority Trial," was published in *The Lancet Infectious Diseases*. This was, it's all in the title I guess, a prospective, pragmatic, non-inferior, small unit cluster randomized trial comparing prospective audit and feedback, plus standard of care, with standard of care alone in patients admitted to three hospitals in Canada with COVID-19 pneumonia.

I'll start off with a big deep breath. Antibiotics were prescribed for 53% of patients with COVID. Maybe it's because we call it COVID pneumonia, but the majority of folks with a viral illness were given antibiotics. What are they going to do here? The intervention was folks were going to look at the use of antibiotics in those folks with COVID-19, and basically, we're going to give them verbal or written feedback.

Now, a couple things I will say. Apparently, this was only done on weekdays and only those weekdays that were not holidays. I guess in Canada, no stewardship on weekends or holidays, only during the nine to five, Monday through Friday. The primary outcome was clinical status on post-admission day 15. Here, I'll say they did all this feedback and despite lower antibiotic use in the intervention group, people did just fine. You do not need to put all these folks on antibiotics. Stewardship is actually a good thing.

VR: Now, how do you get this information out to those folks who are prescribing these, Daniel?

DG: Unfortunately, I think this really is a call for antimicrobial stewardship. It's really tough. I didn't go into infectious disease to become the antibiotic police, but sometimes, I feel like I have to be. It's just people are so excited to give out those antibiotics. It had an issue today where it was a gentleman, went to an urgent care, and there was a tick exposure, and that the tick panel came back, and the person wanted to start throwing all these medications at them. I'm like, "The tick panel, you do realize that's a serology test. The exposure was four days ago. If they've got IGG on that tick panel, that has nothing to do with what happens four

days ago," but they wanted to give them the Mepron and the azithromycin and just on top of the doxy, which they'd already started.

Yes. We need stewardship. The whole idea, you wouldn't have people just throwing chemotherapy around. We need a system where we really regulate. Otherwise, we are just moving so rapidly towards the antimicrobial apocalypse. It's just [crosstalk] resistance apocalypse.

VR: I like that sound bite. That's good.

DG: [chuckles] OK. All right. The article. This is I think probably the high point of this week. I'm hoping this gets a lot of discussion from people who listen and then discuss, but this is a real - I have to say, this is a very important article. It was an expensive article to get. I think this was the price tag of this article was $500 million, but we'll talk about that.

The article, "Development of a Definition of Postacute Sequelae of SARS-Cov-2 Infection," was published in *JAMA*. What is this? This is the analysis of data from 9,764 participants in the RECOVER adults cohort, a prospective longitudinal cohort study. No pause here, just sort of give a sense of what was going on here.

Quite a while back, the NIH made a commitment of a rather large amount of money to understand and study post-acute sequelae of COVID, or I'm going to say Long COVID, but PASC here. The first thing they said is, "We need a cohort. We need to understand what this is. We need to have some criteria for determining this person has it, this person should be included in this trial, maybe we'll even find some subsets."

Finally, many months later, this is what we have. In this analysis, 37 symptoms across multiple pathophysiological domains were identified as present more often in SARS-CoV-2 infected participants at six months or more after infection compared with uninfected participants. Someone can chew on that for a moment.

A preliminary rule for identifying PASC was derived based on a composite symptom score. We learned that adjusted odds ratio were 1.5 or greater. This is infected compared to uninfected participants for 37 symptoms. I'm trying to figure out where they found the uninfected participants, but we'll muse on that later.

I recommend those really interested in this topic, look at the supplementary table, particularly eTable 7and eTable 8. They go on to create a binary PASC scoring system to use in the creation of research cohorts with 12 symptoms contributing to a PASC score, including post-exertional malaise, fatigue, brain fog, dizziness, gastro-intestinal, symptoms, palpitations, changes in sexual desire or capacity, loss of or change in smell or taste, thirst, chronic cough, chest pain, and abnormal movements.

I think those of us taking care of folks with Long COVID are familiar with a lot of these. We read that the optimal PASC score threshold used was 12 or greater. Now, there's a Table 2, where you can actually see the different scores you get, but before people get too upset, let me explain what's happening here.

Using this criteria, the proportion with a qualifying PASC score in the full cohorts as all-comers was 1,990 of the 8,646 infected participants, or 23%, and 41 of the 1,118 of the uninfected participants, so 3.7. This gives some sense of sensitivity versus specificity using this criteria, but this is my sort of clinical comment. Be careful not to exclude people in the clinic. Also be careful who we include.

Now, using this criteria, the proportion of infected participants with PASC in the acute Omicron sub-cohort was 10%. Then, I think this is something that is sort of growing, I think, that's been happening over time. This study again identified subgroups or different types of PASC.

They end up with four PASC subgroups. I'll go through the four. They have about 477 in Cluster 1, and this is predominantly loss of or change in smell and taste. They have a Cluster 2 with the post-exertional malaise and fatigue. That's a lot of us what we think of as a Long COVID subgroup, brain fog, post-exertional malaise, and fatigue. This is in Cluster 3. Then, they have a Cluster 4, again, with fatigue, post-exertional malaise, dizziness, brain fog, GI issues, and palpitations.

I just wanted to discuss eTable 7 because I don't want people to look at this and say, "Oh, they're only looking at 12 things." You can actually look at eTable 7 and see that certain symptoms correlate with symptoms contributing to this PASC score. It's a really large, long list. There's headaches. There's vision disturbances. There's dry mouth. There's abdominal pain. There's tremors.

I want to just sort of wrap up this before hopefully, Vincent, I have a little bit of discussion with a quotation by Dr. Leora Horwitz, who helped lead the research from NYU Grossman School of Medicine. I'm pulling this from a *USA Today* article written by Karen Weintraub. "It doesn't mean these symptoms are the most common or the most severe or the most burdensome or the most important to people. It just means that these are the ones that help us identify people who have long-term consequences."

VR: Sorry. I noticed, Daniel, that this is a six-month readout. Right?

DG: Mm-hmm.

VR: Six months or more. I hope they follow up and look 12 months, 24, and see what happens to these. Do some go away or what? Maria Van Kerkhove said the frequency of PASC is 10%, 12%, she said, but it goes down dramatically after a year. I would be curious to see - I don't know where she got that number from, but it would be curious to know what happens here.

DG: Yes. I agree, but again, I sort of would ask, "Where'd you get that number?" We have been saying for a while that about 95% of folks, if you get out to a year, are doing better. There's still like 5% or so that are still struggling. Those people, I still have folks that are past a year that I'm working with. That will be interesting to see.

Now, a couple of things I'm trying to figure out from this article. One thing is we're still looking for that biomarker. We're still looking for a validating blood test. We say, "Oh, but we tested you and you have anemia. Your crit is this," or, "You have diabetes. Your A1C is this." People still look at this and they say, "Oh, you've just got a bunch of people complaining. Ugh." These

people are not just complaining. These are people that a lot of us have known well, honest, trustworthy people whose lives have been taken away from them.

What this is going to do is allow us to now move forward. There's really a lot on the table here looking at what might benefit each of these subgroups because what benefits Cluster 1 may be different than what benefits Cluster 4, for instance, but this is really this basis for defining groups to study, because you don't want to dilute it out, and then, miss something that might be of benefit.

VR: Now, Daniel, how do you diagnose it based on these symptoms? Would one be sufficient? For example, if you have loss of smell or taste, which gives you a score of 8 here, it's not the 12 that are needed. Would that be enough to categorize a patient as PASC?

DG: I think for the study population, it makes sense to use a criteria with a pretty high sensitivity specificity. That's what we're talking about here, but clinically, if someone comes in, and take post-exertion, all they've got is post-exertional malaise and a chronic cough. "Oh, 11, you didn't quite make it." I'm not going to send that patient elsewhere.

VR: Yes. Of course.

DG: We're still going to work with them. You say, of course, [chuckles] but some people might just say, "You only got 11. Sorry." When you could say, "I've got abnormal movements. I've got gastrointestinal. I've got dizziness. I have fatigue. I have chest pain. I have palpitations." I'm like, "Let's see. Two, four, five, six, seven, eight. Oh, you only hit nine." Yes. This is not a goal to kick people out and fail to address their concerns. It's just to try to create a nice non-diluted cohort, so we can now start studying what might be a benefit. Once we know what might be a benefit, then we could start looking at applying this to a lot of the folks that suffer.

All right. I will move on to - and I think this is our last article. The article, “COVID-19 and Risk for Mental Disorders Among Adults in Denmark.” was published in *JAMA Psychiatry*. The headline spin on this was interesting. "Risk of new post-COVID mental disorders higher only in older patient, study suggest." That was the headline in CIDRAP. I wasn't sure about that headline.

There are some limitations here as I have some questions about the control group. We keep running into this. Who are the control groups for these studies? We'll talk next week about a blood donor study looking at what percent of folks have been immunized, which percent of folks have been infected, but these are the results of a cohort study, including the total adult population of Denmark, whether you want to be included or not, and covering all SARS-CoV-2 preliminary chain reaction tests.

They report that the overall risk of new-onset mental disorders was increased in SARS-CoV-2 positive individuals. I mentioned right upfront who was in that control group. They estimate the risk of mental disorders and use of psychotropic medication among individuals with a positive COVID-19 test compared with individuals not tested, individuals with SARS-CoV-2 negative test results, those hospitalized for non-COVID-19 infections.

I went back and forth whether or not to include this paper, so maybe best to recommend that those interested spend some time reading it in detail, but I did pull out three highlights. One,

individuals with multiple SARS-CoV-2 infections, so two or more, had an increased risk of new-onset mental disorders compared with individuals with only negative test results. That was 1.66 for that relative risk.

Overall, the subsequently needing treatment with psychotropic medication increased with increasing age and was highest among individuals 70 years of older. Hospitalization for COVID-19 was associated with an increased risk of a new-onset mental disorder - this is big - relative risk of 2.33 compared with the general population not hospitalized for COVID-19, and was even higher among patients with COVID-19 admitted to the ICU. There we have a relative risk of 3.6.

I am going to sort of, we spend a lot of time talking about Long COVID here. I'm hoping this really validates this as a diagnosis. This is a condition. This is something we want to understand, but I do want to put in a reminder that not everything is due to Long COVID. When someone comes in after COVID, maybe they're having post-exertional malaise, maybe they're having these other things, there still might be something going on.

I wanted to tell a story of a woman that I recently had been taking care of, referred to me with several months after COVID of a number of different things going on, sleep disturbances, post-exertional malaise. There were a couple of things. One of the things that was concerning was vision disturbances.

Of course, we sort of saw that was in the list of vision disturbances, but something wasn't quite right, decided it would make sense to have this individual see some other specialists as well. She was sent to a rheumatologist, ended up seeing an ophthalmologist, ended up getting an MRI, and actually turned out that this lady had a pituitary tumor. The vision disturbance was actually due to the pituitary tumor. Yes. She had Long COVID also, but the vision disturbances that were in that mix were due to a second issue. Just a word of caution, let's take these individuals seriously, but let's also keep those blinders off. Let's keep our eyes open for other diagnoses. I will close out, as I have for, well, about three plus years now, "No one is safe until everyone is safe."

I do want everyone to pause the recording right here. Go to parasiteswithoutborders.com and click the ‘Donate’ button. Every little bit helps. That's how we do what we do. We're basically responding and we need your support to keep doing this. Right now, we're in the middle of our Foundation for International Medical Relief of Children Fundraiser, May, June. We're now in June, and July donations made to Parasites Without Borders will be matched and doubled up to a potential maximum donation of $20,000 for PWB to FIMRC.

VR: Time for questions for Daniel. You can send yours to Daniel at microbe.tv. Danika writes, "I'm 30 weeks pregnant today, got my COVID booster this morning. I've had four Moderna doses. Word got out and now, my mother and mother-in-law contacted me in horror. They sent me this article from *Vaccines* entitled, 'IgG4 Antibodies May Generate Immune Tolerance to the Spike Protein.' I'm an epidemiologist and I think there's a lot of speculation here, but I'd love a breakdown, especially of claims like protection that the vaccines confer, or is now being questioned following an outbreak in an Israeli hospital that resulted in deaths of five individuals, all with comorbidities who were fully immunized. Reviewed data indicate that

IgG4 production does not constitute a protective mechanism. Daniel, would love to hear your thoughts about that."

DG: [chuckles] OK. First, Danika, love the name. Second, I'm going to applaud the fact that you were vaccinated, unless - Let's go a little bit into this. I think this is tough. In the last three years, everyone seems to have become a COVID-19 expert and a COVID-19 researcher, and they feel very comfortable grabbing an article, reading the title, maybe getting a little bit into the abstract, maybe reading a tweet or someone else's impression on it, but let's make it really clear.

Individuals who are pregnant are at high risk, they're at high risk themselves about 20 times as likely to end up in the hospital as their contemporaries who are not pregnant. They're at increased risk of losing the pregnancy. All this speculation about IgG4, I think, we talked about a review article by Shiv Pillai, who talked to -

We do not think that this is a problem, but there are people that have an agenda out there. There are anti-science, pseudoscience folks, anti-vaxxers out there. Unfortunately, they have billions of dollars. There's a lot of nutraceuticals. There's a whole industry that benefits from anti-science, from undermining these incredibly powerful tools. No. I do not see an issue here. If anything, you did the right thing to protect yourself, the right thing to protect your unborn child.

VR: I'm really surprised this was published. It's totally speculative and based on no data. Daniel, the COVID vaccines have worked really well. [chuckles]

DG: Vaccines are our most powerful tool and it is amazing to me, but unfortunately, people pay to get something published in their journal. The journal gets lots of citations, and lots of publicity when they publish something like this. It's an ethical issue to publish pseudo-speculation, pseudo-anti-science stuff like this.

VR: Caroline writes, "My 26-year-old son is planning a rock-climbing trip to a town three hours from Cape Town. Does he need any updated vaccines?"

DG: Oh, so three hours from - It is interesting. He's going to go. There's going to be a plane ticket involved. There's a couple ways to do this. The first is I am going to plug for having him be at a brief meeting or whatever it is with a travel health specialist. It's not just the vaccines. There may be malaria medicine, malaria prophylaxis. I'm going to say more than maybe, probably. He'll want to know what to do should he get traveler's diarrhea. He'll want to know about just even safety issues. There's a whole specialty of travel medicine.

Actually, I'm going to recommend that your son reaches out to them. In the meantime, just to get a little sense, and I'm saying do not do this yourself. Don't get out there on the track and race that car without training. There is a cdc.gov travel site which can give you a little sense of the things to be thinking about.

VR: All right. This next one I think is relevant to the news you reported today. Tom wants to know, he has a plan for in case he gets infected. He's going to take Paxlovid. He's going on a trip and wants to know if he can take Paxlovid with him.

DG: Yes. As of now, this has all changed. Paxlovid is now fully licensed. It is something we can do at our discretion without any issues. We can go ahead and Paxlovid for the purse, Paxlovid for traveling, have it there because remember, time really matters, so have that Paxlovid, have those rapid tests. You want to have more than one because often, it's that second day, maybe the third day when we get that positive test.

No. You do not want to wait and see. You don't want to be in some part of the world where you don't have access to the proper medication. Now is a good time to look through any potential medication interactions, figure out how you're going to sort that, and what exactly you're going to do.

VR: Marcus writes, "I'm a GP in Australia. We've run into a problem where the government is no longer supplying pediatric Moderna vaccine six months to four years due to contract issues. They do have access to the Pfizer pediatric vaccine. For children that have already had one Moderna, is there any evidence for mixing vaccines, i.e., Moderna first, Pfizer second, despite the difference in dosing regimes? Alternatively, there is an option to bring forward the second dose eight weeks later forward to six weeks. Is that a better option? Wanting to do the best by my patients?"

DG: Yes. The CDC actually has a nice what-to-do-if A then B. Let's take a situation here. Let's say the individual, the child here, got their first Moderna vaccine. Now, you don't have the option of doing another Moderna vaccine. You can then go ahead and do a second and third with your Pfizer vaccines.

At this point, here in the U.S., those would both be bivalents. That might change going forward. I think that makes sense. I also like spacing things out a little bit more. We've talked a little bit about over time. Four weeks between the first two doses is less than ideal, probably 12 weeks, probably that three months makes more sense.

You wait three months, you get your Pfizer shot. You wait three months, you get another shot. It's confusing, I think, that they have - the Moderna is two, the Pfizer is three, and we're only talking about this little window where everyone else it's three, but, yes, there's actually nice guidance there. Just for this one shot, just to give you a straight answer, I would wait three months, get a Pfizer shot, wait three months, get that third Pfizer shot, and call it a day.

VR: Laurie writes, "I'm a partner in a busy pediatric practice in San Francisco. The FDA has come up with confusing new recommendations mandating that we get rid of the ancestral vaccine-" No. "-and replace it with the bivalent. As part of this new recommendation, we're supposed to start giving infants the 6 to 12-year-old dose or we can give Pfizer. Is there any science behind this? What does the FDA advisory committee think about this? Should we implement this before the ACIP weighs in? Appreciate any insights you can provide."

DG: Yes. I have to say we brought this up several times. I think my buddy, who runs our pediatric [chuckles] group. Yes. When he's confused, then, yes, the recommendations are confusing. As I mentioned, they have these recommendations where the Moderna is two shots, but the Pfizer is three shots, and then, everyone needs, at some point, get a bivalent thrown in.

We have science on this. I think it would make sense to just simplify based on what we know. Yes. Let's see what we've got here. We're supposed to start giving infants the 6 to 12-year-old dose, or we can give Pfizer. Yes. Those are both fine options. I actually think that the next step, hopefully, with the new XPB we're going to know in about two weeks, will be just to make it all simple, just make it three shots because in the future, where will COVID vaccination fit in? It's probably going to be the youngest coming into this world, completely vulnerable. Maybe the mom got a last trimester dose and now at six months or to six months to four years, they'll get a regimen. Then, there may be some subset where we're doing some kind of a boost to get a temporary rise in those neutralizing antibodies.

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

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

[music]