This Week in Virology

TWiV 996 Clinical Update

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Guest: Daniel Griffin

Aired 1 April 2023

pdf of this transcript available (link)

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

[music]

VR: From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 996, recorded on March 30, 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, we are creeping up on number 1,000 and we're getting there sooner because we did three episodes a week for a while and now you and I do one and we do another one. It's quite interesting where we ended up with this little podcast.

DG: I was looking back and when the pandemic started, *TWiV* was only in the 500s.

VR: Exactly. I remember you called one day and said, “let's do this week in COVID.” I don't know, maybe it would've been better to do that because having COVID in the name would've maybe brought more people, but I thought we had an established base for *TWiV* and so wrap it in, but maybe COVID would have - then we have morphed into other viruses as needed so maybe it's OK the way we did it.

DG: I have to say, I think it's a good idea the way you've gone with this, making it *This Week in Virology,* because hopefully people are learning a little bit more about viruses in general, and hopefully there'll be an audience that stays with *TWiV* and realizes that this is important stuff to know.

I say, and I'm not sure how to characterize that I say this, but we are still expecting that flu pandemic, all these other pandemics. This may have only been a shot across the bow. This is stuff that's relevant and hopefully it's stuff that people are finding interesting, that edutainment theme. Hopefully people will stick with us.

VR: Daniel, we're going to keep at it, but frankly, there's no one else doing this at a frequency and at a depth that we do. Just for that reason alone we have people listening.

People are leaving and I understand, but we still have more people than when we started, so that's a good thing.

DG: We're here, and as long as people keep supporting us so that we can continue, I think this is an important resource. We will get right into it. “It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.” That's from William Osler. Actually, I quoted this on rounds this morning at Columbia.

Just talk about how important it is, I think the art of medicine, the caring, the compassion. We can often come from a science background and we're fascinated by the disease and we're so focused on understand the diagnosis. I think there's a lot of wisdom here in taking as much time as you do figuring out what the disease is, trying to understand your patient. What's important to them, who are they, and how can we really address their fears, their concerns?

It's just sort of my sappy stuff right up front. Now we will move on. I'm going to put this right up front. Remember that company Lucira, with their COVID-19 and flu test? You can now buy them online for the low price of $34.99 and I ordered some Tuesday and guess what, Vincent? Look what I've got right here.

VR: Wow. Are you just going to try one or are you just going to wait to get some sniffles?

DG: I'm going to actually wait till there's a reason to use the $34.99 investment. They're not sending us any money, but if you want to, that would be great, Lucira. I know you're going bankrupt. You might want to get rid of a little bit of that money before your debtors take it. That said, I also want to start off with a headline.

Actually I created my own headline. We were talking last time about how people write these articles and then someone else writes the headline. This is a headline I created in response to a recent study. I've stolen this headline and I think I've improved it from CIDRAP, “Antibiotics Don't Reduce Risk of Death from Viral Respiratory Infections,” and, this is one I add, “May Double the Risk of Death.”

This was in response to a study presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases, of adults admitted to Norway's Akershus University Hospital from 2017 through 2021. This is not going to be just COVID. They looked at folks that had a nasal pharyngeal or throat swab that was positive for influenza, RSV, or SARS-CoV-2.

The researchers looked at which of those patients received antibiotics, calculated antibiotic days of therapy for people with just a virus, and assessed the impact of antibiotic therapy on survival with 30-day all-cause mortality as the primary outcome. I'll say right up front, they excluded people that actually had a bacterial infection, because some percent of the time you come in, you've actually got a bacterial infection. It is appropriate to treat bacterial infection with antibacterial agents.

Of the 2,111 patients included in the analysis, 44% had influenza, 20% had RSV, 35% had SARS-CoV-2. Are you ready for this? This was painful. Sixty-three percent received

antibiotics for respiratory infection during hospitalization. Apparently the standard of care is to treat viruses with antibiotics. The 30-day mortality rate among the entire cohort was 8%.

Of the 168 patients who died within 30 days, 119 received antibiotics on admission, 27 received them later in their stay, 22 did not receive antibiotics after they adjusted for the virus, which type, the age, sex, severity disease of baseline comorbidities. The researchers found that patients prescribed antibiotics at any point of their hospitalization were twice as likely to die within 30 days.

The risk of mortality increased by 3% for each day of antibiotic therapy. I'll take a deep breath here and say there may have been differences. This is not a prospective randomized control trial, but just not something we encourage, and unfortunately, something that happens to be occurring a little too much. All these antibiotics being given for folks with no real proper indication, no bacterial infection, really being admitted for a viral process.

VR: Now Daniel, what do you think is the reason for increased death on antibiotics?

DG: I was thinking of a couple things. One is here comes in a person, they've got a viral infection, they've got a disturbed microbiome and what do we do? We blast them with a sledgehammer. We clear out all those bacteria that may have actually been in some sort of a symbiotic relationship.

Now maybe they end up with C. diff, maybe they end up with a hospital-acquired pathogen because we've now caused a problem. I can think of it that way. The other is, I can think of these were sicker people and when someone's getting sicker, they get antibiotics. How much of this was a marker of people heading in the wrong direction? How much was it causal? I'm not sure I can say for certain from this, but this whole concept of, "I'll feel a little better because we've started those antibiotics."

Maybe we shouldn't feel a little bit better when we start unnecessary antibiotics. Maybe people should withhold those life-saving antibiotics when they may actually be life-not-saving antibiotics.

I am going to go right into norovirus or as we like to call it, winter vomiting disease. Did we just all stop washing our hands? I for one, am now eating all my meals at Chipotle and bathing in their high potency hand sanitizer. What was that about that stuff only being for the hands? I pasted in the chart of, oh my gosh, are we headed to the moon? The percent of positive GI PCRs for norovirus just keeps rising. Please wash your hands. I guess eventually everyone will have had norovirus.

VR: Daniel, I do think that most people use the sanitizer, hand sanitizer, thinking it's helping and it's not.

DG: Get that soap and water. I noticed today, maybe I'm a little overboard. My mom unfortunately is currently in the hospital. She had a little bit of an issue today, and after visiting her, not only did I hand sanitize but then I also soap and water. I'm hitting all bases.

COVID update. How to keep track at this point. This is really a challenge. When people ask about COVID cases, it reminds me of another William Osler quotation, "To confess

ignorance is often wiser than to beat about the bush." I'm just going to say it's really hard at this point to keep track of where we are with COVID. We do have wastewater monitoring and I'll leave in a link. You can see on this map when folks go to the link, that'll be in our show notes, certain areas where the virus levels are actually quite high. Other areas, looks like it's doing better. I'll leave that.

Excess mortality, that's another approach, but we're having issues with getting frequent enough updates, so I'll leave a link into that. It's another place where people can look, but the reality is that it's much harder to know in real time what's going on in the moment. Ideally, I'd like a wastewater app on my phone, so just like the weather, I could check and see how safe it is to go out. There'll be like pollen counts, there'll be the wind and the temperature, and then there'll also be my different pathogen levels, so if anyone wants …

VR: Thanks, Daniel. We have a wonderful surveillance system for influenza, and would you say that the COVID surveillance system is not as good and should it be?

DG: I actually think that there's a lot to be said for investing more in better surveillance systems. Yes.

VR: You know the data we get from CDC on influenza is remarkable, right?

DG: Yes. Even just, I brought up the norovirus, it's updated every week, we're getting these results. Yes, I would like better data. Maybe we got a little spoiled, Vincent, but I would like to continue to be spoiled. All right. Now another, I suspect a few people are still interested in the topic of blood types and COVID, so just for those still following the article, "ABO Blood Types and SARS-CoV-2 Infection Assessed Using Seroprevalence Data in a Large Population-based Sample: The SAPRIS-SERO Multi cohort Study," was published in *Scientific Reports*. I don't know if people remember this.

This whole idea that maybe certain blood types had lower or higher risk. Well, this study included 67,340 French participants in this multi-cohort project. They looked at serology, so this is going to be during the period of time pre-vaccination, so this is actually older data. This is the early days looking at some serology stuff. Actually at the end of the day in this study, the blood type O people were at the lowest percent of SARS-CoV-2 positive tests, with the AB people having the highest.

We will get right into children COVID and other vulnerable populations, and the article. I think I suggested that I was going to be discussing this because going to just come out when we were getting together to record last week. The article, "Maternal Third Dose of BNT162b2 mRNA Vaccine and Risk of Infant COVID-19 Hospitalization," was published in *Nature Medicine*. As I'll say right up front, before people send me the hate mail. Certain topics are very emotional, so I'm going to share the science and its implications. If you're going to send some hate mail, I think that goes to Vincent@microbe.tv if I'm not correct.

VR: [laughs] Sure.

DG: As the authors start by repeating, infants are at a higher risk of coronavirus disease, so COVID-19 related hospitalizations, compared to older children. We've shared the data on the thousands, and yes, that is thousands of young children under the age of 4 and many

less than 6 months of age, that have and continue to be hospitalized due to COVID-19. You're not born with that herd immunity, or are you? Well, children are not eligible for vaccination until age 6 months, so what strategies could we employ here? Here the authors investigated the effect of the recommended third maternal dose of BNT162b2 COVID-19 vaccine during pregnancy, on rates of infant COVID-19 related hospitalization.

Now these are results from a nationwide cohort study of all liveborn infants delivered in Israel between the 24th of August 2021 and 15 March 2022. This is a large group among 48,868 liveborn infants included in the analysis, rates of COVID-19 hospitalization were 0.4% in the third dose group, 0.6% in the second dose group, and 0.7% in the unvaccinated group. For the newborns of an unvaccinated mom, that's about 1 in every 143 kids ending up in the hospital in those first four months. Compared to the second dose, getting that third dose was associated with a reduced infant hospitalization with an estimated effectiveness of 53%.

Greater protection was associated with a shorter interval between vaccination and delivery. A third maternal dose during pregnancy reduced the risk of infant hospitalization for COVID-19 during those first four months of life, as they say, supporting clinical and public health guidance for maternal booster vaccination to prevent infant COVID-19 hospitalization. I will say the scientific evidence supports pregnant individual getting three doses of vaccine with a shorter interval between that last vaccination and delivery, to reduce the risks of newborns being hospitalized in the first four months of life.

As we move into the pre-exposure period, as we keep reinforcing, have that plan. Know what you're going to do and know who's going to help you do it. Remember those masks. They only work if they are worn. This is a respiratory virus, so keep that in mind. Outdoors is safer than indoors and let's all breathe clean air.

All right. Going into COVID early viral, upper respiratory non hypoxic phase. What are our goals here? What are we trying to do when someone gets COVID? Well, we're trying to prevent the disease from progressing. We don't want them to end up in the hospital, we don't want them to die, and we don't want them to end up with long-term sequelae.

We care about post-acute sequelae of COVID. We care about Long COVID. I'm going to discuss this article more in the Long COVID section, but number one is Paxlovid and I'm going to discuss the article, “Association of Treatment with Nirmatrelvir - Paxlovid - and the Risk of Post-COVID-19 Condition,” recently published in *JAMA Internal Medicine*, where we're going to look at some published peer-review data demonstrating that early treatment with Paxlovid is associated with a reduced risk of Long COVID.

Number two, remdesivir, then we have molnuvirapir. Remember convalescent plasma? An option for the COVID-19 folks who are immunosuppressed with no other treatment options with that estimated 37% reduction in mortality in this population. And as we keep saying, avoid doing those harmful and useless things like treating viruses with antibiotics or using them steroids too soon.

Moving into the second week, the cytokine storm week, no rebound here. We have steroids and we've talked about in whom it's appropriate, what the timing is, what's the dose,

anticoagulation, and we have mentioned pulmonary support a few times. I'm also going to mention here the article, “Mechanically Ventilated Patients with Coronavirus Disease 2019 Had a Higher Chance of In-hospital Death if Treated with High-flow Nasal Cannula Oxygen Before Intubation,” published in *Anesthesia and Analgesia.*

I was a bit surprised by this result, but perhaps I can make up some story that explains this single-center retrospective study that examined patients with COVID-19 related respiratory failure from March 2020 to March 2021 who ended up with high-flow nasal cannula intubation or both. How did they find this data? Well, data was abstracted from the electronic health record, use and duration of high-flow nasal cannula intubation were examined, as well as demographics and clinical characteristics. They assessed the association between high-flow nasal cannula - I'm going to pause there and say, what are we talking about Dr. Griffin?

Those folks that have seen those shows where someone ends up in the hospital, they almost always put them on this like plastic thing with these prongs sticking in their nose. That's the oxygen, that's your normal low-flow nasal cannula. What we've started using more and more of is what is called a high-flow nasal cannula, So think of that from the shows, but this is a larger caliber. Those prongs that go in the nose, they are big and they pretty much fill the nares, the nostrils, and we deliver many, many liters. Not just four or five or six, but 40 liters a minute, so a high-flow through those large nasal cannulas.

Here looking at this issue of when someone is having difficulty, do you go ahead and immediately intubate them and put them on that ventilator, or do you try high-flow nasal cannula for a while? See if you can avoid intubation, see how well they do. Here they look at this and they use Cox proportional hazards models. They adjust for age, sex, race, ethnicity, obesity, hypertension, diabetes, prior COPD or asthma, number of other factors. A total of 440 patients were identified. 70.7% received high-flow nasal cannula before intubation; 29.3% were intubated without high-flow nasal cannula. Here's the result. Patients who received high flow nasal cannula before intubation had a higher chance of in-hospital death, hazard ratio 2.08, so about twice as likely to die. Initially I look at this and I'm trying to figure out, does this make sense? Well, the authors referenced some other research showing increased mortality rates with high flow nasal cannula when used in disease conditions such as cardiogenic pulmonary edema, COPD.

There's even an editorial in the same issue called, “High Flow Nasal Cannula and Outcomes in COVID 19: Reading Between the Lines.” Now, couple points. The first and very important point is that this is a retrospective analysis that only included patients who were intubated, so only those that failed high flow nasal cannula.

Let's think about it this way. You got an individual and you're trying to decide. They're having a lot of issues. Are we going to ventilate them or are we going to try to do the high-flow nasal cannula? A lot of people get high-flow nasal cannula and then they end up not being intubated, and that's a success but we don't look at them, we move them away. We're only looking at the people that failed. They reference in this editorial, other studies showing that high-flow nasal cannula can prevent the need for intubation and mechanical ventilation. The answer we want is, what happens depending upon that initial fork in the road between high-flow nasal cannula and going straight to mechanical ventilation, not

what happens in that subset that failed high flow nasal cannula, ends up intubated, compared that those that were mechanically ventilated.

VR: All right, so what you're saying is they didn't do the right comparison.

DG: Yes, I don't think they did, and I worry about where they go with this. I think that other comparison is much more useful and I think we have other evidence suggesting that high-flow nasal cannula keeps you off the ventilator, and that's a success. As we mentioned, once they end up in the hospital early enough, maybe remdesivir, immune modulation, and again, some folks need antibiotics, but most don't, so avoid those unnecessary antibiotics, unproven therapies.

I was going to suggest, Vincent, I have noticed that when you actually start putting in catchy titles, it seems like the YouTube views go up. Maybe we'll have a catchy title for this one that mentions the fact that we are now going to spend a little bit of time, actually more than a little bit of time on the late phase PASC and Long COVID.

The article, "Severe Infection and Risk of Cardiovascular Disease: A Multicohort Study," published in the journal *Circulation*. What I like here is the absolute increased risk, not just the relative increase in risk. Here the investigators looked at 331,683 UK Biobank participants without cardiovascular disease at baseline, and then they replicate their main findings, an independent population from three prospective cohort studies comprising 271,533 community dwelling participants from Finland. Cardiovascular risk factors were measured at baseline. They diagnosed infectious diseases. That's the exposure, and then incident major cardiovascular events after infections, defined as myocardial infarction, cardiac death, fatal or non-fatal stroke. That's the outcome from linkage of participants to hospital and mortality registers. Then they computed adjusted hazard ratios and 95% confidence intervals for infectious diseases as short- and long-term risk factors for these major cardiovascular events. Let me point out right up front, this is not just COVID, but the impact of an infection severe enough to require hospitalization on the incidence of major cardiovascular events such as myocardial infarction, cardiac death, fatal or non-fatal stroke.

In the UK Biobank, and I'm going to help, I'm going to do the math for you here. They're going to follow these folks up for 11.6 years. They're going to follow up 54,434 participants hospitalized for an infection. How many 11,649 had an incident major cardiovascular event at follow-up. I just want everyone to think about these numbers. Everyone's so excited to clap these folks out at discharge and call it a success, but that is 21% or more than 1 in 5 people having a heart attack, a stroke or dying. In the next, I'm going to point out 11.6 years. We're following them for a while. Now that's a long time to follow up. Maybe people just do that. Maybe people just have heart attacks and strokes. Well, now you got to compare to background. Relative to participants without this infectious disease, those who were hospitalized experience increased risk.

This was strongest during that first month with a hazard ratio of 7.87, almost eight times as likely to have a stroke or heart attack or die in the next 30 days. This did remain elevated during the entire follow up. They then looked at this in the replication cohort and also got the same 7.64, so almost an eight-fold increase. It's really, I'm going to say, an interesting point because there was the study we were discussing this morning during rounds at

Columbia, where if you tell people to get vaccinated for the flu because they think it's going to keep them out of the hospital for the flu. What really persuaded was, actually a Danish study, was saying if you get a flu shot, you may end up not ending up in the hospital, but you may also reduce your risk of a heart attack, a stroke or death.

People are persuaded by that, interesting enough. The article, "Risk Factors Associated with Post COVID-19 Condition: A Systematic Review and Meta-analysis," was published in *JAMA Internal Medicine*. The goal of this study was to evaluate the demographic characteristics and comorbidities that have been found to be associated with an increased risk of developing post-COVID conditions, PCC. We have so many acronyms. There's PASC, there's PCC, I don't know how many, but basically folks that end up having a problem post-COVID. I like the concept of PASC. I like the concept of PCC because I think of Long COVID as just a subset of the many bad things that can happen to you after COVID. The initial search yielded 5,334 records of which 255 articles underwent full text evaluation. They ultimately identified 41 articles and a total of 860,783 patients.

The findings of the meta-analysis showed, and I think it's consistent with what other studies have suggested, that female sex put someone at a higher odds ratio, 1.56. Age, so older age, 1.21. Higher BMI, 1.15. Smoking 1.10. In addition, the presence of comorbidities, previous hospitalization or ICU admission was found to be associated with a high risk of post-COVID conditions. We had odds ratio of 2.48 and 2.37.

Now this is one thing I keep hitting on. Patients who have been vaccinated against COVID-19 with two doses, we only had two doses here, had a 43% lower risk of developing post-COVID conditions compared with patients who are not vaccinated. That odds ratio of 0.57. I think I pointed out too, that people that get COVID, if you get vaccinated you actually reduce your risk after the fact.

Those vaccines are best done before you get COVID. Actually if you're unvaccinated and you've had COVID, getting vaccinated can reduce your risk of developing those post-COVID conditions. I think I promised last time that I would discuss this. The article. "Association of Treatment with Nirmatrelvir and the Risk of Post-COVID-19 Condition." I even promised this earlier in the show. This was published in *JAMA Internal Medicine* and provides published peer-reviewed data demonstrating the early treatment with Paxlovid is associated with a reduced risk of Long COVID.

Let's see what we've got. These are the results of a cohort study that use the healthcare databases of the U.S. Department of Veterans Affairs, the VA, to identify patients who had a SARS-CoV-2 positive result between January 3, 2022 and December 31, 2022, who were not hospitalized on the day of the positive test result, who had at least one risk factor for progression of severe COVID-19, and who survived the first 30 days after SARS-CoV-2 diagnosis.

It's really interesting. I always comment about this. In a sense, the benefits of Paxlovid are even better because I think of a combined endpoint of death or Long COVID. Anyway, they identify individuals who had a SARS-CoV-2 positive test and were treated with oral nirmatrelvir within five days after the positive test. We're looking at 35,717 and individuals who had that SARS-CoV-2 positive test who received no COVID-19 antiviral or antibody

treatment during the acute phase. That's our control group with an N of 246,076. In terms of Long COVID or PASC, the investigators looked at a pre-specified panel of 13 post-acute COVID-19 sequelae, so components of PCC, right? That's our new word, post-COVID conditions. We can always talk a little bit about what is post-acute sequelae, but they found that compared with a control group, nirmatrelvir was associated with a 26% reduction in the risk of post-COVID conditions, so relative risk 0.74, including reduced risk of 10 of the 13 post-acute sequelae. Which are these in the cardiovascular system? Dysrhythmia and ischemic heart disease, coagulation and hematological disorders, pulmonary embolism and DVTs, fatigue and malaise, acute kidney disease, muscle pain, neurocognitive impairment and dysautonomia, shortness of breath.

In addition, something we've talked about is the issue with delayed death from COVID after those first 30 days, right? We've talked about what is that case fatality rate, pre-vaccine, one or two percent. That's in the first 30 days. They found that nirmatrelvir/ritonavir Paxlovid was also associated with a 47% reduction in the risk of post-acute death, hazard ratio 0.53, and a 24% reduction in post-acute hospitalization. Nirmatrelvir was associated with a reduced risk in people who were unvaccinated, those who were vaccinated, those who were boosted, those for whom this was the first infection and for those who was a reinfection. Actually, I encourage everyone to spend a little time looking at Figure 1 and Figure 2, because it really breaks things down.

A lot of people say, I don't even know what PASC is. What are post-acute COVID conditions? Here you can say, OK, well some of the ones that we can have, cardiovascular, as we mentioned, you can end up having a heart attack. We see that 29% reduction in heart attacks, ischemic heart disease. You could end up with a pulmonary embolism and we see about a 40% reduced risk of a pulmonary embolism. You can end up with that subset that we think of as Long COVID, right? That fatigue, that malaise. Debilitating, not like I'm just tired and didn't get a good sleep last night. That's again, about a 20% reduction. Acute kidney injury, that's not something that people are just making up in their head. That horrible muscle pain that we see. You can actually follow this over time and you really see a separation of the curves.

All right, and I'm going to wrap it up here, with what I've been saying for quite a while and will continue to say, is even though we might be losing interest in some parts of the world, when we look around, no one is safe until everyone is safe. I want everyone to pause the recording right here, go to parasiteswithoutborders.com and click the Donate button. Even a small amount will help. We're only able to do this, put out these broadcasts and shows, because of your generous support. We're also only able to help our sister organizations out there, thanks to your support.

We are still in the middle of our American Society of Tropical Medicine and Hygiene Fundraiser. February, March and April, donations made to Parasites Without Borders will be matched and doubled up to a potential donation of $30,000 from PWB to American Society of Tropical Medicine and Hygiene.

VR: Time for your questions for Daniel. You can send them to Daniel@microbe.tv. OK, Daniel, not Vincent.

DG: I get the questions. You get the hate mail, right?

VR: Oh, hate mail convention. OK, got it. Sherry writes, "I've done such a good job protecting myself from COVID by always wearing a mask in public and washing my hands that I haven't gotten any kind of illness for the past three years. I've regularly gotten my flu and COVID vaccines, but otherwise I don't feel like my immune system has had anything to do. Could this be a bad thing? Could I be weakening my immune system by not giving it anything to do? If so, what should I do? Forgive me if this is a stupid question."

DG: It's a brilliant question, actually. You may not be getting sick, but don't worry, your immune system is not dying of boredom. None of these immunity dead, all these new things that folks have invented. There's plenty of microbes out there that your immune system is interacting with on a regular basis. If someone put a swab up your nose, you know, there'll probably be some staph up there. If they swabbed your skin, there might even be some fungal stuff, things like that. Your immune system is just fine.

VR: Margie writes, "I'm wondering if Gilbert's Syndrome is a reason not to take Paxlovid if I test positive. While I don't see it mentioned in the fact sheet, I wonder if my primary care physician would even know if Paxlovid or any other drugs might be problematic. Gilbert's Syndrome was mentioned at my first adult physical 20 years ago with the comment that it's nothing to worry about. Now I'm 72, not on any meds, but I wonder if Paxlovid is recommended in the event I test positive again."

DG: Yes, so Gilbert's, which actually I think is supposed to be pronounced as though you were French. [laughs] It is really something where incidentally, someone might notice that the bilirubin is a little bit high. It is not a contraindication. Paxlovid, good stuff. Go right ahead. Do not worry.

VR: Sandy writes, "My 34-year-old daughter who's immunized has gotten infected three times, each time being no more than a small cold. Since infection, she has developed one, four-centimeter kidney stone that caused quite a bit of pain, but did pass. Now she has a small stone in each kidney diagnosed by her urologist. My daughter's normal weight, no kids, hardly drinks alcohol, vegan diet, drinks her water. I'm asking Daniel if there's a possible correlation through studies of this happening. Could this be Long COVID that she may not even realize, she be seeing any other type of doctor besides a urologist?"

DG: Yes, this is an excellent question and the first answer is, we're not sure, right? We're still trying to sort out what conditions that occur after COVID are actually in an increased incidence where it would make sense to attribute it to some sort of ongoing inflammation or some sort of perturbation that resulted from the SARS-CoV-2 infection, so not sure if this is actually being driven. I would say at this point going beyond working with the urologist there's still data-free, but it's an area that we're working trying to better understand. At some point we may find that there's a connection and if we do, we may understand the mechanism. There may be something more to do, but at this point, boy, that's a big stone. Ouch.

VR: Janet writes, "I was listening to Clinical Update 994 in the topic of is it worth boosting all the time for the general population, not immunocompromised or in an elderly care home

came up. Again, I understand the arguments, antibodies will only be boosted for three months. The ICUs are no longer swamped with COVID patients, et cetera, but I can't help feel there's something missing from this public health calculation, Long COVID. Shouldn't that be factored in as well? My understanding is that the big picture impact of Long COVID is significant no matter what measure is used, healthcare costs, loss of productivity, et cetera. Am I missing something?"

DG: You are not, maybe a lot of people are, I will say. I've been talking about Long COVID and probably I should go back and listen. I should say I've been taking care of folks with Long COVID since the early days. Probably about June was when people started meeting the definition, right? We started getting healthcare workers getting sick, people that I knew, non-healthcare workers, patient of mine who would end up in the hospital three months later. They're not better. They're struggling. We've been working and, hopefully, we've been making a point every week of mentioning and keeping the awareness up about post-acute sequelae of COVID. Then what I say is a subset of that, the Long COVID. No, this is a consideration.

When we were discussing some issues earlier this week, we were talking about this study where, boy, Paxlovid could reduce your risk of getting post-acute sequelae even if you've been vaccinated, even if this is not your first infection. This is part of that metric, and this question is, is what makes the most sense going forward? Yes, getting infected. We talked a little bit today about who looks like they are at higher risk. You're female, maybe you're older maybe you've got certain comorbidities. Maybe we'll even understand at some point the genetic basis between who gets Long COVID post good sequelae and who doesn't. But no, I think the whole metric here when we talk about everything is being sick acutely, which is not great. Getting severe disease, which can include progression, hospitalization, or death, but also post-acute sequelae of COVID, it should be part of our decisions and our thinking.

VR: It's very hard Daniel, because you can't predict who's going to have Long COVID or PASC, right? You have to do something for everyone and you, would it be then the decision to immunize everyone every six months or to have a plan where we know Paxlovid reduces the incidence of Long COVID. I think it's a hard decision to make.

DG: Yes, I'm going to keep talking about this because I think this is important and I think our listeners think it's important. We presented data today that - We presented data - I'll talk about vaccines first. Getting vaccinated before you get COVID is going to significantly reduce your risk of ending up with Long COVID. Getting vaccinated after you get COVID, if you've never been vaccinated, can also reduce your risk. First vaccine has the biggest impact. Second vaccine more. Third one you're getting down to a little bit, and by the fourth we're talking about, maybe at least from the studies that I've been looking at, about a 1%. Again you can say, if I don't get COVID I can't get Long COVID, so I understand that. Yes, we may be getting to the point where we don't necessarily have to talk about one size fits all.

We could actually start talking about what makes sense for certain individuals. Again, Vincent, I think you're right on. We know who's at risk for hospitalization and death. We're still really trying to sort out that few percent. That single digit percent that still gets post-

acute sequelae of COVID post-vaccination. Who they are, number needed to vaccinate, frequency of vaccination.

VR: The problem is that even with multiple boosting, you're still going to get some kind of COVID at some point, right? I don't think that's the solution. I think if Paxlovid is reducing it substantially, that makes a lot more sense, but hey, they don't ask me, they ask you Daniel.

DG: [laughs] No, I think it's important to have a discussion. It's important to be honest. What's the science? What can the different approaches offer? The best way not to get Long COVID is not to get COVID.

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

DG: No, thank you and everyone be safe.

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