This Week in Virology

TWiV 1096 Clinical Update

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Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick. From Microbe TV, this is *TWiV, This Week in Virology*, Episode 1096, recorded on March 14, 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: What do you have on your bow tie today, Daniel?

DG: According to some artist, it's supposed to be hepatitis B, I think, but who knows sometimes.

VR: I don't see virus particles. Are there virus particles on it?

DG: I think there's these little round guys.

VR: There's a big red blob on the left side. What is that supposed to be?

DG: Who knows?

VR: Is that like a liver?

[laughter]

DG: Sure, let's go with that.

VR: OK.

DG: All right, well, we've got a lot to cover today. Let's jump right into it. I'll start with our quotation, which actually was given to us by one of our emailers, I think, for *This Week in Parasitism,* perhaps. “Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.” That's Margaret Mead. Maybe that's, I like to think, a tribute to our listeners who hopefully are out there spreading the word.

I got an article I was looking at today. The biggest threat to our future is not any particular pathogen, but disinformation. Hopefully, our listeners are helping lead the charge with honest, accurate science. Along those lines, that puts me right into measles. I mentioned I

would mention measles. I like that. It was that nice alliteration there. The CDC actually has a page, and I'll leave a link. You can go and get information about measles cases, measles outbreaks. You do a little bit of your own investigation here.

Why am I talking about measles? As of March 7, 2024, a total of 45 measles cases were reported by 17 jurisdictions in the United States. The reason they say jurisdictions and not states is apparently New York City is its own jurisdiction. That's cool. The District of Columbia, that's a jurisdiction as well. Let me give a little bit of context. I mentioned we've already gotten 45 measles cases, and we're mid-March here. What's been going on over time?

Last year, 2023, we got up to a total of 58 measles cases. We're almost there. At this rate, we're going to be there shortly. Go back in 2022, 121. Not a great year. 2021, 49; 2020, 13. Seeming pretty good. 2019, we had 1,274. That was the greatest number of cases since 1992. You can follow this over time. What happens is we have these outbreaks, and then you end up with these absurd numbers like over 1,000. What's going on? What do you think's going on, Vincent? Do you have any theories?

VR: There's a very low level of - There are unvaccinated people in the U.S. The virus is introduced from overseas, where there are far more cases in other countries, especially countries that are under-vaccinated. The virus is very good at ending up in those unvaccinated people. Then the one year where we had over 1,200 cases, I think that was associated with some communities who do not vaccinate on a big scale. The virus is introduced into them, and you have larger outbreaks. That's what I think is happening, Daniel.

DG: I think the data will support that. We're going to be talking about measles this week. We're going to be talking about it again next week. One of the challenges of measles is it's incredibly transmissible. Anyone who's got their head in the sand thinking like, oh, it's not a problem here in the U.S., well, obviously it is. We do not have a wall around our country. People come back and forth. Measles is a problem throughout the world. As I've been saying forever, no one is safe until everyone is safe.

As long as there's measles in the world, there's going to be measles coming into our country. I should point out, and we'll talk about some cases next week, a lot of times people are sick, a lot of times people are contagious before the characteristic rash. You can have quite a bit of transmission before anyone realizes that they're dealing with measles.

VR: Daniel, I thought there was a wall on the south of the U.S.

DG: Apparently there is, and apparently, they've been adding sections.

VR: Would that stop measles virus, though?

DG: I believe that that wall at the southern border is pervious. Is that right? We're pervious to measles. All right. Moving on to maybe a little bit of good news, RSV. We've really seen the numbers come down. We're really getting through the RSV season, which is great. A nice thing is, as we're getting to the end of the RSV season, we get a chance to look back at our success with the new passive vaccination approach using Beyfortus or nirsevimab. We've got the *MMWR*, "Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus-associated Hospitalization – "

VR: What did you say? Respiratory?

DG: Respiratory. Apparently, we've had some e-mailers that they feel like we're the only ones that actually pronounce it correctly.

VR: Not respiratory?

DG: I think when you drop the R, respiratory. No, respiratory. I'm pronouncing all them letters associated.

"Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus-associated Hospitalization among Infants Entering Their First Respiratory Syncytial Virus Season - New Vaccine Surveillance Network, October 2023 through February 2024." First, a little bit of kudos to the title because whenever we talk about effectiveness, we've been hammering we want to know effectiveness doing what.

This is RSV-associated hospitalization and even defined among infants. In August 2023, the CDC's Advisory Committee on Immunization Practices, ACIP, recommended nirsevimab, this long-acting monoclonal antibody, for infants aged less than 8 months to predict its RSV-associated lower respiratory tract infection during their first RSV season and for children aged 18 to 19 months at increased risk for severe RSV disease.

This analysis provides the first U.S. estimate for post-introduction nirsevimab effectiveness among U.S. infants during their first RSV season. We get this from the New Vaccine Surveillance Network. It's a population-based prospective surveillance platform for acute respiratory illness in infants, children, adolescents that monitors pediatric respiratory viruses across seven U.S. pediatric academic medical centers to assess immunization effectiveness.

Demographic clinical immunization data were systematically collected through parent/guardian interviews, medical record abstraction, state immunization information systems. Respiratory specimens were collected from the enrolled children, tested for RSV and other common respiratory viruses by PCR. Receipt of nirsevimab was ascertained through parent report, verified through state immunization information systems, birth hospital or primary care provider records.

Nirsevimab effectiveness against RSV-associated hospitalization was estimated using a test negative case control design. Case patients were infants who had a positive RSV test result. Control patients were infants who had a negative RSV test result. I'm going to say exciting, good news. Overall, nirsevimab effectiveness was 90% against RSV-associated hospitalization.

VR: Yes, except they only had six patients that were treated. It's a small number.

DG: Let's see what we had here. No, I think it was, and this is why I've got to check my notes. I think they only had 1% of the case patients end up getting RSV. That was the comparison here. In the control patients, you end up with 18%, where if you look at the folks that got nirsevimab, it was only 1%.

VR: Yes, so six case patients received nirsevimab.

DG: Nirsevimab and got - Yes.

VR: Then among those six, 90% of them were not hospitalized.

DG: No, I would say this. Yes, let me do the math. One percent would be 6. 600 case patients, only 1% of them. Only six of the 600 ended up with RSV, where if you look at the control population, you're dealing with like over 200, 300. There we're seeing 18% ended up getting RSV.

VR: Because in your notes, you say -

DG: I know, my notes are terrible.

VR: Oh, they're not right.

DG: Yes, let me go right to the article so we don't misinform. Here we go. Let's get it. Because yes, in my notes, it's very confusing. Here are the results. We have 1,000 eligible infants, 699 meet the inclusion criteria. We end up with 407 of our case patients. We end up 292 in our control patients. That's where we get our 1% versus our -

VR: Of those case patients, 90% effectiveness.

DG: Ninety percent effectiveness, yes.

VR: Did all those case patients, 400 some odd, get nirsevimab and half did not, or what were the numbers there?

DG: I think the way they put this is a little bit confusing. Because they're talking about the case patients. You end up with the case patients, only 1% of the folks that get RSV, so the cases had nirsevimab, where 18% control patients received nirsevimab. Yes, the way they present this is it's a little bit confusing to sort out that 90% effectiveness. I will fix my notes.

All right, and we'll move into flu, but encouraging. A 90%, that's even better than we were anticipating from the randomized control trials. Still focusing on children, we'll move into flu. A bit of sobering news is that the CDC just announced that we have passed the number more than 100 children, up to 103 when I last looked at the data, in the U.S. have died of influenza. More than 100 children, the United States, have died of influenza so far this season. We're already over 20,000 adults.

Now, a couple of things I want to point out. This is for the people that ask the next question, well, what about these children? I want to point out, the majority of these children had no obvious medical issues before their influenza infection and death, but 90% were not fully vaccinated. The reason I say fully vaccinated is that, if you're below a certain age, it's a two-shot to get that full protection. Flu is still going strong. We had a peak, it came down, went back up again, started to come down. Actually, a little bit of an uptrend here.

We're still looking at a solid amount of influenza circulating. Again, as we've been talking about, it's regional. New Jersey is not doing great, even a little bit worse than the week before. Out West, they're doing much better. New York, as long as you're not talking about New York

City, is doing a bit better. We do have a lot of these regional differences, but still a solid amount of influenza circulating.

VR: Daniel, does anyone follow people who recover from influenza to see if they have any post-acute sequelae?

DG They do. Actually, there is a phenomenon that we refer to as long flu. I think it's a great question because for a lot of people, Long COVID is the first time they're learning about this idea that you get an acute illness, and then you have trouble going onward. Well, with the first SARS, 40% of people that survived SARS, the first one, 40% of them at two years still have issues. We have people after Lyme disease have issues. We certainly have people have ongoing issues after dengue, chikungunya, influenza. A lot of our infections actually are associated with a certain percent, and it varies by infection, with a long post-infectious sequelae syndrome.

VR: Would be very interesting to know if there are similar mechanisms at play for these different viruses.

DG: Yes, I think a lot of us, when I've talked to people at other Long COVID centers who also take care of people with other post-infectious sequelae, a lot of us are taking some of the results that we're getting from the Long COVID studies and starting to look at these other folks. Are they getting these really high EBV serology results? Do they have the low serotonin? Do they have low AM cortisol? We'll talk a little bit about the orthostatic and autonomic issues that we're seeing, actually, in a lot of the post-infectious sequelae.

VR: I think it's important for people to understand that this happens with other infections, and admittedly, the numbers for COVID are much bigger because we're just coming out of this pandemic, but it's nothing new, and they all have to be taken care of, clearly. We have to understand how they all work and how to prevent them all. It's not something special about SARS-CoV-2 other than it's a new virus.

DG: Yes, it might be difference, what percent. There may be some characteristics, but no, this is something that we've been seeing, and we've been dismissive about for decades, unfortunately. All right, well, COVID, still going strong. Still about 15,000 in hospital. Still about 2,000 in ICU. We're still seeing over 200 deaths a day. I keep talking about how great the wastewater data looks, but it's still going strong. We're still seeing a lot of COVID up there. Mentioning the wastewater again. It's supposed to be getting better, Vincent.

Looking at the CDC data, looking at the Biobot data, everywhere it's going in the right direction. There still is a solid amount of SARS-CoV-2 being detected in the wastewater. What to do? I'm glad that we talked a little bit about post-infectious sequelae because right here in the children's section, I'm going to talk about the article, “Vaccine Effectiveness against Long COVID in Children,” published in *Pediatrics.* One of the reasons I like to have this special section on children and other vulnerable populations is that we have not been great at embracing vaccination in children.

There's this idea that, oh, it's not a big deal in children. Over 1,000 children died from COVID. Not only do we see children end up in the hospital, but we have a growing number of children who three, four, five months later, they're not doing OK. In this article published in *Pediatrics,*

they look at a retrospective cohort. It's a retrospective cohort study that used data from 17 health systems using the RECOVER PCORnet electronic health record program for visits after vaccine availability.

They examined both probable, so symptom-based, and diagnosed Long COVID after vaccination. Just to make sure we're being critical, what was the criteria? What's this probable or diagnosed Long COVID? The case definition for diagnosed Long COVID was two or more visits with diagnosis codes specific for Long COVID. Someone is making that diagnosis. A single diagnosis code fell within the case definition for probable Long COVID.

In addition, to account for incomplete availability or use of these Long COVID-specific diagnosis codes, especially for patients with early signs of Long COVID, the case definition for probable Long COVID included having that COVID-19 diagnosis or a positive test, plus at least two Long COVID compatible diagnoses, 28 to 179 days after infection. That's that chronic fatigue and some of the other that we've talked about. Now, the vaccination rate was 67% in the cohort of 1,037,936 children. Pretty impressive level there.

The incidence of probable Long COVID was 4.5% among patients with COVID-19, whereas actually seeing that diagnosis of Long COVID was 0.8%. A couple things there. I don't think we can look at this and say, "Oh, we now know the incidence of Long COVID in children." These are comparative numbers, but it does show that even when everything looks like Long COVID, it seems to take quite a bit before that Long COVID diagnosis actually gets made. Now, what were the results? Adjusted vaccine effectiveness at prevention of Long COVID within 12 months was 35% against probable Long COVID and 41.7% against diagnosed Long COVID. The vaccine efficacy was higher for adolescents. I think it was at 50.3%. The vaccine efficacy was higher at 6 months, 61.4%. This is interesting. It actually decreased to 10.6% at 18 months.

VR: Daniel, what do you think is the mechanism here? Is it because vaccination is preventing severe disease, and why is it going down with time then?

DG: I spent a little time trying to sort this out. What are these? One of the things, and we've seen this in a lot of studies, is vaccinated people are less likely to get Long COVID. It may be that we have a less dysfunctional, we have less of a prolonged immune response. Maybe we're better able to clear the virus early on and whatever remnants might be triggering that ongoing immune dysfunction. We have data supporting those. Why does the vaccine efficacy decrease? I think because, and this is very positive, 95% of people with Long COVID will be better at 18 months.

The natural history is to get better. If people are getting better, you've only got 5% left to be working on. That vaccine may prevent you from feeling crummy for months and months, but ultimately, if you get out to 18 months, there's only going to be a few percent of people still with Long COVID. All right. We'll move into another vaccine paper and the article, “Impact of Vaccination on the Association of COVID-19 with Cardiovascular Diseases: An OpenSAFELY Cohort Study,” recently published in *Nature Communications*.

I feel like we've done a bit, there's a theme here, Vincent, where we talk about how viruses don't just kill you in the first one to two weeks. There's this increased risk of cardiovascular issues. I think this is an important paper as it reinforces one of the short-term negative

consequences of getting an infection about which we've really tried to raise awareness. It is unfortunate but true that the incidence of cardiovascular issues, such as strokes, heart attacks, and clots, increases during and in the weeks right after an infection.

This is not just SARS-CoV-2, not just COVID-19. Infection with SARS-CoV-2 is associated with an increased risk of arterial and venous thrombotic events. Here the investigators looked at whether vaccination was associated with a reduction in this risk. They used electronic health records for about 40% of the English population. They compared a pre-vaccination cohort with over 18 million people in the wild-type/Alpha variant eras. I like that.

Vaccinated and unvaccinated cohorts, so 13,572,399 and 3,161,485 people respectively, vaccinated and unvaccinated cohorts. During the Delta variant era, they found that the incidence of each arterial thrombotic, venous thrombotic, and other cardiovascular outcomes was substantially elevated during the weeks one to four after COVID-19 compared with before or without COVID-19. Hazard ratios were higher after hospitalized than non-hospitalized COVID-19, and higher in the pre-vaccination and unvaccinated cohorts than the vaccinated cohort.

We get some numbers here. The incidence of arterial thrombotic events, such as myocardial infarction and ischemic stroke, during weeks one to four after COVID diagnosis compared with before or without a COVID diagnosis was elevated in the pre-vaccination 4.40. The adjusted hazard ratio, more than four times. Unvaccinated cohorts, 8.53 adjusted hazard ratio. Less markedly elevated in the vaccinated cohort. About double if you've been vaccinated. In the pre-vaccination, it quadruples. If you go forward into the Delta period without getting that vaccine, more than an eightfold increased hazard ratio.

VR: Daniel, what is the mechanism of these cardiovascular events after SARS-CoV-2 infection?

DG: A little bit of science, I think that helps us here. There is a bit of endothelial dysfunction. I think one of the things we've come to realize over the decades is that people can have these cholesterol-laden plaques that are undergoing this dynamic change. When you get an acute infection, you can actually get exposure of some of the moieties in the endovascular environment that actually lead to clots forming. Yes, there's a very interesting and evolving understanding. This is not just, as we pointed out, it's not just SARS-CoV-2. We see this after influenza. The major impact that we see in our UnitedHealthcare populations on getting the flu shot is preventing heart attacks, preventing cardiovascular complications.

VR: Where are these events, these endothelial events happening? Are they mostly in the pulmonary area because that's where most of the virus is?

DG: Interesting that not just. We see a lot of pulmonary emboli. Early on, before we routinely used anticoagulation, we saw a lot of pulmonary emboli. We also see lower limb deep venous thrombosis. We're seeing venous thrombi forming, clots forming in our legs. We're also seeing cardiac, so clots forming in those small vessels that supply the myocardium, and strokes.

VR: The implication is the virus is getting to these places somehow.

DG: We're not sure. I don't know if the virus is getting there, or if it's just it's triggering this inflammatory response. Because a lot of these are not happening in the first week during viral replication. A lot of it is happening in week two, three, and four.

VR: Yes. I remember cytokines and chemokines can go anywhere, not just locally.

DG: Yes. That's always the take. People are like, "Well, if there's a problem here, it means the virus has to be there." At week three and four, not much virus are in these places.

VR: I agree. I always had trouble with this idea that the virus is replicating like crazy in the endothelium. You can do that in cells and culture, but it doesn't mean it's happening in people. You're right. If it's late, it has to be an inflammatory thing.

DG: All right. Moving into you test positive, the early viral phase. I think I'm just going to leave in going forward the NIH COVID-19 treatment guidelines so people can share those with their colleagues who are following the media, not the science. Still, number one, Paxlovid. Number two, remdesivir. Three, molnupiravir. Some circumstances, still convalescent plasma. We have that updated isolation guidance. Just a reminder, that updated isolation guidance is broader now. It's the CDC's updated respiratory virus guidance, what to do when you are sick. You can still kill somebody with RSV, influenza, and other things.

A negative COVID test is not licensed to go to your workplace or spend time around higher-risk individuals. I will point out, and this is actually a lot of discussions around this. We have not had updated guidance for health-care personnel since September 23, 2022. This does not apply to health-care workers. Those of us that take care of high-risk individuals, this is not saying go back there on day three and get your patient sick.

I have to say, it's very challenging because this came up in the last week as we're having discussions on the National Infection Committee. What's really tenable? Let's say you're a clinician who takes care of cancer patients, patients who are immune compromised, they're at high risk. You're feeling crummy, and you go, and let's say it's Sunday night, and you go, and you get a positive test, and you realize, yes, I started feeling crummy Sunday, I've now got COVID. A lot of areas, the recommendation is 10 days of staying out of the workplace.

That's challenging because most of us only get 20 days off a year. You're losing half your days off, but let's look at the other side. You're talking about losing days off. Bringing this virus into the workplace, you're talking about losing patients. All right. Second week. As we talked about, a lot of those cardiovascular issues are not happening in the first week. They're happening in the second, third, and fourth. That second week is when we've moved into the inflammatory phase. The cytokine storm week, steroids, anticoagulation, pulmonary support, maybe still a little bit of a window for remdesivir and immune modulation.

A little bit of time, we're just going to talk about a couple articles here. I'm going to give everyone maybe a little bit of a break this week. We won't be an hour and 20 minutes like we sometimes get. Talking about late phase PASC and Long COVID. First, I'll say a little bit of encouragement. We are moving forward. The NIH has opened a couple more Long COVID trials to evaluate treatments for autonomic nervous system dysfunction. As a little bit of a preview, next week, I'm going to be talking about a nice study, looking at just the incredibly high incidence of autonomic nervous system dysfunction in folks with Long COVID.

Here we have two phase two clinical trials that will be testing the safety and efficacy of three treatments for adults with autonomic nervous system dysfunction. They're going to be looking at a form of IVIG. They're going to be looking at ivabradine, which is an interesting oral medication that reduces heart rate. They're also going to have a coordinated guided non-drug care, which includes a series of activities managed through weekly phone calls, wearing a compression belt, eating a high-salt diet. A lot of things that we recommend for POTS patients. Interesting to get a little bit of potentially that next level.

You find something, and then you say, we'll just treat it the way we treat that. It's nice to actually do that, and then get some data on the impact. We also have, The Impact of Nirmatrelvir/ritonavir on Myocardial Injury and Long-term Cardiovascular Outcomes in Hospitalized Patients with COVID-19 amid the Omicron Wave of the Pandemic," published in *Cardiovascular Drugs and Therapy*. In a sense, this is a question of, can we reduce the long-term sequelae, in here the cardiovascular long-term sequelae, by jumping in early with that Paxlovid?

These are results of a prospective cohort study that identified hospitalized adult patients with COVID-19 between April 19, 2022 and June 9, 2022 amid the Omicron wave of the pandemic. We have matched nirmatrelvir/ritonavir treated, so Paxlovid treated, and non-treated cohorts. They're forming these using the propensity score matching method, try to get those groups really matched. The primary outcome of the study was the incidence of major adverse cardiovascular events, MACEs. What are those? Cardiovascular death, myocardial infarction, stroke, new onset heart failure, heart failure hospitalization, or ventricular arrhythmia from 30 days to 16 months after the diagnosis of COVID-19.

More of those cardiovascular outcomes. Two, 949 patient cohorts with balanced baseline characteristics were formed. During the follow-up period, 59 patients in the Paxlovid group, 86 patients in the control group developed major adverse cardiovascular events. The differences were mainly reflected in new onset heart failure or heart failure hospitalization. They found, they looked through a number of arrows, really Paxlovid was the independent protective factor for the occurrence of these major adverse cardiovascular events. Interesting, they actually have a nice Figure 3. We can see actually over time, starting at about three months is when you actually start to see this separation. It's really continuing as you go out to 15, 18 months.

VR: This is a complement to the study we talked about just now, earlier, which looked at vaccination. Here we're looking at antivirals on cardiovascular outcomes.

DG: Yes. Not only vaccination, but early appropriate treatment can reduce these negative cardiovascular outcomes. All right. I will wrap up as I've been doing for a while. Before we get to emails, no one is safe until everyone is safe. We're in our American Society of Tropical Medicine and Hygiene fundraiser. For February, March, we're halfway through, and April, we will double your donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Deron writes, "In your latest video, you said the CDC is going to allow a springtime COVID booster for people 65 and older. What about immunocompromised people? Does the data that supports this for people 65 and older not support it for immunocompromised people?"

DG: Yes, that's tough. We talked about the data when this was introduced, and then we talked about the data the next week on what are we seeing right now with the monovalent XBB booster that we're using. A lot of this data was, you've got a large pool of people, 65 and over, that you can draw on to come to these conclusions. A lot of us would think this extrapolates to the immunocompromised. I was thinking about it today. I don't think I've had any issues with immunocompromised individuals trying to get that next shot, now that they've unleashed the floodgates. If you have a conversation with your physician, and you feel like it's appropriate, and you're interested, I don't think that they're going to prevent the immunocompromised from getting another shot.

VR: Yes, as far as the data go, there aren't any really.

DG: I think that's what we talked about is that we're out to about 120 days with the current one. It seems to be holding pretty steady at 50%. It's one of those, we'll know next year whether or not it was really critical to get that extra shot.

VR: Daniel, writes. We have another Daniel who is a physician, although retired, but still a loyal listener of *TWiV*, writes, "The ending of the five-day quarantine for most seems reasonable for almost all, especially since so few are following the guidelines in the first place. I'm concerned, however, about certain health-care workers returning to work while still infectious. I would hate to have an anesthesiologist intubate me while he/she were infected with SARS-CoV-2. My question is, shouldn't certain healthcare workers wait an extended period of time before returning to work or at least before performing certain procedures? I'd appreciate your thoughts."

DG: I'm glad you bring that up because, very clear, the guidance that just came out does not apply to health-care workers. There is separate health-care worker guides. As mentioned, it has not been updated since September of 2022. Let's talk, what is the health-care worker guides? There's two separations there. One is they basically say for health-care workers, and the whole idea is that we're going to be around vulnerable populations, it is seven days before you go back to work with a well-fitting mask, and only seven days if you go ahead and do a negative test within, it's 48 hours of that return, or it's a full 10 days if you don't use test out based approaches.

Now there's a little bit of a caveat there, is at one point in time, and we can leave a link in our show notes, is there was a surge exception. This was if you are under surge conditions, if you're having trouble meeting staffing needs, if you're going to leave those patients without providers to take care of them, then you could use the five-day rule. Five days, and then returning with a tight-fitting mask, that's an N95. A lot of institutions just decided they were always in surge staff shortage conditions.

That's one of these discussions about what's actually tenable. The point very clearly in the guidance by the CDC is they're acknowledging that people have been, and under this guidance, will return to the workplace infectious to others, putting others at risk. I really think we've got a different standard, and we need to have a different approach for health-care workers, but no, this guidance is not for health-care workers.

VR: Sharla writes, "We love your weekly virus updates. Thank you so much for sharing important information that's trustworthy. It seems hard to find these days." Do you think, Sharla? "I'd appreciate your opinion on this study done in British Columbia. It's the basis for very limited access to Paxlovid here. Under these rules, my family member who is 68, diabetic, asthmatic, with high BP and morbid obesity was told he does not qualify for Paxlovid."

This is a paper in *JAMA Network Open* that I think we did discuss here. It's, "Nirmatrelvir-Ritonavir in COVID-19 Mortality and Hospitalization among Patients with Vulnerability to COVID-19 Complications." They conclude the treatment was not associated with reduced risk of death or hospitalization among individuals who were not extremely vulnerable to complications regardless of age. Sharla says, "My question is, what has shown to be more effective at keeping vulnerable people out of the hospital: Paxlovid or a booster shot? If my elderly family members were to refuse a booster shot for over a year, then they would qualify for Paxlovid. I really worry about my mid-70s parents who have not had COVID yet. Would love to hear what you think."

DG: That's a great question. This reminds me of a couple things. One is the study that we talked about, it was one or two episodes back, where we showed what was the impact of different doses of vaccination, one, two, three, and then we've talked about getting the booster and the number, this long list of studies, showing the benefits of Paxlovid. I'll talk about this. Actually, I've got a paper that's accepted, which will be coming out in the next couple of weeks.

Really, it's a commentary on a meta-analysis of the Paxlovid data out there. We have hundreds of studies, and we actually have about 18 really solid studies showing that Paxlovid really significantly reduces the risk of hospitalization and death, even in vaccinated, even during the times of Omicron. The Paxlovid does quite a bit. It's always painful when the government is deciding, what to do with regards to your health care based upon a single study that maybe helps with their confirmation bias.

Put it in context, we've seen about a 90% reduction if you get those three initial vaccinations. When we talk about studies, another 50% reduction in ending up in the hospital, we're talking about on top of that 90%. As we talked about that study, the last couple of weeks, if you then jump in with an antiviral like Paxlovid, you're talking about taking that risk and really dropping it 50% or more. Really, the ideal approach is both. You shouldn't have to choose. Get that booster and also get Paxlovid.

VR: Bob writes, "I need to convince my PCP to prescribe Paxlovid for me to take with me while traveling so I can begin to take it immediately if I test positive for COVID. What are the best resources to persuade him that it is both legal, i.e. within the licensed use, and recommended for me to get a supply on hand before testing positive? If I fail to persuade him, will a pharmacy sell me Paxlovid if I show them a positive test, or do I need a prescription, or might a pharmacy based urgent clinic give me a prescription if I show them a positive test or test me on the spot?"

DG: Very troubling. The first thing I'll say, you shouldn't have to convince your physician that Paxlovid is what should be used to treat you if you end up with COVID-19. If you have to convince your doctor, you need a new doctor. I wonder, are we going to let the lawyers get

the physicians into line? Do you have to have a number of your patients die, and then get sued that you didn't treat someone who was high-risk, that you've decided that your reading of the media is better than the NIH and the ID Society of America treatment guidelines?

Where are we going with this? In all honesty, I think we, as consumers, I'm a patient too. I choose which doctors I go to. If your doctor is not up-to-date on how to treat COVID, what else are they not up to date on? What other bad advice are they giving you? Number one, you should not have to talk your doctor into something. Your doctor should know more about COVID and COVID treatment than you. That's the first thing. Find a doctor who's up-to-date, who knows what to do.

You can share the COVID-19 treatment guidelines with this provider as you're out searching for a new one. Paxlovid is a licensed medication. It's recommended by the NIH and ID Society, and it is fully licensed. None of these hoops have to stand between you and the ability, as we've seen, the effectiveness of early treatment.

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

DG: Thank you, and everyone be safe.

[music]

VR: You would think that the respiratory is an extension of respire. Not a totally different word like respiratory because you don't respire, you respire, right, Daniel?

DG: Yes.

[00:41:29] [END OF AUDIO]