TWiV 1270 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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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 1270, recorded on November 11 2025. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today here in Toronto, Canada, Daniel Griffin. You might have to turn it on.

Daniel Griffin: Hello, everyone. [chuckles]

VR: Daniel, what are we doing in Toronto?

DG: I don't know, actually. No, I do. I do actually. [laughs] I drove up through a snowstorm to go to a -

VR: - tropical medicine meeting.

DG: That just doesn't make sense. There's a tropical medicine in, what is it, -3, 26 degrees Fahrenheit. It's snowing. It's slippery out there. I am never going to get back across the border trying to explain that I went to Toronto for tropical medicine. Yes, we're at the ASTMNH annual meeting.

VR: Right, where we just did a *TWiP*.

DG: We just did a *TWiP* Now, we are doing a *TWiV*. We're in the middle of this.

VR: You have a bow tie on, and I can see it. I don't even have to guess. It's a Parasite Without Borders bow tie.

DG: Exactly. It's the world with an *Ascaris* wrapped around it.

VR: With a nice sharp point, right?

DG: Yes. Oh, my gosh, that Dickson Despommier back and forth, that point, that tail. It had to be just right.

VR: What people cannot see is that you're wearing Parasite Without Borders socks.

DG: Yes. I probably shouldn't do the leg raise to demonstrate.

VR: You don't want to raise your leg?

DG: Everyone, can -

VR: There you go. See that?

DG: All right. All right. There you go.

VR: I need to get some *MicrobeTV* sock.

DG: You do. You do. Most definitely.

VR: All right, you gave me a good idea. All right.

DG: Shall I jump in with my quotation? Everyone ready for the quotation?

VR: You know how to do that.

DG: We have a large studio audience.

VR: Yes, it's very good. Thanks for coming. We appreciate it.

DG: This is great. Everyone, thank you. Fantastic.

[applause]

DG: All right, so I'm going to start with an E.O. Wilson quotation. "Blind faith, no matter how passionately expressed, will not suffice. Science, for its part, will test relentlessly every assumption about the human condition."

VR: What do you think about that, Daniel?

DG: I was curious what you thought. I obviously love it. It just is as excited, as passionate. We're not as smart as we think we are. We really have to look, to see, to test.

VR: I believe, and not everyone agrees with me, I believe that science can explain everything. There are people who say that's not true, but I don't agree. I think we may not be good at understanding everything yet. We have a lot to go. Science has brought us where we are, keeps us healthy, and it's going to eventually explain everything about life. That's what I see in that quotation. Science will test every assumption about the human condition.

DG: It can and it should. This is our ability to find out if what we believe is true or not. It matters, as you point. We think about where we are with relative to disease and longevity and so many other things. You go back hundreds of years when half the kids wouldn't make it. What changed that? What is science? It's a method for asking, do things work?

There was a point in time in the UK when bathing was controversial, when hygiene was controversial. You find these newspaper articles, more people have died from a bath than who knows what. I'm like, "Really?" Even just the concept of hygiene, American Society of Tropical Medicine and Hygiene, but hygiene and all this other stuff, that's science, is understanding that.

VR: What really bothers us, and I'm saying "us" because I know you agree, is that science is under attack in the U.S. This is really bad. We went to a session yesterday about, a panel discussion about attacks on science. It's very scary what's happening in the U.S., and it's

going to spread elsewhere as well. We all have to worry about it.

DG: Parasites know no borders. [laughs]

VR: They don't know any borders. That's right. Parasites Without Borders, and viruses are parasites, too.

DG: We should mention who was at that panel, because I think that makes--

VR: It was chaired by Angie Rasmussen, and then we had David Morens, and we had Peter Daszak, and then a lawyer who defends climate change scientists. This is very interesting. The lawyer works for a nonprofit whose very existence is to defend climate scientists who are under attack. You may think, "Oh, what's the big deal if you're under attack?" You should have heard what they do. You have to get a lawyer, and it costs you hundreds of thousands of dollars.

You lose your house, you lose your job, you're screwed. This is coming to biology, biological sciences, and public health, and so forth in the U.S. Peter Daszak can no longer have an NIH grant in the U.S. He's going to be charged probably with all kinds of things, and he has to get a lawyer for it. David Morens used to be the assistant to Tony Fauci. He got fired from NIH. Fauci, they're going to try and put in jail. This is crazy, this stuff that we heard about yesterday, right?

DG: Yes, but it's important to mention them. I think a lot of people duck and cover, distance themselves. They don't want to get - but if we let them pick off one at a time, it's a question of what happens next.

VR: That's the thing. He said they will go through all your old emails and find the ones to embarrass you. Then one by one, they'll release them. You will never feel the same again. Then they go after another scientist and another scientist. This session was just eye-opening. I hope you just speak up in defense of science. The problem is many of us are at universities, and the university doesn't want us to talk. Well, I'm at a university. I'm at Columbia University in New York, and be damned if they're going to muzzle me. I'm going to say whatever I want.

[applause]

VR: People ask me, where am I going to go live? What country? I'm not going anywhere. I'm staying and fighting, folks.

DG: We're just briefly here in Canada. We are going to go back to the U.S. afterwards if they let us back in.

[laughter]

VR: You're going to bail me out, right?

DG: [laughs] All right. Let's jump in.

VR: There you go.

DG: [laughs] First, we're going to talk about bird flu, H5N1. People were wondering why we

were talking about turkeys earlier, just moments ago. We read in *CIDRAP*. I always like to give shout-outs to *CIDRAP*, the U.S. Department of Agriculture's Animal and Plant Health Inspection Service. They have a nice acronym. Sounds like something you don't want in your garden, or something you do in APHIS. Confirmed five more avian flu outbreaks in three states.

Indiana reported three outbreaks involving a duck farm in Elkhart County affecting nearly 21,000 birds. I should mention, we used to have a lot of ducks on Long Island. No more commercial ducks. It's all been decimated. It's gone. A 10-bird backyard flock in Johnson County, a duck-breeding facility in LaGrange County affecting 4,800 birds. In Michigan, 113,000 birds were affected in an outbreak on a turkey farm in Ottawa County. The state's third detection in commercial turkeys in less than a week.

Washington reported an outbreak affecting nine poultry in Snohomish County. That's the great state of Washington as opposed to D.C. Turkeys in both. In the past month, APHIS has noted avian flu in 32 commercial flocks, 35 backyard flocks affecting a total of 3.72 million birds. It's interesting. I don't think you really hear about this stuff. Think about millions of affected poultry. I want to give people a little context here. Per the USDA, there are more than 378.5 million egg-laying chickens in the United States.

In 2023, more than 9.4 billion broiler chickens, 218 million turkeys, not all in D.C., were processed in the United States. We actually expect detections to be higher this time of year because of the migrating birds. When people look up, I was driving up here and I saw the migrating birds. I'm ducking low, making sure the windows are all up in the car. We see the wild birds. Basically, that's what they're doing. They're spreading the virus as they head home. It's like a Hitchcock movie. Maybe I think there was a Hitchcock movie.

VR: Yes, there was one called *The Birds*, yes. He didn't know about H5N1.

DG: Actually, we'll post, I guess, in our show notes. I've got a nice map.

VR: They don't have Washington, D.C., on this.

DG: Imagine that.

VR: Let's see who listens to *TWiV*. Which part of the U.S. has the most turkeys?

DG: Yes, I'm seeing DC out there from the crowd.

VR: Did somebody say DC? Good. According to this map, it's Minnesota and Indiana. Commercial flocks, not just turkeys. We should put that up. The other thing I learned at dinner last night, I went with the members of the panel, is that we're not testing people anymore in the U.S. for H5N1. You noticed you used to say, we had this positive here and there, but they're not doing that anymore.

DG: The best way to not get a positive test is to not do a test. We talked about in Tanzania, that's how they got rid of COVID. If you don't do a COVID test, no one has a positive test. Same for H5N1.

VR: What do you think of that, Daniel, the strategy of not testing people, especially like dairy -

DG: I think it's called the ostrich strategy, right? [laughs]

VR: Canadian ostriches -

DG: We're all going to live on Dr. Oz's plantation in Florida after a while, right?

VR: We had a story for a few weeks about ostriches in Canada, which probably you all know about, right? They were killed recently. They were culled. That story is over.

DG: All right. Shall we move on to measles? All right, so measles. Actually, yesterday, a bad day for Canada. We'll get to that in a moment. There's a couple of different ways that we track measles. The U.S. government has actually started, and it's minimal activities, actually giving us some updates. We'll get an update in a couple of days, but we're doing early. Last update we had in the U.S., 1,681 confirmed measles cases. Canada, week 44, 23 new measles cases. We're up to 5,162.

As of yesterday, we're recording here on Tuesday, so as of Monday, Canada has officially lost its status as having eliminated measles. This was considered wiped out in the country in 1998. We get a statement from the Public Health Agency of Canada. The Pan American Health Organization, PAHO, has notified the Public Health Agency of Canada that Canada no longer holds measles elimination status. Basically, they've reviewed the recent epidemiological lab data. This confirmed sustained transmission. Same measles virus strain in Canada for a period of more than a year.

VR: Now, I understand the U.S. is going to follow in January, correct?

DG: By default, the Americas region, which we're a part of, we lost status as part of this region. There's been a 30-fold increase in 2025 compared to 2024 in the number of measles cases. Yes, basically, we're on track in January 2026 for the United States to lose status as well of having it eliminated.

VR: What does that mean?

DG: Basically, we have now ongoing transmission. What happened in the past, and I think maybe this is important to mention, is when there would be an outbreak of measles, we would step in. Vaccination, there'd be education. That didn't happen this time. This time, there was lots of misinformation. "Go on this guy's website, give him lots of money, and get your nutraceuticals." We never really tamped this down. We really just let it run.

VR: Does this have implications for travelers who want to visit Canada or the U.S.? Do they make sure they're up-to-date on their measles vaccination?

DG: I think everyone. This really is a problem for the unvaccinated. I say that because we talked last week about a couple of doctors in Israel treating a child. They ended up getting measles, but they got mild cases. You're at risk of transmitting it should you get it. If you're vaccinated, it's much lower. It's not zero, but it's about a 400-fold reduction, so it's much, much lower.

All right, so flu. We're not getting any updates from the government, but we are getting some updates from Yale. We'll have a nice map up there. Flu is starting. Actually, around the world, we're seeing an early flu uptick. Not only early, but we're seeing quite an uptick. We're predicting a bad year. In the U.S., we're already starting to see a rise in cases. The flu

is starting to come up in the great state of Florida. What is that? What's that other? Louisiana?

VR: That's Louisiana.

DG: Texas. We're starting to see some.

VR: Good job on your geography.

DG: Am I doing OK? Maine. We're starting to see a little activity in Maine. Flu is starting. Anyone here not get their flu shot? OK, I'm not going to shame anyone. OK. Your hand is up because you got it, or you didn't? You should get your flu shots.

VR: I got mine. Did you get yours?

DG: I got my flu shot. There's a couple of reasons to get the flu shot. One is it's going to reduce your chance of getting flu. You don't get flu, you can't give it to your loved ones. Maybe we care about that. The others, if you do get flu, a lot less severe, right? We lose tens of thousands of people every winter in the U.S. Thousands of people up here in Canada from the flu. As people say, "It was just the flu." If you get the flu shot, you can still get the flu. My famous question when someone ends up in the hospital, "Dr. Griffin, I got my flu shot. How come I still got the flu?" Did you die? Going to reduce the chance of that.

VR: Daniel, I got the high-dose flu vaccine this year. Is that any good?

DG: That is good stuff. We've covered some studies on it. You know what? Let's talk about another study. We have the article, “Effectiveness of High-Dose Influenza Vaccine Against Hospitalizations in Older Adults.” That's you, Vincent. It's amazing what older means. It should be 90, I think. This is 65. This is 60. It's getting too close for me. All right. This is a pooled analysis published in *The Lancet*. Two large-scale trials compared high-dose inactivated influenza versus the standard-dose. HD versus SD, high-dose versus standard-dose. These were conducted in Denmark and Spain.

I was supposed to go to Denmark last week. Apparently, according to my wife, I travel too much. I don't think that's true, particularly if I'm going to go to Denmark or Spain. Here, they analyze the pooled data from these trials to enhance the generalizability and assess the relative vaccine effectiveness. Primary endpoint was hospitalization for influenza or pneumonia. They've got a bunch of secondary endpoints as well. Primary endpoint, hospitalization for influenza or pneumonia occurred in 1,312, so 0.56% of the 233,311 participants in the high-dose group compared with 0.62% in the standard-dose. Not that impressive, right? Relative vaccine efficacy of 8.8%.

VR: It's very close.

DG: I hope they didn't charge you extra for that high dose.

VR: I didn't pay anything.

DG: [laughs]

VR: We have good insurance.

DG: OK, so we're also seeing reduced incidence of cardiorespiratory hospitalization. I want to point that out because we focus a lot on, "You got the flu. You ended up in the hospital because of flu." A big thing that we see, and when I used to be employed by UnitedHealth Group before I failed to be properly socialized to the corporate messaging and had to move on, it's a problem in industry as well, is we really saw the big benefit is people get the flu, and then they have a heart attack or stroke in the next month.

They don't necessarily connect the two, but the health insurance companies that have to pay the bill, they connect the two. They really want people to get those flu shots. Then we go on and we see some other, and particularly, I'll say all-cause hospitalization. We see some relative vaccine efficacy, but not quite as impressive as I think we would like. All-cause mortality, similar in the groups. They're doing ICD-coded hospitalization for influenza, comparing that. Some benefit, but not as impressive, I think, as I would like.

VR: Presumably, the high dose is in an older population, right? I don't know if the standard dose is in the same population. It should be. If it's not, that would explain no difference, perhaps.

DG: Yes, you try to correct for this stuff when you do the comparisons. Yes, that's always a challenge.

VR: I'm surprised that it's so close, frankly.

DG: Yes. We've talked about some other studies that were, I'll say, more impressive. The high-dose, there is some evidence behind it, depending on the study you look at. Now, let's do another study, right? “Relative Effectiveness of the High-Dose Versus Standard-Dose,” this is going to be in Italians, “Vaccines for Prevention of Laboratory-Confirmed Influenza Among Italian Older Adults During Three Recent Seasons,” published in the *International Journal of Infectious Diseases*.

I'm thinking this is more appropriate for you. Let's look at the old Italians and see how they do. Here, the outcome is getting the flu, right? Not hospitalization. Among 1,238 vaccinated older adults included in the analysis, we see that the prevalence was lower in high-dose than in the standard-dose. Here, we're getting a relative vaccine effectiveness of 29%. Then, if we actually move it up and we look to the older adult, so 80 or older, then 54%.

VR: That's much different numbers, which shows you should do all your trials in Italy.

DG: [laughs] OK. All right, so what's -

VR: The other thing that I'm wondering is whether the durability is any different with the higher dose, right? Because here you have, if you get your vaccine in October, then with the standard, by the end of the year, you're susceptible again. I wonder if it's any more durable with high-dose. That would be an interesting study, right?

DG: Yes. One thing we've talked about, which needs to be, I think, better studied, is the issue about - this year, we're predicting an early flu season, right? Hard to predict the future. Isn't that Yogi Berra? What's the hardest thing to predict? The future. You get an early season. Theoretically, people that got their flu shots are still riding at that high level. A lot of times, we get a delay. Maybe it's February, March when we get our peak. By then, you've got your vaccine in September, October, 15% drop per month. By then, you're losing

a lot of efficacy. That's an issue, too. Timing matters.

VR: The way I look at it, Daniel, is when you come to a fork in the road, take it.

DG: Yes. [laughs]

VR: It's also Yogi Berra.

DG: Yes, but he didn't say half the things he said. [chuckles] All right, so RSV. Yes, RSV season, we're well underway. It's interesting. Usually, in the U.S., we see this. It comes up from the south and then sweeps through. We're starting to see the activity down there in Florida, Georgia. What is that state right next to Georgia?

VR: It's Alabama.

DG: Alabama, the only state in the U.S. I've never been to, so I don't recognize it. Interestingly enough, we're also seeing quite a bit of activity up there in Maine. Maybe there's some sort of a conduit back and forth.

VR: I don't know, Daniel. The differences may be also related to how well the states do, how they're keeping up with screening. I'm not sure, at this point, differences mean all that much. What do you think?

DG: RSV is tough, right? We talked about this last time, but a thought experiment. RSV, why is it hard to track RSV in wastewater? We'll think it through, right? The little kids, 1 to 2 years of age, where's the poop and the urine going? Is it going in the toilet? Are these kids all super potty-trained, or is it going in the diapers, going in the trash? It's hard for us to look at wastewater, right?

VR: This chart, though, also has ER visits per state, right?

DG: That's what we look at, yes. The ER visits per state is when we start to get a sense because, yes, the wastewater, not as helpful. We start seeing it in the older adults, right? We do. Older adults, it's an issue. A lot of us were taught in medical school, "RSV was just for kids," but we lose 10,000 to 20,000 older adults, RSV, each winter. What can we do? There's stuff we can do.

We have the article, “Long-Term Impact of Nirsevimab on Prevention of Respiratory Syncytial Virus Infection Using a Real-World Global Database,” published in the *Journal of Infection*. This is a multicenter retrospective study. They used the global database TriNetX. Participants were children under 24 months of age. You had to have microbiological testing for RSV, so it had to be PCR or antigen-confirmed, July 2023 to June 2025.

Children who received the last dose of a nirsevimab within 6 months, or 6 to 11 months, or more than 12 months. They're going to compare these different groups. They're going to compare them to folks who got no nirsevimab. We're going to end up with a total of 4,627 that get nirsevimab within 6 months, 861 that get it 6 to 11 months, and then 532, where it's more than 12 months. We're looking, again, just kids under 24 months.

Really nice. I really love the figure, but let's cut to some of the results. If you look at folks who received nirsevimab within 6 months, 0.49, about a 51% reduction. 6 to 11 months, 0.67. It's about a 33% reduction. Then if you get beyond, you're really not seeing any

benefit. Really seeing most of that benefit if you're within the first 6 months, but then it really looks like you're going to be needing to do repeated dosing to get that benefit.

VR: It's not surprising. The monoclonals have a limited half-life, right?

DG: It's definitely true. Having been involved in the development of one of these monoclonals, you can tweak around the half-life. Yes, it's really hard to get more than that six months. Certainly hard to get more than a year.

VR: How are these given? Are they IV or just IM?

DG: Let me actually see. That's a good question. Anyone know? Anyone know? Are these IM shots? I think they're IM shots.

VR: They're very young babies, so IV would be tough, right?

DG: Yes, IV's tough, so I'm pretty sure it's IM. All right, moving on to COVID. Is COVID still a thing? We had these nice, really multicolored curves. You could look at the whole U.S. The U.S. government used to produce that for us. That's why I was most upset when the shutdown occurred. No, just joking. We still can go to the Yale Public Health and get some data. Looking at COVID ER visits, we're actually starting to see some activity in the Northwest part of the U.S. The lull may be over. We may be starting to head into it. We're seeing activity in Montana, Wyoming, Idaho, New Mexico. A little bit of stuff going on in the Central U.S.. We're starting to get some activity.

VR: Yes, it's IM. Nirsevimab is IM.

DG: All right, so what can we do about COVID? We're going to talk about the article, "COVID-19 and Influenza Deaths in Australian Children 2018-2023: A National Case Analysis*,"* published in *JPIDS*, the *Journal of the Pediatric Infectious Diseases Society*. I hope people pause and decide to pay attention with a title like that. Many people tell us that COVID is not a problem for children.

Now, I think children dying from a viral illness is a problem. I don't know how many people have gone up there and said, "COVID's really not a problem in children." We're talking about children here that died. That's a problem. Here the authors aim to estimate and compare mortality rates attributable to COVID-19 and influenza in the Australian pediatric population. Case series of children aged less than 18 years, hospitalized with lab-confirmed SARS-CoV-2 or flu, and recorded as deceased.

COVID-19 cases were ascertained January 2020 to September 2023, and influenza seasonally from 2018 to September 2023 at eight sentinel children's hospitals in Australia. Cases were assessed by an expert panel to determine the causal attributability of each virus to death, and those with primary or contributory causal attrition used to calculate this attributable proportion. Basically, let's go into it.

In children who died with SARS-CoV-2 or influenza infection, basically looking at how much of this attributable in-hospital mortality, 11 of 19, or 58%, and 79%, respectively. Died from SARS-CoV-2 or died from flu, so the majority of these deaths. Among COVID-19 and influenza attributable deaths, about half of them, no preexisting comorbidity. I think that's a big thing. There's a lot of the rhetoric now as well, "Not every kid needs the flu shot. We

should target it to those high-risk groups." Well, the high-risk group is being a child.

50% of these kids, there was nothing special going on. We've certainly seen in the U.S., a significant drop in the COVID boosters, in the yearly flu shots. Now, I'd say the minority of our kids are getting those where, prior to the pandemic, the majority of kids got the flu shot. It was just a standard thing. Here, we're seeing these kids dying. In addition to about half of them having no identifiable risk category, we read that the 10 deaths where COVID-19 vaccination was known, 40% were vaccinated, so we're not doing 100%.

Most of the deaths were due to Omicron. That's the other thing I want to point out. Remember, it was big and bad, and there was that early, it's early, and then Omicron, and it's all mild. The majority of pediatric deaths have been due to Omicron. Just point out when people talk about how it's gotten so mild. For flu deaths, the vaccination rate was only 19%. Sort of leave that food for thought there.

VR: You think about the four vaccinated children who died, what's going on there?

DG: Yes, no, it is tough. Our vaccines are not 100%. I think we got a bit of criticism. Once you get the COVID shot, you don't have to worry about getting COVID. You do have to worry about getting COVID. That's why when we get into our active phase is that there still are situations where, let's say you've been vaccinated. Let's say you get COVID. If you're at risk of progression, you still want to jump in.

There really is this hesitancy. "Let's wait and see. Let's see how you do." That strategy doesn't work well. It's seven days in. Now, you're getting hypoxic. Now, you end up in the hospital. Most of our opportunity to make a difference has gone. I don't think I have any studies today here, but I'm going to respond to an emailer where we talk a little bit about some of this push to limit jumping in with those antivirals.

During that early viral phase, still recommending, particularly in people at high risk of progression, jumping in with early antivirals. Still very similar during that second phase, not giving steroids to everybody, but giving it to the high-risk people, pulmonary support, and all the rest. We're still seeing these people end up in the hospital, hundreds of thousands of hospitalizations each winter in the U.S. I expect it to be a little worse this year because we're seeing less awareness. We're seeing less early testing. We're seeing less early treatment, and the impact on vaccination.

All right, and we have a lot of emails this time, so I'm going to wrap us up with what we've been saying now for over five years. No one is safe until everyone is safe. Should we do that all together with the audience participation? No one is safe until everyone is safe. This seems like a great format for doing that, so thank you. Everyone, we're going to pause here.

You guys can do this afterwards, our studio audience, but go to parasiteswithoutborders.com. This is Vincent's favorite time of the year. We do our *MicrobeTV* fundraiser. Every dollar that people donate, we are going to double that up to a potential maximum donation to *MicrobeTV* of $20,000. Parasiteswithoutborders.com, click on that Donate button. Every bit helps. I think we've got some emailers, right?

VR: Yes, I included an extra one because I figured we had a little time here. It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Lori writes, "I so appreciate that all that you and Dr. R are doing to keep us informed. I always listen to clinical update

first thing on Saturday mornings, as well as many of the other podcasts offered by *MicrobeTV.* My question to you is, how soon after a bout of shingles can the first Shingrix vaccination be given?"

"A friend's wife developed shingles in late August. She has been suffering with it since then. The lesions were on her face near her eye. She also developed post-herpetic neuralgia, which is ongoing. The blisters are long gone, although she still has some brownish residue on the affected skin there. Receiving varied advice on when she should get her vaccination. I told her I'd ask you."

DG: All right, so giving out medical advice, which actually I'm allowed to do, being a doctor.

VR: You are licensed, yes.

DG: I can do that. [chuckles] OK. Yes, really, when is the best time to get your shingles shot is before you end up with shingles? That ship has sailed in this situation. What do we recommend? What are the formal recommendations? Then we'll discuss it a little. You want to wait until, basically, you're fully through that acute shingles. You want to basically let everything heal, no more vesicles, but then think about it. There has been a little bit of a boost. Let's say it's four weeks out, and that's the general recommendation.

Somewhere between four weeks and 12 weeks. Maybe a little bit of germinal center and then jump in. In general, I usually tell people three months, right? It almost makes it simple to start thinking about that. We're all become immunologists, right? You get your COVID infection. Three months later, you get your booster. You get your shingles. Three months later, you start your shingles series. Then, again, you have the choice of it's two shots. You get your first shot. They say one to three months later, so first shot. Three months later, get your second shot. Really use that basic immunology.

VR: Daniel, there's something unusual here. This person developed shingles in August and still has lesions. This is now three months after the initial lesion. Is that typical?

DG: As she says, the blisters are long gone. The brownish residue, I'm not sure what to make too much of that. One of the features they do have is the ongoing post-herpetic neuralgia. That's tough, right? That can go on for months. I've actually had patients where it passed a year, it still hasn't resolved. Very hard to treat. Feels like you've been burned. Really one of the most horrible things. Now that the blisters are long gone, I don't think there's an active infection going on here.

VR: All right. Gretchen writes, and this is Gretchen from Toronto. Right. Maybe she knew we were going to be here.

DG: Maybe. Maybe she's in the audience. Gretchen, are you here? No, I don't see you here. OK.

VR: "I was listening to your responses to a question on the use of Paxlovid with a couple in their 70s. There was a recent study in Canada that you may not have read that questions the efficacy of Paxlovid in older adults. Can you read the study and comment?"

DG: All right. Gretchen, I did read the study. [chuckles] Gretchen, in her email, she actually leaves in a link to the *CIDRAP*. I'll leave in a link actually to the actual article. It references

this article. This is actually back in February, right? It's the article, “Hospitalizations and Mortality Among Older Adults With and Without Restricted Access to Nirmatrelvir-Ritonavir.” This was published as a research letter in *JAMA*.

It's interesting. We'll go through the methodology because it's an interesting methodology. They use something called a natural experiment. What is a natural experiment? It's a type of observational study where something occurs. There's this natural event, and that creates your two cohorts. The natural event here in Ontario, let's say here in Canada, in Ontario, was they basically said, "You know what? Let's start restricting. Let's have an age-restrictive policy for Paxlovid," and then they're going to use the data.

They say, "Hey, here in Ontario, if you're above 70, you can get Paxlovid. If you're under 70, no Paxlovid for you unless there's special circumstances." That creates this natural experiment. Now, they're going to ask this question, "Is there a difference here?" The way they're going to ask that question is they use fuzzy regression discontinuity. Anyone familiar with that? No, it's crazy. What you're basically going to do is you're going to follow, basically, the line.

You're going to see, is there the expected increase, or now that we're restricting Paxlovid, is there going to be a difference in that analysis over time? They go ahead, and they look at this. We're talking about 20,000 people that get Paxlovid. They do this analysis. Pretty nice. Actually, in our YouTube, you can actually look at this. I think it's open access, this article. They're going to follow this, and then they're going to basically see, "Did this really seem to make a difference, this regression?"

The idea is that you're a little bit over 70. You're getting the drug. You're a little bit under 70. Probably not too much of a big difference. Compare those, and then follow the COVID-19 hospitalization curves. Follow the all-cause deaths. The question they're asking is, getting Paxlovid or not, does that make a difference? First off, to me, it seems like it's a one-sided question, right? Does getting Paxlovid reduce your chance of ending up in the hospital? Does it reduce your chance of death?

The first thing I notice when they do the statistics, because that's what we're going to hear here, is they did not find a statistically significant difference, is they're using a two-sided test. It's really a one-sided question. They're rigging the stats against us to start with. Basically, what they end up saying, they're saying, "You know what? We don't reach statistical significance. Rather than the 5.5 percentage points that we saw in the original trials, we're only seeing a 1.3 percentage point drop." Not statistically significant.

You probably need to treat about 80 people to prevent one hospitalization. Then $1,000 a dose, that's $80,000 to keep one person out of the hospital in a country where we have a public health system. Maybe that doesn't make sense. I know in the U.S., it's about $40,000 per hospitalization. It seems like you're paying too much to keep people out of the hospital. I'm not sure that my takeaway from this study was Paxlovid doesn't work. I think it's just not quite as good as in the original RCT that we saw. Maybe the number needed to treat is a bit higher. The headline takeaway, I'm a little bit concerned about.

VR: I think you get different outcomes in different populations also, right?

DG: I think they're only looking at one particular avenue here. Let's say you prevent a hospitalization. Let's say you prevent a death. How much are you willing to spend to do

that? They're not saying that Paxlovid doesn't work. They're just saying that their threshold wasn't met here. When you start calculating other things, let's say you. I don't know. Let's say you're 68 or 58 o --

VR: Me, 24.

DG: You're 24, and you get COVID. The doc says to you, "Listen, your chance of ending up in the hospital, it's only 1% or 2%. Yes, we can drop that in half, but I'm just not sure it makes sense to spend that money." The other is not only we're looking at the money of the hospitalization, but think about the care after the fact. Think about the lost work. We talked about cardiovascular and other things, so all the Long COVID, all the post-acute sequelae. I think there's a lot more to this story than, "Oh, look, this study, one study in Canada using this fuzzy logic regression and a natural experiment." Not quite as impressive.

VR: Well, the thing is, Daniel, this is an observational study, right? You can only make associations. You cannot make conclusions. The conclusions are drawn from the double-blind randomized clinical trial, which was originally done by Pfizer, and showed this bigger decrease in hospitalization. Those are the data we should look at. Not an observational study, makes no sense.

OK, Susan writes, "I just listened to *TWiV* 1268, where you discuss the human papillomavirus vaccine. I'm 72, and I think I just had my first HPV test, which was negative. I'm wondering if this is a test that should be repeated routinely, or is it a virus that is totally cleared from the body, unlike the BK virus? I am a kidney transplant recipient and taking immunosuppressed meds, so I am probably more vulnerable."

DG: OK, so this is great. I know in the U.S., we have Thanksgiving coming up. I think there's a Canadian Thanksgiving as well, where it's Uncle Bill who's crazy and, usually, you don't have to hang out with, but you got to hang out with him that afternoon. I always get on the schedule to work because I just find some of my family members tough to be around. They're going to come, and they're going to want to talk about crazy stuff like, "I heard about COVID vaccines and turbo cancer."

You're like, "Yes, Uncle Bill, I heard about that, too." Then they'll make you watch the TikTok. I have no TikTok on my phone, but Uncle Bill's got it on his phone. One of the really exciting things is rather than going down that rabbit hole, we have some pretty exciting recent studies showing that, actually, vaccines are treatments for cancer, right? We talked about this on our deep dive, as well as on the clinical update, where people get HPV infection. This is something we really don't resolve.

It becomes this chronic infection that goes on for years and years. In this one study, what they were showing is that women that actually even went on actually had cancer, you could give a vaccine. In the majority of those individuals, the vaccine could trigger you to clear that chronic viral infection, could actually trigger better outcomes for your cancer. Then on the *Puscast* that I recorded last night, we talked about another study. It may have been the same one.

The whole idea that we have mRNA vaccines leading to better outcomes in people getting immunotherapy. We have the HPV vaccines. Now, we have multiple vaccines as cancer therapeutics. Really exciting stuff. Now, 72 years old, if you had HPV, could you clear it or not? Some people do spontaneously clear it, but there is this issue of how many of us

actually have chronic HPV. We might be outside the age where we get it. The whole idea that you need to get your vaccine before the infection. We're starting to realize, vaccines may actually help us clear these infections.

VR: Would you recommend that she get vaccinated?

DG: The tough thing, so she's telling us that she had an HPV test that was negative. Unless this is an individual who's at risk of exposure, we wouldn't necessarily recommend repeated or getting vaccines.

VR: That's a tough question because I don't know what the marital status is or any of that. Let's say she's not sexually active, then probably you would not recommend it, right?

DG: That's tough, right?

VR: Yes, of course.

DG: You're not sexually active until you are, right?

VR: Yes, right, right.

DG: A lot of us, I don't know if she's - I'm 72 and she's single, or maybe she's 72 and she comports herself like she's single. Wink, wink. [chuckles] It's not like you can be like, "Oh, my gosh, she met this really good-looking guy at the ASTMNH conference, and she's thinking something might happen." It's going to take a while for that vaccine to kick in. The amazing thing, HPV, this is one of the most effective, safest vaccines. We target it now for people that are sexually active. Come on. Anyone is potentially going to be sexually active, and they're not going to know months ahead of time that that's going to happen. This isn't like you can just carry it in your wallet like that condom.

VR: The other scenario is that she is married, and we don't know the HPV status of her husband, right?

DG: Or if maybe the husband is comporting himself like he's single.

VR: Yes, he could be lying, right? I would say just get vaccinated, but I'm not a doctor. You say no, so that's the answer.

DG: I think she should have her discussion. She could have shared decision-making with her provider, but it's really tough. Above a certain age, you're going to be really hard-pressed to get access to that vaccine with the current licensing.

VR: Really, even if you pay for it, you can't get it?

DG: Which is really interesting, right? Because the other stuff, like I went and I got my RSV vaccine, even though I didn't really qualify, just because there was some computer glitch at CVS. No, I don't know. There's something about HPV. If you walked into the pharmacy and said, "I'm 72 and I want an HPV vaccine. My doctor recommends it," yes, there may be a barrier there.

VR: Interesting, OK. All right. Wayne writes, "I've been an avid listener of *TWiV* and the Saturday clinical update since the earlier days of the pandemic. Recently became a

supporter of *MicrobeTV* and Parasites Without Borders, and always appreciate both your and Dr. R's objective discussion of data. In Clinical Update 1268, you talked about a study showing vaccines reducing the risk of long COVID in children. 36% and severe long COVID by 23%. That's significant."

"One thing you said in particular really stood out. You said, 'The best thing you can do for your child to keep them safe is to get them vaccinated.' It got me thinking that the risk, even when vaccinated, still seems quite high at 1 in 8 for long COVID and 1 in 20 for severe COVID. It really seems like avoiding infections as much as possible would be a good idea. You talked about how N95 masks can be effective for that when worn in crowded places or whenever indoors. Would you recommend we use N95s more often so we don't roll the dice on Long COVID as much, especially for our children? Thanks for being one of the last places to get updated and accurate public health information."

DG: Yes, this is a good email, Wayne. As people probably know, discussing masking in children is a big hot-button issue, right? "Oh, my gosh, Dr. Griffin said that children should wear masks," and then we're in trouble. I'm hanging out with Peter Daszak, and we're getting doxed. We've got to go hang out at someplace in the mountains to keep out of trouble. I think the data here is concerning.

Kids die from COVID. Kids end up in the hospital with COVID, but maybe the biggest burden is kids get sick with COVID, and then they're not better, and it's a few months later. I've seen some really devastating cases. I had a young girl who came into the office, and I was like, "It's not lost on me that your parents wheeled you in in a wheelchair, and you're showing me videos of when you used to be in dance class." This could be really devastating.

We've talked about how vaccinations can reduce this risk. We're waiting for the data to show that the boosters are going to have that same effect that we saw with the initial series. Then the other thing is what's the best way not to have a post-COVID sequelae? It's not to get COVID in the first place. All the different things you can think about, properly ventilation. If you're going to be in a place where the risk is high, then thinking about, is it age-appropriate to consider masking in those situations?

VR: Janet has a similar question about vaccinating kids to decrease Long COVID, and she wants to know, "Are you talking about yearly boosters? As I wrote last year, my son thinks that the trauma of having his children screaming and crying when getting a vaccination makes it so he only wants to give them a flu vaccine every year. On last year's show, you pointed out, there was much more trauma with getting a worst case of COVID or Long COVID, and his children should just get the vaccine. That's why I'm asking about your report on vaccines and Long COVID. Was the study involved with yearly boosters or just the initial series of vaccines? If the study had to do with yearly boosters, this might be the argument that will convince him to get the kids a booster."

DG: That, I think, as we just mentioned, is the science takes time. That's one of the problems with science. It actually takes time to get the truth. It's a lot easier to just throw an opinion out there. We have the data from the initial vaccines. One dose, two doses. We're going to take time to get that data on the boosters. Long COVID in kids is a real thing. We clearly have the data. If you get that booster, you're less likely to get COVID. If you don't get COVID, then you're not going to get Long COVID. It's not a big logical step to go from one to the other. Again, as E.O. Wilson told us, you got to do the science. As smart as we think we are, we've got to test that and see if it's true.

VR: Our last one is from Gail. "How often would you suggest that someone in their 70s with a very low T-cell count, CD4, currently in the low 80s, get the COVID vaccine in addition to PEMGARDA? They have idiopathic CD lymphopenia, so aren't taking any meds to raise the count since the cause is unknown."

DG: OK. Yes, this is great. This is hitting a little immunology, right? We've talked a bunch on *TWiV* about the importance of your T-cells. Your antibodies are coming from your B cells. The PEMGARDA is a monoclonal. It's going to really jump in for whatever issue you're not getting with the antibody levels. It's now every three months. The CD4 lymphopenia, that's low T-cells. The PEMGARDA is not going to do anything to help those T-cells, but the vaccine doses are going to. For a while, we were talking about the fact that you get a vaccine every six months, you get the boost, and then have it come back down. A lot of the idea there is you're going to get a T-cell effect as well as the antibody. In someone like this and every six months would make sense for a cadence.

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

DG: Thank you. Everyone, be safe.

[applause] [music]

[00:51:11] [END OF AUDIO]