This Week in Virology

TWiV 1130 Clinical Update

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Guest: Daniel Griffin

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

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Vincent: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1130, recorded on July 11, 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 you got on your tie there, Daniel?

DG: These are like fecal pathogens. It's a whole bunch of gram-negatives and other bugs that you might get from fecally-contaminated food.

VR: Sounds excellent.

DG: [laughs] It's on the menu.

[laughter]

DG: I was just thinking actually, as you're doing the intro there. It must be hard for you to keep all these podcasts straight, right? It's like a dozen now.

VR: Sometimes I mess up. That's why, in the beginning, I have to concentrate and say, "This is *TWiV.* It's 1130 and it's July 11." Yes, sometimes I mess up. It's OK. It's good to have that problem. That means we have a lot of shows and we're doing well.

DG: Yes, no, it's great to have so much content. Yes, it's something for me to listen to myself as I zip around hospital to hospital.

VR: Well, there are some things outside of our expertise that are different and really interesting. Have you listened to the new immune boosters at all?

DG: Oh, I love that one. I listened to one so far. Makes it sound like there's plural and I got more to enjoy.

VR: The immunologist went to Chicago for an immunology meeting and they recorded about a dozen little interviews with people there. That's what we're calling immune boosters. It was a little experiment and we thought how it would work. When people go to meetings, we can do those kinds of interviews.

DG: Oh, that's fantastic. Yes, I listened to one so far. I'm now excited to know that there's a bunch, but I really enjoyed it. It was the guest on the one I listened to, just so much enthusiasm and energy. It's just like, "Oh, this is great."

VR: Well, this is the other thing is that as *MicrobeTV* gets more and more well-known, people are very enthusiastic to be on our programs and that's great.

DG: Oh, that's fantastic. All right. Well, let's jump in and I will start with a quotation. I always wonder. Sometimes these quotations, have I used them before? I'm going to quote Ernest Hemingway. "There is nothing noble in being superior to your fellow man. True nobility is being superior to your former self." I just really like that.

VR: What's a former self, Daniel? What does that mean? [chuckles]

DG: Well, I think the whole idea is that you continue to grow. You continue to learn. You continue to be a better person. Don't judge yourself against all the other folk out there. Judge yourself against your former self. Where was I yesterday? Look at how much more I've learned. That's from Ernest Hemingway. We will jump right into bird flu. This is an article published in *The Colorado Sun*, right? Because we usually say the article and people are thinking, "Which august scientific journal?"

This is the article, “Nearly 1.8 Million Chickens Will Be Culled in the Latest Bird Flu Outbreak at a Colorado Poultry Farm.” Colorado, another state hit hard by H5N1 in dairy herds, has recently reported a few outbreaks in backyard birds but has now reported its second largest outbreak in commercial poultry since the virus emerged in U.S. birds in 2022. The facility, it's a layer farm housing more than 1.7 million birds. That's amazing.

It's in Weld County. That's where the farm is located. It's been heavily affected by the H5N1 outbreaks in dairy herds. On July 5, the Colorado governor, Jared Polis, declared a disaster emergency due to the poultry outbreak. Also, dengue. I was asked about a couple of headlines by my colleagues. I don't know if you caught these, Vincent, but “CDC Issues Dengue Warning for U.S. as 142 New York Travelers Sickened.” I read it in the Patch. You read a bit further and maybe you catch that word, "travelers."

We read that as of July 2, all dengue cases in New York were reported in residents who were traveling, according to the CDC. No cases have been locally transmitted. News 12, right? I've appeared on News 12 quite a bit. We get a headline there. CDC issues dengue warning. Up to 16 cases reported on Long Island. We read that officials are warning about cases of dengue that are reaching an all-time high, spreading through an infected mosquito bite.

VR: These are all travelers, Daniel, because the mosquito of dengue, Aedes aegypti, is not present in the New York area. It can't be locally transmitted. Although maybe one day, it will be present. It isn't at the moment.

DG: We can get local transmission. There was a case about a decade back in Huntington, New York, a teenage boy. Some of our local mosquitoes, though not as, I'll say, efficient vectors, he didn't travel anywhere, got bit. You can have this double bite. Yes, you're right to say we're not quite in as bad a situation. We've got this wonderful thing called global warming, global climate change.

VR: Oh yes.

DG: If you believe in that. [chuckles]

VR: Well, it's not a belief. It's science. It's results, right?

DG: Yes, it's compelling. I was giving a lecture this morning for a class in South Africa. It's a wonderful thing about time zones and electronics. One of the young ladies in the class asked was climate change and the impact on infectious disease. I have to admit. I just feel like we're missing the ball in this. What a tremendous impact climate change is having. Vectors are moving into new areas. The wet, dry cycles are changing.

VR: Besides Aedes aegypti, Aedes albopictus can transmit dengue. That is present in the U.S. for sure.

DG: Yes, exactly. A beautiful mosquito if you forget about the impact on human health.

VR: Yes, it is beautiful, quite. [chuckles]

DG: Yes, it really is. Some of these insects are just spectacular. All right, moving into COVID. A little bit disturbing here. Percentage of provisional deaths due to COVID-19 in the past week by state, territory, United States. As we've always mentioned, it's always a little bit of a lag here. They break it down into these different colors based upon, is it 0% to 1% or so? Is it less than 2%, less than 4%, less than 6%, less than 8%, greater than 8%? Puerto Rico is now greater than 8% of all people who died in Puerto Rico died due to COVID. I just want people to stir on that. This is Omicron.

Remember the "mild form" of this virus that we don't have to worry about? Well, those folks died. Looking at what's happening in the rest of the U.S. and, again, that delay, we are seeing things are rising most everywhere across the country, but particularly in the West. I have to say, I'm not sure this is even tracking as well with what we're seeing locally because, locally, we're really seeing an increased number of cases, an increased number of folks ending up in the hospital. Yes, we are in our summer surge. I guess we've now started to call it the winter peak, the summer surge.

VR: It's really interesting because influenza doesn't do this in temperate climates as you know.

DG: I think it's going to challenge a lot of our explanations for why do different things happen because, normally, I think a lot of us were having this idea that it would settle into an influenza-like winter pattern. It's interesting that, now, we're several years in and we're still seeing this summer surge. All right, moving into children. Remember all that hubbub about antacids and COVID?

We have the article, “Proton Pump Inhibitors and Risk of COVID-19 Infection in Children,” in *The Journal of Pediatrics*. These are the results of a retrospective case control study that included all children less than 21 years of age undergoing COVID-19 PCR testing at a tertiary children's hospital between March 2020 and January 2023. A large period of time there. Then the exposure, right? That's how you do this.

The exposure was PPI usage versus non-exposure, not using a proton pump inhibitor. The primary outcome was COVID-19 infection. The secondary outcome was COVID-19 hospitalization. You probably have a sense of which we care more about. In total, 116,209 patients aged around 8.5 plus or minus 6.2 years underwent 234,867 COVID-19 tests. The current PPI use was associated with a decreased risk of COVID-19 test positivity compared with PPI non-use, relative risk of 0.85.

We're actually seeing about 15% and we're getting good p-values, 0.002. However, when they looked a little bit more closely, there was a significant interaction with time of testing. When you analyze the little bit of data a little farther and followed this out past the lessening of COVID-19 precautions, really, it went away. Also, the PPI use was not associated with risk of hospitalization in patients who are positive for COVID-19 once you did all these adjustments.

Be careful of the headlines here because the authors conclude by saying, "We did not find an association between PPI use and increased COVID-19 susceptibility or severity in this pediatric sample." Just full disclosure on that. All right. I want to make sure we keep giving a plug here to passive vaccination with Pemgarda. Still sort of limited access. We got to get our centers up and helping with access there.

All right. Just really reinforcing COVID early viral phase, right? We have the NIH COVID-19 treatment guidelines. We've got the IDSA guidelines recommending with different degrees of confidence. Number one, Paxlovid. Number two, remdesivir. Three, molnupiravir. Four, convalescent plasma. Remember that isolation guidance we've talked about several times? You're the most contagious during the first five days and there still is some transmission after day five out to about day 10, but really falling off after that peak during the first five days.

Early inflammatory, that's that second week. Steroids, right time, right patient. Anticoagulation, pulmonary support. Remdesivir still in the first 10 days. Immune modulation. As promised, the bulk of our episode today is going to be a focus on Long COVID. First off, I'm going to share a resource. This is a brand-new resource, *Long COVID The Answers*. You can go to longcovidtheanswers.com.

A few of us have worked with Funmi Okunola. This website just launched January 5. I don't know if anyone's actually getting paid. I think most of us are just volunteering our time to help make this happen. Just a reminder to many out there that are suffering that many of us care. In the words of Peter Gabriel, "Don't give up." I have a little blurb here from the group running this. Funmi sent this my way. What are they? What is this website? What is this organization?

The goal is that this will be a credible, evidence-based destination for long-haulers, people that take care of folks with Long COVID, and healthcare professionals who want to learn about Long COVID and find credible information and relief. I will say one of the nice things, this is vetted. This isn't just, what are people doing. This is evidence-based. What's so special about

this resource? Well, they're going to bring together Long-COVID information in this one safe space.

I say "safe space." We've actually looked at it. Let's not have bright lights flashing in people's eyes if they have Long COVID. That can be an ocular trigger. Let's have credible information about symptoms, relief, research information. We're going to potentially have a practitioner, a long-hauler practitioner directory. You can actually find someone to help you specifically. This is already being updated with news and there'll be some accredited educational materials.

The big thing is this is going to be medically reviewed. A number of us in this space are going to be looking through, making sure this is evidence-based. We're going to filter out all that misinformation, all that snake oil. There's going to be a Long-COVID podcast, Vincent, and this has already been a little created. They're going to have a number of podcasts. There's going to be credits. You'll be able to use these for continuing professional development.

There's a number of podcast guests. There's a number of what they say, Funmi says, "amazing, knowledgeable advisors making this happen." I'm in that list. I don't know if I was considered amazing or knowledgeable, but I am in the list. [chuckles] They mentioned a number of other folks here. There's also going to be a monthly Ask an Expert section. I volunteer to be the first week's Ask an Expert where you can send in questions, and then we give you credible answers.

We're really hoping to not only provide credible answers, but we're going to hopefully bring hope, credibility, and visibility to this debilitating disease. We will leave in a link to longcovidtheanswers.com. Let's go ahead and let's take this moment. This will be the second. A number of months back, we did a bit of a Long-COVID update. I'm just going to go through several bits here. Hopefully, people can bookmark this, share it for people that either have Long COVID or providers that are taking care of folks with Long COVID.

Let me start off first with the diagnosis of post-acute sequelae of COVID, PASC, Long COVID. All right. The first thing I will start off by saying is that there are many different terms out there. Many different terms have been used to describe this continued suffering and the development of new problems that follow after the first two weeks of acute COVID infection. Patients themselves started using the terminology "Long COVID," "long-hauler COVID."

Others introduced the terms, "post-acute sequelae of COVID, PASC," "post-COVID conditions, PCC," to try to encompass the broader group of patients that were impacted. The WHO gives us a definition. They define Long COVID as the continuation or the development of new symptoms three months after the SARS-CoV-2 infection with symptoms lasting for at least two months with no other explanation.

The U.S. CDC defines Long COVID as signs, symptoms, and conditions that continue or develop after acute COVID-19 infection. I want to make a comment here that Long COVID is not a diagnosis purely of exclusion but instead, like many diagnoses, one where there's a consistent history. In some cases, objective physiological abnormalities. In other cases, objective biochemical abnormalities and, in all cases, where one needs to be careful not to attribute all issues to this one cause without a careful evaluation for other abnormalities.

I think one thing we've all agreed on now is Long COVID requires a clinical diagnosis of acute COVID-19 at some point, but you don't have to have that molecular test. You don't have to show me your papers. A lot of folks, depending upon timing and resources, maybe were not able to actually get that molecular positive test. All right. Well, we've come a long way in our understanding of what are the possible mechanisms driving Long COVID, moving from just speculation to, now, a bit of evidence.

Ongoing immune activation or dysfunction, remnant SARS-CoV-2 RNA or maybe remnant SARS-CoV-2 protein, so evidence that this is going on. A lot of controversy about and a lot of failure to find replication-competent variants. A growing amount with regard to dysbiosis. Actually, as I'm going through this list, I'm going to pause on dysbiosis because I really have to say some exciting stuff.

There really is an increasing amount of evidence to suggest that a disturbance in the gut microbiome or this gut microbiome dysbiosis is really a significant factor, not only associated, but we think driving Long COVID and some of the different phenotypic manifestations. We've talked about some of these studies, but metagenomic sequencing of the gut microbiome and microbial pathways have revealed depletion of certain bacteria such as the Bifidobacterium and the Roseburia hominis, and then enrichment of certain other bacteria such as Clostridium species, Flavonifractor.

You actually can end up, based on some of this analysis, seeing actually different gut microbiome phenotypes. Continued interest in endothelial dysfunction of the clotting system. We continue to share data on neuroinflammation and blood-brain barrier dysfunction. Neural dysfunction, particularly an interest in vagal nerve dysfunction and a little bit of controversy there, I've noticed. Mitochondrial dysfunction.

Then, very clear, there are certain folks that just have residual damage from the acute infection. They have pulmonary scarring. They have cardiac damage and that's black and white. People end up with damage during the acute infection and then they continue to suffer after that. This is a list. I don't know how we'll leave a link to this or how we'll do this. The good or bad thing as we learn more is there are actually objective biochemical and immunological abnormalities.

Maybe the good thing is we're able to do a panel of tests and then share with our patients. We found certain things that are consistent with the Long-COVID story that you've shared with me. The depletion of commensal bacteria, research setting, not so easy for us to check in the clinic. Things we can check in the clinic, markedly elevated Epstein-Barr virus serologies. We see these levels. Positive might be 20, but we're seeing greater than 750 for some of the IgG levels.

Markedly elevated CMV serologies, markedly elevated VZV serologies. Not necessarily available in the clinic, but research setting is abnormal activation of CMV-specific CD8-positive cells. Again, in the research setting, this viral antigen persistence, maybe RNA, maybe protein. Again, as we've really talked about this, not really clear if that's unique to people with Long COVID versus just something we're seeing after this infection.

Something, again, that we can check in the clinic, low serum cortisol without a compensatory ACTH elevation, this post-COVID, PASC adrenal insufficiency. Again, anemia, abnormal levels of serum iron, lymphopenia, thrombocytopenia, so low white cells, low lymphocytes, low platelets. Very striking diminished serum serotonin. Apparently, this assay goes down to 10. I see patients with less than 10 when a normal level would be probably about 150.

Abnormal coagulation studies, PT/PTT, D-dimer, low albumin. Elevated serum aminotransferases, the AST/ALT. Everyone calls those LFTs, but they're not liver function tests. They're aminotransferases, by the way. Abnormal lactate dehydrogenase levels, elevated C-reactive protein, elevated erythrocyte sedimentation rate, elevated bilirubin, elevated lipase, and then again, research setting, elevated levels of neurofilament light chain.

VR: Daniel, if you run some of these tests, how many have to be different to say, yes, this is Long COVID?

DG: Yes, so we don't have any criteria like we might have with a rheumatological where, OK, consistent story and then three of the following. This is really just something we'll use not only to say consistent with, but sometimes it also helps us with treatment, right? Folks that have particularly low levels of serum serotonin, we're going to be looking at ways that we intervene to help with that. People with particularly low serum cortisol without that ACTH elevation.

Part of this can be just helping us to support the diagnosis. Part of it can also be helping us direct therapy. There's no like, "Oh, you only got three. You don't get enough." No, there's no disqualifying you because we don't find enough of these abnormal. Now, the other, and I guess it's really going to be the same thing, Vincent, is looking for other abnormalities that are consistent with, that help us with the diagnosis, but also abnormalities that help us with treatment.

We will find quite frequently physiological abnormalities if we do testing. Really, I think all my patients are familiar with the abnormal or the modified NASA Lean Test. This is where folks stand with their feet about eight inches from the wall. Yes, you can pause the recording after at this point and try this out on yourself. Then you're leaning against the wall. What you're doing is you're not marching. You're not moving your muscles. You're just standing there.

You've gotten a baseline blood pressure, heart rate, pulse, and then you're going to repeat this roughly every minute for 10 minutes. I say "roughly every 10 minutes" because you're hitting the button on the machine. It takes a certain amount of time to inflate, calm down, give you a number, have someone help you if possible. We'll see people do this. Normally, you stand up. Let's say your heart rate is 70 and it stays in the 70s. We'll see people shoot up to 130. We'll see people start to get dizzy and need to sit down halfway through the test.

The Abnormal Sudomotor Assessment. That's basically a sweat test where, normally, people sweat. A lot of times, people with post-acute sequelae of COVID, they lose the ability to sweat, which is really an issue. It really becomes a problem during hot weather and the like. There's also this exaggerated orthostatic blood pressure response that you get when you do the heads-up tilt table test. We see some significant issues with the tilt table test.

We'll often see a significant heart rate variability if we do Holter monitoring. The other is this interesting exercise, post-exercise issue where when you exercise, normally, your heart rate will recover with a certain amount of time. People post-COVID, a minute later, they're still tacking along. They still get really fast heart rate. We see this abnormal heart rate recovery that we can assess, identify. Again, it can help us with treatment selection.

Abnormal cardiopulmonary testing. We might see dysrhythmias if we do ECG monitoring. You might see that on that Holter. If you do formal pulmonary function testing, we include this diffusion-limiting capacity, the DLCO. You're actually going to see abnormalities there. These will help us pull things into different phenotypes. We're asking about symptoms. We're doing a bunch of testing. Then it's actually helpful to break down and say, "OK, what type of Long COVID are we dealing with here? Are we dealing with the ME/CFS phenotype?"

I'm going to circle back because you can have that as a second diagnosis as well. Is this more of a cardiovascular phenotype with tachycardia and dysrhythmias, more of a respiratory with breathing difficulty, more of an endocrine, neurological, gastrointestinal? This is interesting, a reproductive phenotype, and then the allergic immune activation phenotype. I do want to just point out, the ME/CFS, is that you can have more than one diagnosis.

You can have your COVID, your post-acute sequelae of COVID, and then you can have an ME/CFS diagnosis. You can have an autonomic dysfunction, orthostatic tachycardia. There are the ability to have second diagnoses as well. With all that, how do you prevent having this and what are the therapies? That's what's going to wrap us up today. "How do I keep from getting Long COVID?" "I don't have it yet." "I don't want to get it."

Well, number one, making smart decisions to avoid infection. If there's that big crowded party during a time when there's lots of SARS-CoV-2 circulating, you might want to try to avoid infection. We've talked about masks and stuff there. Vaccination, consistent data that vaccination reduces one's risk of Long COVID. Early antiviral treatment, growing evidence. Convalescent plasma. Interesting enough, corticosteroids in the right people during the right situation during that second week.

Therapeutics, and I think this is going to be, hopefully, the ray of hope for our listeners. There are things we can do. I still see new patients with Long COVID. I still continue to help people with Long COVID. It's huge to sit down and say, "Listen, there's stuff we can do." What are those things? Evidence-based vaccination after infection, particularly if a person is unvaccinated. Melatonin in a 3-to-5-milligram dosing range, not just to help with the insomnia.

The bifidobacteria-containing probiotics, that 10 billion twice a day that we've talked about studies supporting. You can use exercise, but only after screening for post-exertional malaise and being really careful not to make things worse. This is one that, really, I've been rather impressed by. Active cycle of breathing techniques such as this box breathing. That's where you breathe in slowly, pause, breathe out slowly, pause, and then you repeat that 10 to 15 minutes in the evening before you go to sleep.

A lot of success using acetylcysteine, NAC, N-A-C. We talked about how sometimes the biochemical abnormalities are going to drive certain therapy choices. In some of the folks with

really low serotonin, if it's a little low, we might use the SSRIs. If it's completely down in the tank, we might switch over to other medicines that work through different pathways. Some of our allergic phenotypes, we might do antihistamines. We might use topical nasal steroids.

Some limited evidence for hyperbaric oxygen therapy, very limited, very preliminary just to throw that in the mix. The big hope is that we have many underactive investigations. There's lots and lots out there that we're studying, we're learning more. For clinicians and patients, COVID-19, it's a new disease, as is Long COVID. Long COVID is not something we were taught about in medical school and has required the efforts of scientists, physician scientists, and the integration of all this knowledge by scientific clinicians.

Unfortunately, there's more disinformation than actual information in this area as many peddle misinformation for personal gain. Oh, my. Really, this review here is really just one more step in our attempts to understand this challenging disease. All right, I'm going to wrap it up there, Vincent. As we've been saying for a while, no one is safe until everyone is safe. I want folks to pause the recording right here.

Go to parasiteswithoutborders.com and click Donate. You can also go to microbe.tv and click Donate as well. Every small amount helps so we can keep getting this information out there. We're doing, as we continue to do, our fundraiser for May, June, and July. We're hoping to double those donations up to a maximum donation of $20,000. We're doing FIMRC at the moment. In August, we'll switch over to Floating Doctors.

VR It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Leah writes, "What would be the downside of a person over 65 who does not have a specific condition that lowers their immune response using Pemgarda? Is this the CDC protecting Medicare from having to pay for it?"

DG: [chuckles] I don't think there's any kind of conspiracy to protect Medicare from big expenses. A lot of it is when these companies want to go ahead and they want to try to get approval for something. What they'll do is they'll do the study. They'll present to the FDA, "This is our data. This is what we think the indication is. Do we have the data to support that?" That's ultimately what leads to the indication.

Is there really a downside? Let's say you say, "Hey, I'm ready to ante up. I want to go ahead and do this." I don't think there's going to be much of a downside. We always come back to the fact that if something works, if something is biologically active, it is biologically active. One in a thousand could actually have an adverse reaction. Again, you want to find this balance between things that are evidence-based, put in front of the FDA with this bit of data, and so that's what I think is going on there.

VR: Julie writes, "You've mentioned that you plan on getting a Novavax COVID-19 vaccination in the fall due to potential longer durability. Two questions. One, do you think it will be less effective against current variants than the fall mRNA vaccines because Novavax will target the JN.1 variant? Two, would you consider getting it in the arm that hasn't gotten other COVID vaccinations based on a prior Novavax study suggesting more durability of switching arms? PS, I did get two Novavax shots in the clinical trials, one in each arm, but switched to the mRNAs when they got emergency approval and Novavax struggled."

DG: You can tell who listens to our show. Very sophisticated questions here, Vincent. Julie, first off, good show. These are great questions. I was speculating. We were talking a bit about, and also talking about, there's a paucity of data here. It is speculation about possibly the Novavax, maybe even J&J. These other alternative approaches may be having a potential longer durability and my interest in Novavax for this coming fall. I don't know. I don't think it's going to be less effective. I don't think it's going to be particularly variant selection-sensitive. We will certainly keep you updated when that goes from speculation to any actual data to help us there.

The other is, yes, should I be getting it into a different arm? We've talked a little bit about this idea that some of the data may be that if you get it in the same arm and you check really quickly, in a sense, you might get a little bit of a head start. If you then check two months, three months later, you're probably getting to the same level. I don't know yet if I'm convinced that there's any importance to which arm I get the Novavax in. I tend to get a lot of my shots in my left deltoid, maybe because I don't like my left arm as much as my right arm.

VR: Ian writes, "I'm an emergency medicine doctor and avid Paxlovid prescriber and grateful listener. I was hoping you could clarify and summarize the evidence regarding the ability of people to transmit COVID during the early inflammatory phase, commonly but erroneously known as COVID rebound. You'd said many times that once someone tests positive for COVID to stop testing, isolate and then come out 24 hours after symptoms improve and they feel better."

"My understanding is that the symptoms during the rebound phase are from the inflammatory response and not from active viral replication and shedding. If this is the case, I wonder why the CDC isolation guidelines recommend to re-isolate if symptoms return. Also, I have known many people who have done serial tests and have had two negative tests 48 hours apart only to have a positive test during the rebound period."

"If this is not due to increased shedding of infectious virus, what can explain this shedding of non-infectious viral particles that are only now being released during the inflammatory phase? As any good evidence-based and science-based practitioner will admit, my understanding of this phenomenon may be entirely wrong or that, as often is the case, we do not have the studies or evidence to know for certain."

DG: OK. Ian, this is great. Let's walk through it and make sure that very clear communication on what we know. During the first five days of an acute case of COVID is when we see most of the transmission. The number, about 85% of the transmission occurs during the first five days. Now, there is some transmission after those first five days, six, day seven. When I say 85% in the first five days, we see about 10%, 15% of the transmission after day five, but before day 10, right?

The CDC, when they make their recommendations, when they say, "Hey, isolate for the first five days," but then they clearly say, "When you are past those five days, you are still contagious. You should wear a properly fitting mask. You should basically avoid spreading it to other people. You're still infectious." I just want to make that really clear now. Here we are. Let's say it's day 11, it's day 12. You felt better. Now, you got a little bit of a sniffle as you had a little bit of a cough.

You've got what people will recognize listening to this show is the inflammatory period. There's no massive increase in viral replication. Sometimes you will end up with a few negative tests. Now, when that inflammation kicks in, you're going to actually be shedding cells that have antigen, that have protein, that have RNA in those cells. That will be enough material to turn a test positive, but that's not going to be replication competent virus at day 12, day 13, day 14.

Now, what is the CDC isolation guidance? What happened? What is the history here? Why did they say, "Oh, my gosh. If you have symptoms, you've got to re-isolate"? That was triggered by a pre-print, which I think eventually got published at David Ho's lab at Columbia. I know some people at that lab quite well actually, including David himself. That triggered this whole idea. It was really interesting.

It was like an article with his family members in it for whatever that's worth, and then suggesting that there may have been transmission during that second week. It was transmission during the second week and it was suggested and I'm OK with that. As I just said, day six, seven, eight, nine, 10. In that second five days, we see about 10% to 15% of the transmission. I'm not sure the science supports the CDC idea that if it's day 11, you get return of symptoms and a positive antigen test that you need to re-isolate. Science really doesn't support that.

VR: All right. From last week's *Office Hours* live stream, we had a question, "Do IL-17 inhibitors help reduce COVID disease?"

DG: Yes, so it is being studied and there is some data suggesting that there might be a role of IL-17 inhibition. At this point, I'll say more to come as we learn more about that. That's an active area of investigation.

VR: Anonymous writes, "My mother-in-law tested positive for COVID this week. She was reluctant to make the effort to get Paxlovid. My wife, a pulmonary intensivist said, 'Well, we give it to our patients because we don't have anything else, but it doesn't actually do very much.' I showed her the IDSA guidelines you linked to in the show notes. To my surprise, those rate Paxlovid as only a conditional recommendation with low certainty of evidence. To be fair, that was last updated over a year ago, but I'm wondering if I'm missing something."

DG: I'm wondering why you're anonymous. I'm trying to figure out if that's because you're writing about your mother-in-law or you're trying not to get in trouble with your wife. A couple of things here, right? I linked to the IDSA guidelines. I linked to the NIH guidelines. Yes, they do. If you read closely, they say, "This is what we recommend," but then, remember, this is evidence-based. They're going to say, "Listen, most of the randomized control trials, sort of a high standard for IDSA guidance. We're done on unvaccinated people."

They're not necessarily taking those hundreds of other studies that we've discussed and build this compelling story. Now, the NIH guidelines, which we also link to, they go ahead and they say, "This is A2A," so we have an A-level strong recommendation for this. They actually will go ahead and call it moderate quality of evidence. Just to say you're getting these two professional organizations both recommending this, both just viewing the quality of the

evidence straight through the recommendation a little bit different, but low to high level of confidence here.

I think if you listen to our show, you probably would take a little bit of an issue with the idea that this doesn't do very much. It is an interesting perspective on a pulmonary intensivist like, are they analyzing the data or is this looking at their experience? Because they probably will not be seeing very many people ending up in an ICU who were both vaccinated and received Paxlovid during that first week. I'm just going to lay that out there for you.

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

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

[music]

[pause 00:41:20]