This Week in Virology

TWiV 1154 Clinical Update

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

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VR: From *MicrobeTV,* this is *TWiV, This Week in Virology,* Episode 1154, recorded on October 3, 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: Not Friday, so it's not time for clap on the tie, so today's Thursday.

DG: What do we have on the tie? It looks like a shepherd's crook. If you were going into the city, this might be easier for you.

VR: Shepherd's crook, that should give it away.

DG: What really should give it away is if you were going into the city and walking into that room at the incubator and looking at that beautiful bit of art on the wall.

VR: It's shepherd's crook. That's right, Ebola virus.

DG: Yes.

VR: What is a shepherd's crook? It's the thing that they use to walk with, like a stick?

DG: Exactly. Very soon, people will know why am I wearing a filovirus bow tie.

VR Yes, we have a little outbreak, don't we?

DG: Yes. Let's start with our quotation. I put this in here because I've had several of my Long COVID patients ask me about this particular book, this particular writer. We'll start off with our quotation. "There are a lot of people who will give money or materials, but very few who will give time and affection." This is from Daniel Keyes and the book, *Flowers for Algernon*. I don't know if our listeners are familiar with that book, but this has come up with a lot of, let's say, my very high-functioning pre-COVID patients who've had that just devastating cognitive impact that's persisted after an acute COVID.

Just highlighting just the parallels that they see where they remember a time when their mind worked much better and now they're struggling. Let's get into filovirus. Marburg, Rwanda, is having its first outbreak of Ebola's cousin, Marburg virus. So far, about a 30% mortality. German officials are investigating symptoms in two train travelers, one of them a medical student who had arrived by plane from Rwanda where he had contact with a patient who was later diagnosed with Marburg virus infection. I just want to keep that on people's radar. We'll see where that goes.

Just a reminder, all these places in the world, they're just one plane trip away. There's almost a nonstop flight from every region of the world. We can't cover everything, but I just want to make sure I mention this. We're really seeing lots of cases of mycoplasma and pertussis. Even a pediatric case of mycoplasma followed by PANS. People are familiar with Pediatric Acute-onset Neuropsychiatric Syndrome or PANS. This is a clinical condition characterized by a sudden and dramatic onset of obsessive-compulsive disorder. The person gets mycoplasma and then three to four, so many weeks later, all of a sudden that individual develops obsessive-compulsive disorder. This could be devastating.

Actually, one of the infectious disease doctors with which I work had this happen when they were younger. I joked with them that it hadn't fully gone away, but that was insensitive of me. No, this is really a devastating thing. Now, the U.S. is in the midst of the biggest pertussis outbreak in a decade with over 15,000 cases. We've had a couple of deaths. Big issue in the schools, who gets prophylaxed, who had a close exposure. Just making sure that that's on everyone's radar.

RSV, we've got some updates here, the good and the bad. Now, really, this should really be becoming a historical issue.

I was looking forward to telling people, I remember the days when the hospitals would fill up with kids with RSV. This week, we have the *MMWR*, "Maternal Respiratory Syncytial Virus Vaccination and Receipt of Respiratory Syncytial Virus Antibody, Nirsevimab, by Infants Aged Less Than 8 Months, United States, April 2024." It turns out that only 33% of eligible pregnant women reported receiving an RSV vaccination. Among women with a live birth, 45% reported that their infant received nirsevimab and so Beyfortus. Basically, only 56% of infants were protected against severe RSV disease by either of these strategies last winter.

VR: What do you think is the reason for that low uptick?

DG: I think there's two issues. I hope we move forward with, I'm going to discuss a WHO recommendation, but we have to be careful, stop making things so complicated, because we're worried about whatever we're worried about. There was this idea last winter that people would have a choice. Either mom would get that vaccine during the last trimester, or you would wait and the baby would get the nirsevimab. Then a lot of women decided, "I'll just go with my baby getting the nirsevimab." Then we have a shortage of nirsevimab. That impacted things.

If you went with the, "I'm going to give my baby the past monoclonal," now there was a shortage. I think that was part of it. There's also an awareness issue. You want to get everyone

on board. A simpler message is actually what the WHO is recommending. We read that the WHO recommends maternal vaccine and the antibody shot to prevent RSV in infants.

Here's the strategy. Pfizer has this RSV shot sold as ABRYSVO. It's the only vaccine that's actually approved for this indication, giving it to pregnant women during the last trimester. What happens is they get this. This should become a routine thing. If you're pregnant, last trimester, you get your RSV shot, you get your COVID shot, you get your flu shot, you get your pertussis shot. All this is last trimester. Then by the way, even if mom got the vaccinations, infants and toddlers can still go ahead and get the Sanofi, AstraZeneca antibody, Beyfortus, the nirsevimab.

I'm hoping this simpler message is going to be associated with better protection for the kids. All right. Now, the brief article, and I went through this and then came back to it, but this is the article I'm going to put on my glasses for this. I don't know if that means it's more important or my print is too small, or maybe, I don't know how I pronounce this, but Ziresovir, what would you do? Vincent, you do that? Ziresovir?

VR: Ziresovir, yes.

DG: Yes, Ziresovir. "Ziresovir," now that I've said that three times, "in Hospitalized Infants with Respiratory Syncytial Virus Infection," and the associated commentary, "Creeping Toward Effective Antiviral Agents for RSV Infection," both published in *The New England Journal of Medicine*. Now, when it comes to RSV, we're still basically in the world of supportive care. There's the aerosolized ribavirin. This is this nucleoside analog licensed back in the 1980s.

It's the sole antiviral agent that's approved for the treatment of hospitalized infants with RSV infection, but marginal clinical benefit, concerns about toxic effects, cost, just the whole production. In the lead article, I've got two articles we're talking about, the lead article, they're actually looking at an RSV antiviral. They're presenting the results of a two-part phase 3, double-blind, randomized, placebo-controlled trial of Ziresovir. This is orally bioavailable fusion inhibitor, right? This is oral, given it to infants up to 24 months of age, hospitalized with RSV infection.

Remember, we want to be preventing that. It is probably more promising than the data suggest. This article does show that it appears to be safe. There appears to be some efficacy, but I want to point out the median time from symptom onset to the first dose was four days, a time when the viral load already declining. We already have data suggesting that illness severity is driven by the early virus-induced host inflammatory response, not the actual viral replication or viral cytopathic effects. You end up with this delayed innate interferon response.

Now, similar to COVID, the flu, other illnesses, timing matters and getting this drug started within 48 hours might give us even better results. I had hoped that we learned from the early days of COVID with monoclonal antibodies that we need to treat these infections before the kids end up in the hospital. We need to jump in, in our primary care offices, in our urgent care clinics. I'm going to remind people of a conversation that Steve at UHG and I had in their early days.

This is like early August. No, this is early April. It's April, 2020. This is a conversation with the folks at Regeneron. I just want to talk about the role of timing. They've started this trial. They're going to give the monoclonal antibodies to people week three in the ICU. Steve and I get in the phone with the folks at Regeneron. We say, "What are you guys doing?" Their response was, "Well, we've got all these partnerships with hospitals and ICU docs. We don't really know how to do treatment in the first week. We do think the first week is when we can make a difference."

We basically said, "You know what the danger is here? If you wait too long and you give monoclonals to people in week three, you're just going to get negative data. Everyone's going to say this stuff doesn't work. If you do it in the first week, turns out this ends up being true. You might get an 80, 90% reduction in people progressing. You might get a 90% reduction in people dying." That actually turned out to be the truth. We really need to learn that lesson and don't just do your trials in a setting where you've got your partners.

You got to make those partners who are going to say, "Hey, if we want to study an effective antiviral, we got to make those relationships with urgent care clinics, with pediatric offices. You start antivirals within the first 48 hours, not once the kid has already ended up in the hospital." All right, I'm going to step off my soapbox, trip on the way down, and then just mention again that mpox, this is good news.

We read in Reuters that more than $800 million has already been pledged for the mpox response. We hear this from the African CDC and I'll leave in a link. We're getting close to that $1 billion that is hopefully going to turn the tide.

COVID, all right. We're looking at the map, Vincent. What is that state in orange at greater than, is that like greater than 8%?

VR: 8%?

DG: 7.9, yes.

VR: Or is it 6 to 7.9?

DG: Yes, I think we're in the 6 to 7.9.

VR: West Virginia, right?

DG: Yes, West Virginia. Yes, the home of the mountain highways. As we look at our wastewater, we see that we're coming off that peak. Wastewater numbers are heading down, but this is that late indicator. It takes time for people to die. These are folks that got infected a few weeks ago, entered that cytokine storm. This is that 28-day mortality that we see.

VR: It's going down, Daniel.

DG: It's going down, and here's where we're going to find out. My prediction is we're going to have this really nice seven-day break in November, Vincent, is we're going to have a break till next summer, right?

VR: Yes, I'm hoping.

DG: Yes, I'm hoping, too. I'm just trying to be honest and not as optimistic. All right, we've got a good article in the transmission section this week. This is the article, “Doff Thy Gown-Shedding Contact Precautions for COVID-19,” *CID*. That's very clever. We don is to put on a gown and to doff is to take it off. What about these contact precautions? I go to the hospital, everyone's putting on these yellow gowns or putting on gloves.

We've got our N95. I agree with that, right? This is respiratory transmission. Here we read that, yes, SARS-CoV-2 is spread via respiratory transmission. However, the U.S. Centers for Disease Control and Prevention continue to recommend the use of contact precautions, a gown and gloves for the care of patients with COVID-19. I'm going to say the authors really go out on a limb here and suggest their words, not mine, that infection prevention guidelines should reflect the current science and eliminate this wasteful practice.

VR: Isn't that what you said months ago, Daniel?

DG: What is 200 gallons a week of waste is generated from this outdated practice per patient? Yes, this is very much a wasteful practice. When you have the science. Early on, we didn't know, but now we know. It's like maybe one in every 10,000 infections is spread through contact. Yes, let's follow the science and eliminate this wasteful practice. All right, now we've got a really exciting paper. Vincent, when you sent this, you probably noticed I responded right back because I was already excited about this paper.

We have the article, “SARS-CoV-2-Specific Plasma Cells are Not Durably Established in the Bone Marrow Long-lived Compartment after mRNA Vaccination.” It's published in *Nature Medicine*. The authors start by saying, severe acute respiratory syndrome coronavirus 2, (SARS-CoV-2) mRNA vaccines are effective at protecting from severe disease, but the protective antibodies wane rapidly. Now, they're not just saying they wane, they're not saying they contract, they're saying they wane rapidly. They then have this section, “declined serum S2P, not flu, tetanus or total IgG.”

What they're doing, and actually, I would have loved to see this really nice curve, but what they're doing is they're looking at responses out to 38 months after the first SARS-CoV-2 vaccine. We read that from subjects with at least two sequential serum correlate with the vaccine-specific bone marrow IgG, long-lived plasma cell responses. Basically, I'm going to make this simple. What they were seeing is that waning trajectory is much more rapid after the mRNA vaccines than we see with getting tetanus or flu. Instead, what we see is that something about the mRNA vaccines fail to establish this bone marrow long-lived plasma population.

They're going to look at all the genetics. They're going to look at samples at different points in time. Basically, what they're trying to get is what is going on here with these? They have some really nice flow cytometry. We can actually see the different populations, the long-lived plasma blasts, the other cell populations. They're going to wrap it all up. Vince and I can chat a little bit about this.

They point out that while serum IgG titers specific for influenza and tetanus correlate with IgG long-lived plasma cells, serum IgG levels for SARS-CoV-2 wane within three to six months

after vaccination and were associated with IgG from non-long-lived plasma cells. Their study suggests that the rapid waning is really accounted for by the absence of the generation of these bone marrow long-lived plasma cells after mRNA vaccines. What is my question, Vincent? What about Novavax? What about using other treatments?

VR: Yes, you'd have compared it to Novavax. This is actually surprising to me that there are no long-lived bone marrow memory B cells, basically, right?

DG: Yes, that's basically how people would, I think, use it. We have this purist, B cells cease to be B cells and become these long-lived plasma cells. Yes, they're B cells. We're not making these bone marrow long-lived B cells. Is that really something about this antigen? Is it something about the vaccine platform? Yes, I can't believe the reviewer number two didn't say, "Grab some people that got Novavax and show us the data."

VR: Yes, it is a surprising result, frankly, that there would be none. In contrast, flu and tetanus is OK, right?

DG: Yes, they seem to go ahead. Particularly, we know the durability of our tetanus. We know the issue with flu is you keep having different flu. What we're really trying to figure out here is are we vaccinating everyone once a year because the virus keeps changing and we're trying to chase variants? Is that what we're doing? Is that why we see this efficacy data that we do see with boosting? Or is it that there's something up with the mRNA platform? We got a little bit of a hint with the RSV data. Well, here's the first part of the puzzle. I just want to see this done with a non-mRNA platform.

VR: This is actually something we brought up some time ago. When maybe we're, as you just said, we're chasing the variants, but maybe it's actually the vaccine that's not durable, right?

DG: Yes.

VR: Now, we do know that T cell response is somewhat durable, right?

DG: Yes, and they do make the point. Now, I sometimes notice our listeners make some comments about this, is that those vaccines are still effective at protecting against severe disease. There is a certain durability and that is probably the T cell. The antibodies are waning more rapidly than we would expect.

VR: Right.

DG: What's going on with that? That suggests to me, a vaccine platform. The only way we're going to know for sure is you got to go do this data. I would love to see these curves, take a whole bunch of people, some people get AstraZeneca, some people get Novavax, some people get the Moderna mRNA, some people get the Pfizer–BioNTech, follow the antibodies over time and look for these plasma, long-lived bone marrow plasma blasts.

VR: It's really a very provocative finding, I think.

DG: Yes, so really interesting. All right, we will move into the COVID early phase. Now, we still have our NIH and our IDSA guidelines. Just point out to those doctors that are not following

the expert guidance, and I think spending their time listening to social media and the mainstream media, number one, this is recommended Paxlovid, number two, remdesivir, number three, molnupiravir, number four, convalescent plasma, and a cautionary tale, right? Early on, a lot of people had ideas about what was going to work.

We have the article, “Effects of Losartan on Patients Hospitalized for Acute COVID-19: A Randomized Controlled Trial,” published in *CID*. Here, the authors hypothesize that since SARS-CoV-2 down-regulates the angiotensin-converting enzyme 2, potentially increasing angiotensin II, losartan, an angiotensin receptor blocker, or commonly known as an ARB, compared to usual care would decrease mortality and be safe in patients hospitalized with COVID-19. This seems so obvious to many that they were just doing it. They're just like, "I'm sure that works. It makes so much sense. Why even bother doing a study when it just makes so much sense?

I guess these guys are sticklers. They want to dot those I's. They're going to actually go ahead and admit that they don't know until they've done the science. They go ahead and do this trial, and they end up noting that the serious adverse events and hypotension were significantly higher in the folks that they gave losartan to versus usual care. "Yes, oh my gosh, wow. We're not as brilliant as we thought." Serious adverse events, 39.8%. Almost 40%, almost half of the folks had a serious adverse event when they were given the losartan versus 27.2. About a quarter of the folks that were not given. Hypotension was a big one. It was twice as common that you were going to trigger hypotension.

VR: This is why we do clinical trials, right, Daniel?

DG: I think that's the reality. The quotation, “some things you just know are true.” We're not that brilliant. You actually have to test stuff.

VR: This is funny because I was just reading an article yesterday about this, and they're like, "Oh, this is so obvious. We just should do it."

DG: Now this is published, and oh my gosh, not so obvious. Right? That was early on. They're like, "Oh, this is the receptor. Why don't we block that receptor? Obviously, this is going to work." Places wrote this into their standard of care before anyone bothered to actually do the study. Now the study's -

VR: ARBs are used, as you know, but never in the context of COVID, so you have to test it.

DG: Yes. This is a new disease, and we've got to figure out what works and what actually, in this case, is harmful. Then the second week, the early inflammatory week, I don't like when people call this rebound because we've been talking about this for years before anyone had that bad terminology. That first week. That's the viral replication phase. We even talked about this with RSV. What kills you is not the virus. It's the cytokine storm. It's the inflammatory response. Just to remind people, this is the bad week. This has always been the bad week.

That first week, you feel like you got a virus, and then in the words of Ian Lipkin, then you really get the COVID. You've had COVID all along, and actually, the virus is on the way down. The inflammation is on the way up. Starts at the right time in the right patient. We have

anticoagulation guidelines, pulmonary support, remdesivir if it's not too late, immune modulation.

As promised, we have a couple of interesting articles this week about Long COVID. We have the article, “Mechanisms of Long COVID and the Path Toward Therapeutics,” published in *Cell.*

Here, the authors review the current state of knowledge regarding the biology and pathophysiology of Long COVID, focusing on how the proposed mechanisms explain the physiology of the syndrome, how they provide a rationale for the implementation of a broad experimental medicine and clinical trials agenda. The article is not very long, and there are some really nice accessible figures. You're sort of left with this, "Here's a biological mechanism, and here's a therapeutic that we're looking at." I recently got together with all the ID docs in my group, and Marilyn Fabbri, she's our sort of office-based provider.

She was saying what she really liked about the article that I recently published in *Open Forum* is it really gives that practicing clinician a number of evidence-based therapies to start trying out. This has the idea linked to things that are under investigation. There is a little bit here. You see the dysbiosis gut translocation, and then they mentioned probiotics. They don't necessarily mention the bifidobacterium that's been tried or the dose that we saw from that Hong Kong trial. They also mentioned the theories about mitochondrial dysfunction, and they mentioned the N-acetylcysteine, some other sort of things here.

Worth reading, not very long article. We also have a review on pediatric Long COVID. This is the article, “Post-Acute Sequelae of COVID-19 in Pediatric Patients within the United States: A Scoping Review,” published in the *American Journal of Medicine Open*. They focus on the epidemiology, the prevalence, how to make the diagnosis. There's actually a little bit in here about how it can be different. The manifestations we're seeing in kids is different than adults. This is really worth the read. Of course, they call out for more research to optimize and better understand this in the kids, prevention, treatment, other things.

Then I will close out, and this is maybe the *Flowers for Algernon* quotation. Just one more article on the impacts of COVID on the brain. The article, “Post-hospitalisation COVID-19 Cognitive Deficits at One Year are Global and Associated with Elevated Brain Injury Markers and Grey Matter Volume Reduction,” published in *Nature Medicine.* Here, the authors report the one-year cognitive serum biomarker and neuroimaging findings from a prospective national study of cognition in 351 COVID-19 patients who had required hospitalization compared to almost 3,000 normative match controls.

The cognitive deficits were global. We're about a year out here. They're associated with elevated brain injury markers, reduced anterior cingulate cortex volumes, a reduced brain volume a year after COVID-19. A couple of things that they point out is the severity of the initial infective insult, post-acute psychiatric symptoms, and a history of encephalopathy were associated with the greatest deficits.

VR: I remember about a year ago, a similar study was published just focusing on grey matter volume reduction. It was criticized because the person doing it just took controls from a database. Are these any better, these normative matched controls?

DG: I think you could say they're similar challenges because what is normative match controls? Ideally, you want baselines for folks and then you want to almost match them to their selves. You take people who are all matched at baseline. Some people end up with COVID-19 in the hospital, you follow them over time. Other folks end up not being hospitalized, you follow them over time because there will be a certain volume reduction over time.

VR: Yes, you would like to know if a certain fraction of COVID patients do not undergo this grey matter reduction, right?

DG: Yes.

VR: That would be a good control.

DG: All right. Now, we'll close this out with no one is safe until everyone is safe. We're in our Floating Doctors fundraiser. This is the last month, we're in October. August, September, and October. We will double your donations up to a potential maximum donation of $20,000 for Floating Doctors. I know folks that have gone down there. In March, we're going to be doing our CME. I'll be down there in March, seeing patients, doing some teaching. Not only can you support Floating Doctors, but maybe you want to join us in March.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. DR writes, “Recently I saw a Twitter post where someone apparently immune compromised was testing COVID positive for the sixth consecutive month in a row. How is this even possible? Doesn't the nasal pharyngeal epithelium run out of cells at that rate? Thoughts?

DG: We keep making new cells. We're not going to run out of cells. There's still going to be cells there. Unfortunately, and there have been a few case studies we've shared where if you do in someone who's immune compromised, you actually can end up getting these pretty significant CT values. Normally in some of our studies, we talk about remnant mRNA. We talk about remnant antigen, but in immunocompromised individuals, you could actually have ongoing replication. You can even see pretty significant rises.

Then in some of those case-control cases we've shared, doing antiviral therapy can actually have an impact. There have been a couple of cases where they've done Paxlovid and remdesivir dual therapy and finally gotten these folks cured, I guess I would say.

VR: Jared writes, “My 5-year-old has a question about *TWiV* 1152. She wants to know if you were in the dungeon. Apparently, the stone in your background reminds her of a dungeon.

DG: Yes. The answer for your 5-year-old is yes, that is down in the dungeon. When I record, like here I am up on the first floor, I can see sunlight, but that is down in the basement. I live in this house that was built in the 1800s, so it's an old house. Before we moved in, they dug out by hand a basement. In the very bottom of that basement, in a dark corner with appropriate lighting, that's where that is, yes.

VR: Laura writes, “My first time coming sick with COVID was unfortunately on our vacation in Italy, ironically in Venice, the origin of quarantines, LOL. Luckily, I had brought Paxlovid, although a challenge to convince my doctor to prescribe it as she seems to believe in Paxlovid

rebound. Additionally, I had received a booster exactly two weeks before my first symptom. We also masked on planes and trains, but not elsewhere.

“OK, questions. As a COVID case investigator in 2021, I remember the CDC rules changed so that if one was exposed but not fully vaccinated, they did not have to quarantine unless they started to experience symptoms. Does this rule still apply? Is it because a fully vaccinated or currently boosted person transmits a smaller or negligible amount of virus?” All right, let's take them one at a time.

DG: Let's take one at a time. Interesting. We have seen that people who get COVID, so this is, "I got symptoms, I test positive." You compare them to someone who's not vaccinated, who has not been boosted in any sort of reasonable amount of time, you actually will see lower CT values. You're going to see lower amounts of RNA in folks. As we well know, if you get COVID, if you've got viral replication, we see transmission even from vaccinated people in the first five days.

VR: Question number two, “Are fully-vaccinated boosted individuals no longer pre-symptomatically spreading COVID in the 48 hours before onset of symptoms? I ask because we had been in the car for many hours on the two days before my first symptom. Luckily, that person did not become sick because they're over 70. However, I feel terrible exposing them.”

DG: Yes, I think we got spoiled. We had so much data during the first few years. Now, people have been vaccinated. It would be great to redo those contact tracing experiments and find out are people still transmitting for that day or two before they get their symptoms or with, all the immunity and the vaccinations, are we starting to get symptoms before any degree of transmission? I think the evidence suggests that this has changed and that we're not really seeming to see a lot of pre-symptomatic transmission.

We still certainly are. We had a case recently where there was a young lady, she had traveled. She was going to be spending time with her older parents. She was concerned about potentially being exposed. She tested every day and then ended up testing positive. Right about then was when there were symptoms. She immediately isolated. The dad, two to three days later ended up developing symptoms, testing positive. The exposure was before she had symptoms. The exposure was before she got that positive test, she was testing every day with a molecular test.

VR: Finally, “As I look for a new doctor, what papers would you recommend I send to doctors that clearly show that Paxlovid is a key tool in the reduction of COVID hospitalizations and mortality?”

DG: We keep sharing the NIH and the ID Society guidelines. This is what the professional organizations are recommending. Those guidelines have links to all the papers that they base those recommendations on.

VR: John writes, “Since metformin is typically prescribed in the beginning phases of Type 2 diabetes mellitus, doesn't the fact that a DM patient is on metformin indicate that the severity of their diabetes is low relative to other non-metformin patients? Does the PASC risk seem reduced among the metformin population because the severity of Type 2 DM is lower in that population compared to Type 2s on latter-stage drugs?

DG: John, this is brilliant because yes, is metformin just a marker for folks that have a milder form of diabetes or milder stage early on? Is it really that the metformin is making that difference or is the metformin just correlated with something else that's reducing their risk? Always these challenges and science is trying to sort out what's really driving the results.

VR: Jean writes, "As I currently have COVID, I listened even more attentively than usual to listener Ginny's question about antigen tests and suddenly had a question that I hadn't considered before that perhaps you have covered and I missed because I wasn't in the thick of it. I understand that still testing positive on an antigen test that day, 11 to 28 does not mean you are contagious, but if you do test negative on day six, does that mean you are not contagious?

"In other words, where there is no protein, is it likely there is no transmissible virus? Or if I were to test negative for two consecutive days before day 10, would you consider that I could relax and consider myself post-acute COVID and mix as usual? Would the presence of symptoms or lack thereof change this decision?

DG: Yes, these are great questions. Let's talk about what's the science here. There are some confusing recommendations here. What do I tend to tell people? I tend to repeat the science, which is in the first five days, that's when we see 85%, almost all the transmission. Maybe we see some transmission day six, seven, eight. Then after day 10, outside of immunocompromised individuals, we don't see contact tracing showing that there's onward transmission. What about this interesting thing that was introduced, this test out?

Now it's day six, you get a negative test. Maybe you had a negative test on day five, you got your two tests, and now you go out in the world, you don't wear your mask anymore, not like anyone was to begin with. Anyway, sort of this suggestion. Now, we've shared some studies where they actually took people and had them do antigen tests every day. We had them do PCRs every day. We even had them do viral cultures every day.

What was really interesting was that positive or negative antigen test did not correlate with whether or not they actually had a positive viral culture. Really, I think when you try to get into and sort this out, I like to just step away with a simpler message, which is I don't recommend antigen testing after day five. The calendar is the most reliable. The first five days, that's when we see almost all the transmission, and then just a little bit during the second five days, but really, the front load of those next five days.

VR: Five days after symptom onset, no more antigen tests.

DG: Yes. No more antigen tests. Use the antigen test to make the diagnosis. Once you make the diagnosis, you're done.

VR: All right. Then after day five, you can go about your life. OK. That's *TWiV* weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

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

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[00:39:42] [END OF AUDIO]