TWiV 1268 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.

[music]

VR: From *MicrobeTV*, this is *TWiV*, *This Week in Virology*, Episode 1268 recorded on November 6, 2025. 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: I can see that you have an AIDS benefit tie there with the red symbol, right?

DG: That's exactly what it is, right? Yes.

VR: It's like the first thing I could see because it's really big.

DG: [laughs] Excellent. All right, let's jump in. We got a lot to cover. I was actually thinking the other day, Vincent, I was like, "I don't know. I'm not sure if I'll have anything to say."

VR: There's always something to say.

DG: There's always something to say. Let's start with our quotation. "The mark of the immature man is that he wants to die nobly for a cause, while the mark of the mature man is that he wants to live humbly for one."

VR: Daniel, I spent a lot of time thinking about this quote. First of all, it should be person, not man. J.D. Salinger, what did he know?

DG: Exactly. We should start updating our quotations, yes.

VR: I don't understand. Who's the one? Himself? The person is living for himself or herself?

DG: It's for a noble cause. The mark of the immature man, he wants to die nobly for a cause, and then the mature man wants to live humbly for a cause.

VR: I see.

DG: It's interesting. I'm rereading Hemingway. Apparently, there was an interaction. Salinger was a big fan of Hemingway. Hemingway was a fan of Salinger. Then Salinger, then apparently, Hemingway didn't live up to his expectations. He became less of a fan of Hemingway, but Hemingway still liked Salinger. I remember reading a lot of Hemingway when I was younger. The whole Hemingway thing about wanting to die nobly for a cause,

and I think Salinger maybe responding against -

VR: It makes more sense to live if you have a cause instead of dying for it, right?

DG: Exactly. A lot of fiction is that way, someone dying for this cause, where really, once you die for the cause, you can't continue to fight for something that's worth fighting for. That's my take on all that. I do think we have to keep pushing forward. We don't want any of the people on our side to die while they're pushing for real science. Let me put on my glasses for this next one. I have a melon. No, a lab. My black Lab, Hattie, is nudging my elbow. You can see her nose.

VR: There you go. I see a black nose. How about that?

DG: Go back down, Hattie.

VR: Your water has stopped flowing through the light fixture, right?

DG: Yes. That's a good thing. Now, Hattie is in here, hungry. I think she goes through life hungry. All right. Let's start with that. I think this is a good article. I wanted to start with this because actually several people sent me this way. It's the article, and I think it's very timely, "Neurodevelopmental Outcomes of Three-Year-Old Children Exposed to Maternal Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2 Infection in Utero," published in the journal *Obstetrics & Gynecology*. That's the journal of ACOG, the American College of Gynecology. These investigators conducted a retrospective cohort study of 8,124 live births -

VR: 18,000 .

DG: 18,124 live births to individuals who delivered between March 1, 2020, March 31, 2021 within the Mass General Brigham Health System. The exposure was getting a SARS-CoV-2 infection, a maternal SARS-CoV-2 infection. You had to have a positive PCR during this pregnancy. Then the outcome of interest, what they're looking at is the presence of any neurodevelopmental diagnosis up to 36 months after birth. Why am I saying this is timely? There's all this stuff out there about vaccines causing autism. Here, we're looking at maybe actually infections might cause neurodevelopmental issues.

Among the 861 individuals who got SARS-CoV-2 during pregnancy, 16.3%, so we've got 4.8% end up getting exposed. We have 140 of those 861, the offspring ended up receiving a neurodevelopmental diagnosis by 36 months after birth. Compared with 1,680 or 17,263 unexposed offspring. We're really going to see an adjusted odds ratio of 1.29. The largest effects were observed in third trimester exposure. Overall, adjusted odds ratio of 1.36. I got 36% higher incidence third trimester exposures. Maternal SARS-CoV-2 infection in pregnancy was associated with an increased risk of adverse neurodevelopmental diagnosis by age 3 with effects most pronounced after third-trimester exposure and in male offspring.

VR: It's interesting that even without exposure, there's still 9.7% had neurodevelopmental issues. It's a high rate.

DG: It is a high rate, actually, yes.

VR: It gets higher with infection. It's a good question, Dan. Has anyone ever looked to see if neonatal infections associate with autism?

DG: Definitely an area that people are looking into, and I think here it's pretty striking. Let's pick these numbers. You've got a background rate of about 10%, 9.7%, and then getting COVID basically during that third trimester, you're going to bump that up to 17%.

VR: Then there are other infections, too, the mother could get, right?

DG: Yes. It's really interesting. It's all this focus on vaccination and aluminum and Tylenol, but actually, this is pretty compelling evidence, that getting the infection. Unfortunately, we keep discussing, there are a lot of people out there not recommending that women have the protection of the vaccine during this vulnerable period of time. All right. This one I love, Vincent. It was fun. I was listening to *TWiV* 1267.

VR: I said on *TWiV*, Daniel's going to do this on clinical update.

DG: Yes. As you mentioned, I was listening to *TWiV* 1267 at 1.5x. Get through it. I think, as Alan mentioned, they adjust the pitch, so it doesn't sound like I'm listening to chip monks. People are talking at a reasonable pace for me. This is the article, "Impact of Vaccinating Adult Women Who Are HPV-Positive or with Confirmed Cervical SIL with the 9-Valent Vaccine: A Systematic Review," published in the journal *Viruses*. Yes, for a deep dive, I'll leave in the link to *TWiV* 1267. I actually thought Rich did a really good job of the clinical stuff about all the progression of the different pathological abnormalities we see leading up to cancer.

Here's the background. Infection with certain types of HPV. This virus causes anal, genital, head, and neck diseases. You might get warts. You might get the precancerous lesions, and then these might actually progress to cancer. We think that almost all, if not all cervical cancer is due to HPV. I'm going to leave in a link to that. Actually, the majority, I'm going to say over 90% of head and neck cancers are also related to HPV. Tobacco and other things might be related as well. Here's the issue. Since we have a highly effective vaccine, almost all, if not all of these cancers could be prevented.

This is where it gets really interesting. What about jumping in after the fact when a person, maybe they didn't get vaccinated, they've got the HPV infection, maybe they've already developed cancer. Can we use this vaccine therapeutically to help the body clear the virus? Based on this systematic review that identified a number of cohort studies with Breanne. Breanne explained that well, what those are, basically grouping the people, the folks that are going to get the vaccine, people that are not getting the vaccine. They found that complete HPV remission, human papillomavirus remission, was achieved in up to 72.4% of vaccinated women.

That's compared to 45.7% among unvaccinated controls. Then vaccination after conization. What that is if you think of looking at a cervix like you're looking at a bagel or a donut. Conization is basically taking almost a cone excision. It is. It's a cone excision of the interface between the inside, the endo and the ecto cervix, doing a cone resection of that. Vaccination after that conization lowered the recurrence risk by 87%. Benefits seen regardless of timing. The most significant effect was observed when vaccine administration was performed before the surgical procedure. Furthermore, HPV vaccination notably enhanced viral clearance, decreased the likelihood of repeated surgical interventions.

VR: It's just an amazing study. It's a meta-analysis of multiple studies which led to this conclusion, which is great.

DG: I think it really is great. One of the discussions you guys had is, "What are the current recommendations, and will this impact the current recommendations?" Unfortunately, the crowd hanging out at the CDC currently is anti-HPV vaccine for whatever political reasons is really what's going on here. We have a vaccine here to prevent cancer, but maybe there's some idea that, "Oh, if you have sex, you deserve to die of cancer." I don't understand the argument. What are the current CDC ACIP recommendations? Vaccine recommendations. These we're going to see are in line with some of the other groups that I'll mention.

ACOG, American College of Gynecology, CDC, ACIP, which is what we're about to do, American Cancer Society, IDSA. Vaccine recommendations. HPV vaccine is recommended for routine vaccination at age 11 or 12, but you could actually even start as early as 9. ACIP also recommends vaccination for anyone aged 26, if not adequately vaccinated when younger. You go ahead and you give this in a series of two or three shots depending on the age that you start the vaccination. Now, vaccination is not recommended for everyone older than age 26.

This is where this shared decision-making comes in. They're looking at folks 27 to 45, and then you have a discussion with your provider, and you're considering shared decision on what you're going to do. Now, what we're seeing here is outside of a vaccination preventive recommendation, if you're a woman who actually has progressed, you go ahead and get it therapeutically. We don't necessarily have to wait for the CDC to give some guidance here. This guidance can come from these other professional organizations.

VR: Basically, if you are older, you should just get it because if you have infection, it will clear it most likely. There's a good chance it will clear it. Even if you have a lesion, you should still get it.

DG: Yes. It was interesting, when they do the studies, there was this whole idea that, "Oh, if you don't get the vaccine, if you wait too late, then it's too late." What we're seeing here is it's never too late, actually. Even if you've progressed to cancer, the vaccine can boost your immune response.

VR: What would be interesting to do, a similar study in men. That was a study focused on women. Men, I don't know what the age recommendation is. I guess it's the same here as CDC, right? 45 years.

DG: Yes. They now recognize it in men. I think that this study looks at cervical cancer, but what about head and neck cancers?

VR: It would be interesting to look at that. Penile and anogenital could also benefit. I never got an HPV vaccine. Maybe I should. Who knows what I got?

DG: No, you probably didn't, just looking at your age thing. Now, the thing they do have to update on the CDC website is, "Keep in mind that HPV vaccination prevents new HPV infections, but does not treat existing HPV infections or disease. HPV vaccine works best when given before any exposure to HPV." That's not true. [chuckles]

VR: Not anymore. I don't know. Do you have any faith that CDC is going to change that?

DG: With the current crew, I don't see them jumping in and updating that.

VR: I think, and tell me if this is reasonable, people should speak with their physician and say, "There's these studies, and I would like an HPV vaccine." What do you think?

DG: There's also this bias. This is why we talk about shared decision-making. Also, I don't see why suddenly there's this upper limit of 45. There's this idea that after 45, you're not going to be sexually active. You're not going to have new partners. We see a lot of sex in the nursing homes.

VR: I think the 45 was the age at which the clinical trials were done. We didn't trial anyone over 45. These studies now, they're not trials. They're retrospective analyses, but they still are compelling.

DG: Yes. If you're in your late 40s, you're in your 50s, you're going to be having sex. Yes, there's, I think, a broader picture here.

VR: Also, even if you're not having sex, you may already be infected from when you used to have sex.

DG: Actually, that's true, and then you end up with your head and neck cancer. "Hey, I could have gotten this vaccine."

VR: You get vaccinated, you have a 75% chance of resolving the infection.

DG: Yes. There's a lot to be said here. All right. Bird flu, really interesting article. “Asymptomatic Human Infections With Avian Influenza A(H5N1) Virus Confirmed by Molecular and Serologic Testing: A Scoping Review,” they call it. This is in the title. It's published in *JAMA Network Open*. Now, is this really this question of can you get asymptomatic bird flu. Maybe you get it, you don't even know. We always thought that if you're going to get it, you're going to have symptoms. Since 1997, more than 1,000 infections with highly pathogenic avian influenza virus among humans have been reported globally.

The objective here was to identify and characterize reported cases of asymptomatic H5N1 virus infection among humans that were confirmed by molecular testing. They actually identified 10 reports of 18 asymptomatic human H5N1 infection, including two with molecular and serological confirmation, 16 with molecular confirmation alone.

VR: This is so interesting, Daniel, because in 2015 when they made H5N1 transmit through the air among ferrets, everyone was, "Oh, the fatality rate of H5N1 is 50% to 80%." Peter Palese published an article saying, "There are lots of asymptomatic infections. That number is wrong.” We actually had a panel at the New York Academy of Sciences, and Peter was there, I was there, and so was Michael Osterholm. Now, Michael Osterholm said, "Those data are all crap. There are no asymptomatic infections. I don't believe it." Now, we see even *CIDRAP* is carrying that story.

DG: [laughs] That's so funny. Yes, I put in a connection to Osterholm's *CIDRAP*. He can now what, eat dead crow that died of bird flu?

VR: He will never eat crow. What is he to say, "I don't like any of these results?" That's ridiculous. Laurie Garrett was there, and she agreed with him. The 50% fatality rate, nobody had looked for asymptomatic infections. Peter argued that in the countries where they have

a lot of poultry farming, people don't seek any medical care. If you're not sick, you're not going to do serological surveys. There's clearly potential for a lot of asymptomatic infection. Basically, the point is it brings down the case fatality rate.

DG: Yes. I think it's important to realize that unless you do a serology study, some more studies, usually we start off with these super high case fatality rates, and that's what it is. It's a case fatality rate, but it's not an infection fatality rate.

VR: That's right.

DG: Maybe a little humility there from -

VR: Dr. Osterholm.

DG: [laughs] All right. We read in *CIDRAP*, ready for this, "Avian Flu Strikes Turkey Farms in Dakotas, Large Egg Facility in California." I think particularly with the U.S. Thanksgiving on the horizon, I like to focus on the outbreaks in the turkey farm. In LaMoure County, North Dakota, a commercial turkey farm with 24,700 birds was hit. In McPherson, South Dakota, a facility with 63,800 birds affected. South Dakota also had a detection last week on a turkey farm with 56,300 birds. Ottawa County, Michigan, 62,200 birds on a turkey farm impacted.

Elsewhere, two large poultry outbreaks reported in Indiana. Two flocks were hit affecting 43,800 birds total. Last week, California's Sonoma County reported a large outbreak at a commercial duck breeder farm, and now the same county reported an outbreak at a commercial table eggs layer facility with 231,000 birds affected.

VR: What's a table egg, Daniel?

DG: I don't know, actually. You want to Google that and tell me what that is? What is a table egg? I'm thinking they're eggs that you serve at a table or something.

VR: I guess they are fresh, unfertilized eggs sold in their shell for human consumption, as opposed to fertilized, hatching eggs intended for making chicks.

DG: All right. I guess most of the eggs we eat are probably table eggs.

VR: Yes, you don't eat a fertilized egg.

DG: Every so often, you crack an egg, and there's blood in there and you're like, "Oh, what happened there?" All right. We hear from Israel, and this touches home in the measles section now, that two vaccinated doctors ended up contracting measles from an unvaccinated child with measles.

VR: Wow.

DG: That's not fair. Come on. We work really hard. We're trying to do everything we can to take care of folks. Now, these doctors end up getting sick because people decide not to vaccinate their kids.

VR: It says they contracted measles. I don't know what that means. Did they get a rash?

DG: Yes, I guess how sick did they get. That's the nice thing about being vaccinated.

VR: It says here, because both were vaccinated, they developed only a mild form of measles. The vaccine is working, right?

DG: Yes.

VR: They probably are taking care of the case and getting a lot of virus spewed at them.

DG: Yes. The exposure has got to be quite something. You take this two ways. One is that's not nice, that the docs ended up getting a mild case of measles. You also take it, "Hey, these vaccines work. The doctors only got a mild case of measles."

VR: Daniel, if you were treating a child with measles, wouldn't you wear a face mask?

DG: We do because it's the whole N95. You want to use the -

VR: If you have a known case -

DG: Yes, infectious respiratory particle transmission.

VR: Protect yourself.

DG: You're not necessarily going to know ahead of time. As we talked about previously, what is it, 30% of measles cases don't even have a rash. We didn't know that. We thought, "You always get a rash, and that's when you're most contagious." We realize now you could have measles and not even have that rash. We are getting updates on numbers of cases. We're up to a total of 1,681. That's up from 1,648 from last week. Another 30-plus cases. If we look at Canada, we're in week 43, another 29 new measles cases, up to 5,138. Yes, pretty soon, I think it'll be this month, and then in January, both Canada and the U.S. are probably going to lose their measles elimination status.

VR: That's embarrassing.

\DG: It is.

VR: Unnecessary. It's completely preventable. Embarrassment, I understand, is not enough motivation, but measles can make you very sick, as we have discussed a lot.

DG: All these kids, that immune amnesia. Not only are we worried about what's happening right now, but these thousands of kids, in the next two to three years, increased risk of all kinds of problems. All right. It sounds like we might be getting a little bit of flu activity. We're starting to hear some whispers, but I'm really predicting that's going to be a big thing this December. We'll see how that pans out. We're not getting a lot of data, so we're having to keep an eye on the WastewaterSCAN data to see what's happening there.

VR: I thought we were going to have an early flu year.

DG: I think of that as early, starting to hit us in November and then really rocketing in December. What I always worry about is the post-Christmas, post-New Year's, or even worse, is you get it in March after everyone's immunity is starting to wane. I'm still going with early. We are starting to see a little bit of uptick in COVID activity, so we'll see where that goes. Unfortunately, we don't get that nice curve. That's really why we want the government to open, so we can get our curve back.

VR: That's one reason, yes.

DG: Lot of other ones.

VR: We'd also like safe flying in airplanes, too.

DG: People to be able to eat in our country. What is it? 30 million, 40 million people in America face food insecurity without government assistance.

VR: While we're at it, can we get people affordable healthcare? This is ridiculous.

DG: Yes. This one I really like because this seems to be a recurring issue. I think it's really important that at least there's one place where we can have an evidence-based discussion. This is this question of to vaccinate or not vaccinate the young. That's the question. We have this article, 'Vascular and Inflammatory Diseases After COVID-19 Infection and Vaccination in Children and Young People in England: A Retrospective Population-Based Cohort Study Using Linked Electronic Health Records," published in *The Lancet Child & Adolescent Health.*

The goal of this investigation is to look at the incidence of severe diseases following COVID-19 infection versus whatever COVID-19 vaccination-related adverse effects. I just wanted to make sure. I don't know if I can find out. Are the bots listening? There's going to be a whole bunch of comments there on our YouTube about how we never talk about vaccine adverse events. We're discussing vaccination-related adverse effects. All right. Is that going to affect the bots, Vincent? No?

VR: Yes, I don't think so.

DG: I don't know how those actually work. These are the results of a retrospective population-based cohort study where they analyzed whole population-linked electronic health records for all individuals in England aged younger than 18, registered with a general practitioner with known age, sex, region of residence between January 1, 2020 and December 31, 2022. The outcomes they're going to look at are arterial thrombotic events, venous thrombotic events, thrombocytopenias, that's low platelets, myocarditis or pericarditis, and inflammatory conditions. The COVID-19 diagnosis was defined as the earliest record of a positive SARS-CoV-2 PCR antigen test or COVID-19 diagnosis in primary care or secondary care records.

The COVID-19 vaccination was defined as the earliest documented receipt of the BNT162b2 vaccine. That was the dominant vaccine. The Pfizer BioNTech was the vaccine that was basically being used. Then they're going to do adjusted hazard ratios for all of the outcomes. Now, at this point, we don't know the results. I've already decided I'm going to discuss this. However this comes out, we have to live with the data. Hope people on the other side who go into this with an agenda hear. That's the way science works. You do the study and then you live with whatever the results are.

VR: You do the study properly, Daniel, right?

DG: Actually. You do the study properly to get the answer, not properly to get your answer. They're going to look and we're going to ask this question, are the risks of vaccination-related adverse events higher than the risk of COVID? Ultimately, are you doing your best by

your kids by protecting them with vaccine or not vaccinating them? Here are the results. Huge numbers here. 13,896,125 individuals younger than 18, split almost 50-50, female-male. Predominantly white, 71.7% white. You end up with 28.1% with a COVID-19 diagnosis. First, let's go through what happens with COVID.

COVID-19 diagnosis, compared with no or before diagnosis, was associated with a higher risk of arterial thromboembolism. Adjusted hazard ratio of 2.33, so more than doubling of your risk of an arterial clot. Venous thromboembolism, 4.90. Almost a five-fold increase in ending up with a venous clot. Thrombocytopenia, having your platelet levels drop, 3.64. A three to four-fold increase in that. Myocarditis or pericarditis, your risk is going to go up 3.46. Three to four-fold increase when you get COVID. This is the most striking. Inflammatory conditions, almost a 15-fold increase. Just pointing out, COVID's bad, and we're talking about - these are kids. This is just the first week after diagnosis.

That incidence is going to actually remain elevated for about 12 months for a number of these issues. What about vaccines? Now we've got 9,245,395 individuals aged between 5 and younger than 18, eligible for vaccination. Again, the equal split you get there. We're going to end up with 6 million or 72.3% whites. It's our same demographics. 3,407,560 are going to receive vaccine. COVID vaccination, compared with no or before vaccination, the only elevated risk we saw was the well-described, well-known myocarditis or pericarditis within the first four weeks, and that's an increased risk of 1.84.

Six-month absolute excess risk for myocarditis or pericarditis was 2.24 per 100,000 individuals after diagnosis versus 0.85 after vaccination. I just want to repeat that, really clarify. We've got all those other issues that people are getting, that the kids are getting with COVID. Over six months, COVID-19 infection led to 2.24 extra cases of myocarditis or pericarditis per 100,000 kids, compared with 0.85 extra cases per 100,000. This is almost a four-fold higher risk with infection versus vaccine. I should also point out severity, which we don't really talk about. The severity that we're seeing with infection is much more severe, where the myocarditis we see in most cases with the vaccination lasts less than a day, resolves on its own.

VR: Also, they didn't do this in this study, but the first dose has the highest association with myocarditis, and it goes down further after that.

DG: Yes, so that's the thing, too, that at this point in time, we're not seeing myocarditis or pericarditis with boosters. The risk is close to zero where we're still seeing all these issues with COVID. Really nice figure. There's this nice Figure 3. We can really look at arterial thrombotic events, venous thrombotic events, thrombocytopenia, myocarditis or pericarditis, you can clearly see that vaccination is much safer than letting your kid be unprotected and get COVID. Oh my gosh, look at the inflammatory conditions, particularly the youngest kids. You look at the youngest kids here when they include the 0 to less than 18. That's more than a 30 adjusted per 100,000.

VR: There's no question. In every case, the vaccine is far better than getting natural infection.

DG: Yes. That's got to be the conclusion because I know for our poor pediatricians out there, parents are coming in, they've "done their own research," decided not to vaccinate. This is a great study to talk about. Say, you know what, you're being a better parent. You're making a better decision for your child if you vaccinate them versus leaving them unprotected.

Children and young people have these high risks. Vascular inflammatory diseases, particularly high risk in the first 12 months after that diagnosis. The risk of myocarditis and pericarditis is much less than with that infection. Also, the severity is significantly less.

VR: What's the current CDC recommendation for kids under 18?

DG: We do recommend. They still recommend the vaccine.

VR: Without any healthcare issues, right?

DG: They have that caveat for people at increased risk. They did step it back, unfortunately.

VR: From 4 to 8, what is the lower limit, six months?

DG: It's six months to - I think it's five years of age is the one group. I hate to bring up the ACIP recommendations. I think it's pretty clear that the data, the science recommends everyone getting the vaccine.

VR: Of course.

DG: All right. Now, this comes up again also. Paxlovid. You get sick, you get COVID, you're at risk of progression. Does this dangerous medicine, this dangerous expensive medicine, is it worth giving to our patients? Oh my gosh. How many studies do we need to, how many hundreds of studies do we need to go through? We have another one. Just to keep it fresh, "Real-World Effectiveness of Nirmatrelvir/Ritonavir in Preventing Coronavirus Disease 2019-Associated Hospitalization Prevention: A Population-based Cohort Study in the Province of Quebec, Canada," published in *CID*. In the U.S. last year, we had hundreds of thousands of people end up in the hospital. We had tens of thousands of people die.

The question is, "Could we have reduced that number of people ending up in the hospital? Could we have done something?" These are results of a retrospective cohort study of severe acute respiratory syndrome coronavirus-2 infected outpatients between 15 March and 15 October 2022. They're using data from the Quebec Clinical Administrative Databases. A total of 14,756 treated outpatients were matched to controls. Regardless of vaccination status, Paxlovid treatment was associated with a 74% reduced relative risk of hospitalization.

VR: As you'll see in the letters today, we have physicians who continue to insist that it's not necessary. It doesn't work anymore.

DG: As I mentioned, this is regardless of vaccination status, regardless of age. It's across the board. It does make a difference. Just be honest with your patients. If your patient asks, "Hey, I'm sick, is there anything I can do?" There is, and it's evidence-based. Get your knowledge from the literature. Don't get it from your favorite social media or news channel. All right. We have some fun stuff here to close us out. Late phase, Long COVID. Remember that whole IgG4 class switching stuff? Remember that?

VR: I do.

DG: They're like, "Oh my gosh, this is really bad." A lot of us said, "I don't know. Is it really bad? Maybe it's good." We have the article, "SARS-CoV-2 Spike-Specific IgG4 Class Switching Associates with Clinical Recovery in Long COVID," published in the *Journal of Infection*. It actually turns out that maybe this is good. It looks like people that class switch actually do

better. They go ahead. They prospectively enrolled 105 long COVID patients at a specialized post-COVID clinic in Tokyo, Japan, between November 2022, January 2023. all the patients meet the WHO criteria for post-COVID-19 condition.

They had paired serum samples at baseline, six-week follow-up, no reinfection or vaccination during the observation to confound things. Of 105 patients, 45.7% showed clinical improvement during the observation period. They're doing these scores, basically calculating that improved patients demonstrated significantly lower serum IgG1%, higher IgG2%, and higher IgG4% compared to the non-improvers. There's a really nice figure that breaks this down. Basically, you get this enhanced IgG4 class switching. You can end up with 66.7% improvement versus 40.5% in the other patterns.

VR: What about acute diseases, that make a difference? Probably, if it's your first infection, it's not going to come up until later.

DG: It does take time. That's actually the whole class switching thing. You're going to get IgM, and then you're going to switch, and then you're going to switch to specific subclass of IgG.

VR: Of course, this is an association. It doesn't mean anything. That is true. It's a suggestion that IgG4 might play a role in recovery. You could do an experiment, but we don't have an animal model. That's the problem for Long COVID, right?

DG: Yes, that's what you really need. You need to tie this in mechanistically. This is a correlation. It's certainly a correlation that goes back to that original question, is it bad? They were pretty sure the sky was falling, this IgG class. It was all the anti-science, anti-vax people were like, "Look how bad this is." This doesn't look bad.

VR: In the study where they said it was bad, this was induced by vaccination?

DG: It looks like if you're vaccinated, you have a little bit of a preferential towards this IgG4 class switching. We don't know. This might be part of the mechanism for why vaccines can help people or protect people from Long COVID. Yes, you're completely right. Now, we need to dive in. Is there any way to induce this and see if there is a causal connection here? There are a couple of studies, this whole microbiome. I threw in this one. Part of it, it's a little bit confusing. I want to make sure I point out what's going on here.

The title. Let's start off with the title. “Efficacy of *Lactococcus lactis* Strain Plasma in Patients with Mild COVID-19: A Multicenter, Double-Blinded, Randomized-Controlled Trial (PLATEAU Study),” published in *Infectious Diseases and Therapy*. Now, I hate the name *Lactococcus lactis* strain plasma because it sounds like, "Oh, can I get the plasma?" It's like, "No, this is just like a bad name."

VR: I agree.

DG: A bad name for a type of bacteria. Let's just say efficacy of a lactococcus lactis strain. I'm going to just leave plasma out because it's confusing. The PLATEAU Study enrolls 100 folks with mild COVID-19 during Omicron BA.1 endemic period. They either get the *Lactococcus* or placebo in a one-to-one ratio observed for 14 days. Primary endpoint was change in score of these eight subjective symptoms, fatigue, anorexia, headache, cough, shortness of breath, chest pain, smell, taste disturbance. They've got some secondary

endpoints. Included each symptom, SARS-CoV-2 viral load, and the plasma cytoid dendritic cells, the little PDCs. Am I getting that right? Am I pronouncing that wrong?

VR: PDC.

DG: PDCs.

VR: Sure.

DG: I want to just make sure that they're not plasma cytoid dendritic cells.

VR: It's right. That's exactly what they are.

DG: Plasma cytoid dendritic cells. All right. My immune buddies are going to give me a hard time for stumbling with that. The primary endpoint did not show between group differences. However, the proportion of patients without smell and taste disturbance was significantly higher in the *Lactococcus* group on day 13. It is interesting. I'm not sure how compelling this data is. Some interesting stuff where people are now starting to look at what was the microbiome when you got infected? Does that potentially affect your outcome? Are there things we can do with the microbiome to potentially help with recovery? I want to get that out there.

"Preventive Effect of Vaccination on Long COVID in Adolescents with SARS-CoV-2 Infection," was published in *Vaccine*. Now, I put this here because this is one of those things to have in that discussion when the parents come in or maybe the adolescent is involved as well. Adolescents do listen to the clinicians. A nice research study we did on that, and we're going to probably be repeating it coming up to see if that's changed over time. Why are we vaccinating adolescents and children? We had a list of really severe outcomes that we just talked about, but really the most concerning outcome, the highest incidence outcome, is Long COVID.

A lot of cohorts, we're seeing about 20% incidence. That's a lot. Those one in five kids get COVID, it's a month, two, three, four months later, still not back at 100%. Really the question here, straightforward study and compelling results. Participants were recruited from over 60 U.S. healthcare and community settings. The exposure was the COVID-19 vaccination, six months prior to infection, and then the outcome was Long COVID defined using this Long COVID research index. We got vaccinated, 724. Unvaccinated, 507. The adolescents are matched on sex, infection date, enrollment data.

The risk of Long COVID was 36% lower in vaccinated compared to unvaccinated participants. What are the actual raw numbers here? Infected adolescents, the risk of Long COVID was 20.7%, so about 21% in the unvaccinated and 13.3%, so about 13% in unvaccinated, so 36% reduction. The risk of severe Long COVID, 6.1% in the unvaccinated, 4.7% in the vaccinated. Again, we're seeing a 23% reduction if you're looking really at severe Long COVID.

VR: Should get vaccinated.

DG: Yes. No, just when you're having that discussion as a parent, the best thing you can do for your child to keep them safe, because we know you want to be a good parent, and this is the information. This is the truth. This is not the partisan agenda.

VR: Today, we find that if you're pregnant, get vaccinated. If you want to prevent Long

COVID in an adolescent, get vaccinated.

DG: If you're an adolescent, the risk of myocarditis, if that's what you're worried about, it's much higher without vaccine. All right. No one is safe until everyone is safe. We're in our favorite time of the year. I feel like there should be a jingle. We will have you start singing that, our most favorite time of the year. November, December, January, we do our *MicrobeTV* fundraiser, doubling your donations, trying to get a maximum donation of $20,000 for *MicrobeTV*. Go to parasiteswithoutborders.com and click on the Donate button.

VR: These conclusions today about vaccinations, Dan, they're made based on the science. They're not your feelings about it. They are not an ideology. It's based on science, and that contradicts everything going on in the administration.

DG: Yes.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Dana writes, "I listen to the clinical update every week. You keep me informed and give me hope that scientific research and public health initiatives might one day become respected again. Recently, I had several doctors' appointments. I asked each provider if they were prescribing Paxlovid if someone gets COVID. All of these doctors said, 'Absolutely not.'

They said that the rebound makes people sicker than just having the virus. One doctor said that COVID-19 is milder now and there is no need to take a dangerous medication. Another said, 'If you get COVID, your body will build natural immunity, and that will be good.' Am I right that this is not what you think of COVID-19 and Paxlovid? I'm flabbergasted that a medical doctor thinks that getting COVID will build natural immunity, and that's a good thing. What are your current recommendations for prescribing Paxlovid?"

DG: Yes. The data is very compelling. We just went through another study, whether you're vaccinated, whether you're not vaccinated. If you're at risk of progression, if you're at risk of ending up in the hospital, in the study we just shared, greater than 70% reduction in that bad outcome. We had hundreds of thousands of people end up in the hospital last winter, probably going to end up with hundreds of thousands of people in the hospital this winter. We can reduce that number by 70% by just prescribing Paxlovid to the right folks.

VR: Annie writes, "Have rules regarding doctors writing prescriptions for Paxlovid changed in the last year? I'm asking because my husband and I, in our 70s, have for several years always carried Paxlovid with us when we travel. We recently requested fresh Paxlovid. I was told current kidney and liver functions were required. The back and forth of getting these would have put us well beyond the five-day window to start had we been infected. As it turned out, I did pick up COVID and had to use an expired box. Any problem with using expired Paxlovid?

The real problem is seniors on Medicare and making over $63,500 a year do not qualify for any PAXCESS help. This is now $1,500-plus med cost with us with our Part D $700 each. How are we high-risk seniors going to manage if we don't have a lot of money? As always, I'm deeply grateful for all you do to keep us informed."

DG: Yes. This is absurd, actually, on so many levels. I'm sorry. Something is broken here. First, the lack of education on the part of providers has just came up regarding the continued efficacy of this medicine. I don't think there's a problem with expired Paxlovid.

They have to put an expiration date. What they just kept doing was giving us stickers to put over the old one and make it good again. Yes, as you bring up, the access issues, the cost issues, you hate when that's a barrier.

VR: Does Pfizer keep the price high because they think it's all being reimbursed by insurance, including Medicare?

DG: There are people at these companies who calculate this cost-benefit of how to make the most money for their shareholders. I really think that drives it a lot more than, "Hey, we want to get access here."

VR: Do you know how much this prescription for Tamiflu costs, for example?

DG: It's a little over $100.

VR: This should be $100, too, right?

DG: In our perfect world, it should actually be free because just think of keeping all those people out of the hospital. As a society, it makes sense to keep hundreds of thousands of people out of the hospital. Just think how much that costs us as a country. Then all the people that end up in the hospital, and then, oh, they may not work because they may be at a certain age, but then the family is now not able to work, and you're trying to take care of the kids. Just the impact of society. We need to rethink how we're doing all this.

VR: By the way, Daniel, last night on livestream, a woman said, "I don't have a cervix. Do I need HPV vaccine?" I said, "I'm not a doctor, but there are other cancers caused by HPVs besides cervical, so you probably should get it."

DG: You've got a head and neck. Head and neck cancers. You've got an anus.

VR: That's what I told her. Sarah writes, "I'm 61. As far as I know, I never had chickenpox. I was vaccinated soon after having my first child to avoid getting it as an adult. The recommendation seems to be that everyone should get the shingles vaccine rather than trying to figure out who is actually at risk of shingles. I've been dragging my feet because I don't think I'm at risk, and there are so many reports of significant reactions to the vaccine. Now, I'm hearing about other possible protective effects of the shingles vaccine. I'm thinking there might be more reason to go ahead and get it. What are your thoughts?"

DG: Yes, go ahead and get it. [chuckles] It is interesting. We'll go through this. There is a reactogenicity to the vaccine. It's protein-based. A lot of people get the shot. This was when people started with COVID shots were like, "Hey, it could be like getting that SHINGRIX shot where maybe you got to plan that, next day you're not going to feel so hot." We're talking about a day of not feeling so hot, then let's say, three months later, another day of not feeling so hot. Then we've talked about it as the dementia vaccine. Also, if you did have chickenpox when you were younger, it is a very effective shingles preventative, which is great. You're over 50, we do recommend it.

VR: Philip writes, "Please tell us about the new Moderna mNEXSPIKE vaccine for 65 and older."

DG: Sure. We talked about this a little when it came up as options. This was actually based upon some efficacy, not just antibody levels, but efficacy. It was about a 9% lower risk of

symptomatic COVID compared to the other. It tends to have less RNA, so maybe not going to have that same cancer boosting if you're doing your immune therapy for your cancer. It's another option. There is that data suggesting it might have a little bit of benefit compared to the prior Moderna shot.

VR: Instead of the whole spike, it's mRNA encoding the receptor-binding domain, right?

DG: Yes.

VR: Yes. Liping writes, "I have a follow-up regarding shingles vaccine for over 40-year-old The Chinese version of a shingle vaccine was tested for people 40 years old and up." Provides a link to that. "Efficacy and safety. A multi-center randomized double-blind phase 3 clinical trial. It's about 57% effective at preventing shingles. "The Chinese vaccine is live attenuated, so different from SHINGRIX. Can I extrapolate the safety profile from the Chinese clinical trial, safe for 40 years old and above? Can I extrapolate it to all shingles vaccines?"

DG: No. It's different. This is live attenuated vaccine, which is similar to the Zostavax that we used to use, which is actually pretty much what we're using for the kid vaccine, the chickenpox vaccine for the kids. The SHINGRIX is a protein-based vaccine. We actually think of it as safer, but more reactogenicity. Yes, you're really comparing two different vaccines there. As we talked about, when it came to dementia studies, we actually had a comparator where it looks like the protein-based SHINGRIX might be better for that purpose.

VR: SHINGRIX is in the 90s at protecting against shingles, whereas the vaccine made in China - Shouldn't say the Chinese vaccine. That's no good. The vaccine made in China.

DG: China-developed.

VR: China-developed is 57%.

DG: Similar to the Zostavax.

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

DG: Thank you. Everyone, be safe.

[music]

[00:51:53] [END OF AUDIO]