**This Week in Virology**

**TWiV 1070 Clinical Update**

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Guest: Daniel Griffin

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pdf of this transcript available (link)

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

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From MicrobeTV, this is *TWIV, This Week in Virology*, Episode 1070, recorded on December 15, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from Panama, Daniel Griffin.

**Daniel Griffin:** Hello, everyone.

**VR:** Don't have a bow tie on. I can't ask you what your bowtie looks like.

**DG:** I know. I know. People commented about that. “What's different about Dr. Griffin?” when they looked at my video from last week. Let's get right into it because I'm recording from a remote part of Panama. My quotation: “The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom.” That's Isaac Asimov.

**VR:** It's so true, right?

**DG:** Unfortunately, so true. Yes. I just thought I would give people a little bit of an update, now that I've got slightly better bandwidth, where have I been for the last couple of weeks? Though a week ago, ago, as opposed to this most recent week, I was up in the mountains of Eastern Uganda at the Foundation International Medical Relief of Children clinic on the Uganda-Kenya border, working with a great team there. Just so nice to see how well the clinic is doing. It's a real solid clinic connected with the government and just great work being done there.

Then I ended up on a flight through Amsterdam, Panama City. Then this last week I spent in a couple of remote isolated villages, several hours by boat. Apparently, it's the rainy season here as well as it was in Uganda, and it just rained and rained and rained. I am finally dry. At some point you just give up, I guess. Sleeping in hammocks, using the same facilities that the local people use.

My daughter Daisy was with us. She was under the weather in a couple of ways, both under the torrential rains and in other ways, but here working with an organization, Floating Doctors, where they go out to these villages and provide medical care. It's been a wonderful experience, but here we are for our clinical update. I'm going to start, Vincent, with polio.

**VR:** Excellent.

**DG:** Still in the headlines as we keep hearing about cases throughout the world. I actually updated a bit of this when I was in Amsterdam en route from Uganda to Panama, so it was December 9th when I was doing that. We read that Pakistan's last case, its sixth of the year, was reported in the Khyber Pakhtunkhwa, the country's hotspot. We've actually discussed that before. GPEI said intensified efforts are underway in the province, focusing on its southern region to stop WPV1 transmission, wild polio virus type one transmission.

Just to give people a little bit of an overview of what's going on here, I sort of went through Pakistan. We have one wild polio cases, 20 wild polio type 1 positive environmental samples, Algeria. We've got one circulating vaccine-derived polio virus type 2 positive environmental sample in the DR Congo, the DRC, seven of the circulating vaccine-derived polio virus type 1 cases. One circulating vaccine-derived polio virus type 2 case, Kenya. We've got two, let's make it simple and say vaccine-derived positive environmental samples, Mauritania, Nigeria, Somalia. This just is continuing.

I think I just want to keep this on people's radar because there are people who are saying, "Oh, why do I need to go get a polio vaccine? Polio's gone. It's not a thing." Polio is not gone. Polio is a thing and just really encouraging people to take advantage of the protection. Vincent, did you have any comments?

**VR:** Some of these are wild polio, which is, that is just a lack of immunization in Pakistan. The others are all circulating, vaccine-derived viruses. The way they control those is to go in with more OPV, which makes more circulating vaccine-derived viruses. It's an endless situation. The solution would really be to use IPV. It's injectable and that presents other logistics, and it would allow polio virus to circulate indefinitely. There are all kinds of problems here.

**DG:** Yes. Challenges, but I think there is momentum towards injectable polio virus vaccination. Let's see how that goes. The next article is really a warning for clinicians. I was actually surprised by this. As much as I say Occam was not a doctor and a patient can have as many diseases as they please. The article, “Mpox and Chickenpox Co-infection: Case Series from Southern Nigeria,” published in *JID.*

It turns out that in this retrospective cohort analysis of patients with mpox, 28.6%, more than a quarter of them had a co-infection with chickenpox. You see those vesicles, multiple stages of development, and you think, "All right, this is just good old chickenpox." You do not bother to test, but move forward with the confidence of a feral dog, and next thing you know others are getting the mpox. It really reinforces how important testing is to medical diagnosis.

We were taught this like, OK, mpox, they're going to be same stage of development, thicker roof, more purulent, but once you start seeing those classic chickenpox, different stages of development, thinner vesicle, you think you have a diagnosis, but we really need to reinforce, we need that testing to help us. That's just huge the fact that about one in three, one in four had chickenpox and mpox.

I will say it is the season for vaccines. RSV-associated hospitalization rates remain elevated among young children. They're increasing among older adults, and of note, only about 16%, only about 16% of adults, 60-plus, report having received an RSV vaccine. Over 80% are not protected. Just talking about vaccination for adults, but what about nirsevimab or Beyfortus for the babies?

Some of our listeners have written in, a lot of people are raising the alarm. People are listening. Thanks to everyone for speaking up. We just heard that in January, next month, AstraZeneca, Sanofi to supply another quarter million more RSV infant shots to U.S. market. The additional supply means the company will deliver 1.4 million doses of the drug in the U.S. this year alone, over 25% more shots than they had originally planned. Really doing a great job of communicating and people really appreciating the advantage here.

Why do we care so much? RSV is the top cause of hospitalization among infants. One percent to 3% of children under 12 months of age end up hospitalized in the United States each year. That's data from the American Academy of Pediatrics. Where are we with weekly RSV? We may be reaching the peak here for RSV. We'll see in the next week or so, see what the impact of the gathering is for the holidays here, during December in many parts of the world, as well as here in the U.S.

Flu, have all our listeners learned that when you hear about vaccine effectiveness, you need to ask, effective in preventing what? The article, “Vaccine Effectiveness Against Influenza A-associated Hospitalization, Organ Failure and Death: United States, 2022-2023,” was recently published in *CID*. To understand effectiveness of the 2022-2023 influenza vaccine against influenza, associated hospitalization, organ failure and death, a multi-center sentinel surveillance network in the United States prospectively enrolled adults hospitalized with acute respiratory illness between 1 October 2022 and 28 February 2023.

Using the test-negative design, vaccine effectiveness estimates against these endpoints were measured by comparing the odds of current seasonal influenza vaccination in influenza-positive case patients and influenza-negative, SARS-CoV-2-negative control patients. A total of 3,770 patients, including 714 flu cases, 33% vaccinated, 2,993 influenza and severe acute respiratory syndrome, coronavirus two negative controls, 49% of those vaccinated. Vaccine effectiveness against influenza-associated hospitalization was 37% and varied by age, 18 to 64, it was 47.

When they got to 65 and older, it was only 28%. Vaccine effectiveness against more severe influenza-associated outcomes included 41% against influenza with hypoxemia, 65% against influenza with respiratory, cardiovascular, or renal failure treated with organ support, and 66% against influenza with respiratory failure treated with invasive mechanical ventilation.

Now, vaccine effectiveness against influenza-associated death was, I'm going to throw in my own, “only,” 48%. However, the number of influenza-associated deaths was limited, so we have a wide confidence interval here. My conclusion, we need a better vaccine.

**VR:** You still should get this one because it's better than nothing, right?

**DG:** It'd drop your risk of dying in half. That's big.

**VR:** Yes, pretty good.

**DG:** People always say, "Oh, I got that flu shot, I still got the flu." What is my next question?

**VR:** "Did you die?"

**DG:** "Did you die?" You can reduce your risk of death in half, that's worth doing. When should you do it? If you haven't done it, get out there and get it done because we are still seeing a significant rise in the influenza activity.

**VR:** Yes, it's really going up there now in December.

**DG:** Yes, it's really getting that exponential rise, right?

**VR:** Yes.

**DG:** All right. COVID update. I take these numbers from BNO News. A lot of our reporting is sort of falling down. What is going on with COVID? Cases are actually up, in-hospital is up, deaths are back up to 1,682. About a 10% increase in the average weekly deaths. That really goes hand in hand with what we're seeing with the wastewater. Really seeing continued rise in the Midwest, the Northeast, the other parts of the country are rising as well. Beginning to think this copies per ml of sewage may have an upper limit of normal, or upper limit of 1,200. We'll see. We're basically as high as the scale goes, and we'll have to see, can they go any higher?

All right. Children, COVID, and other vulnerable populations. This is really hitting on a theme that I hope our listeners are getting, which is just how much you can do during that last trimester of pregnancy to protect the newborn. The article, “SARS-CoV-2 Neutralizing Antibody Titers in Maternal Blood, Umbilical Cord Blood, and Breast Milk,” was published in the *Journal of Perinatology*. Really straightforward design. A hundred women enrolled at admission for delivery. They looked at previous SARS-CoV-2 infection defined by anti-nucleocapsid antibodies. Discussed that before, how sensitive that might be or not.

Levels of the neutralizing antibodies and binding antibodies against spike receptor binding domain were measured in the maternal blood, the cord blood, and the breast milk. They found that the levels of neutralizing antibodies in cord blood and milk correlated with maternal levels and were higher in cord blood than maternal. Spike protein binding antibody levels correlated with neutralizing antibody and suggested that SARS-CoV-2 vaccination near delivery may boost antibody mediated immunity in the peripartum period. They point out that this study demonstrates that neutralizing antibodies are passed transplacentally and into the milk. They did find that maternal neutralizing antibodies were higher after vaccine and infection than vaccine alone, but they really waned rapidly, and you can see this data in Figure 1 in the paper.

Transmission. I just want to reinforce it's around the holidays. Those of us in healthcare across almost all the facilities when we're patient-facing, we are wearing masks. We are trying to keep our patients safe. I know there's been a lot of loss in momentum. I've been on flights recently and not seeing a lot of masks. Just remember, the surgical masks really protect others from you catching those droplets. In more higher-risk situations, N95 respirators and the like should be considered.

When I do these clinical updates with Vincent, I feel very safe that Vincent's not going to transmit over the airwaves.

**VR:** [laughs] Yes, probably not.

**DG:** The advantages of telehealth and Zoom calls.

All right, testing. I got a lot of questions about the article. Can you imagine this? I'm in remote Uganda and Panama and people are sending me messages? Dr. Griffin, what do you think of this article? The article, “COVID-19 Rapid Antigen Tests With Self-collected versus Health Care Worker-collected Nasal and Throat Swab Specimens - A Randomized Clinical Trial,” published in *JAMA Network Open*.

Now, I have a few issues with how this article is written. Let me just right up front. I like when authors are a little less obvious about their agenda and a bit more focused on their data. Let us dissect what I will call the misleading sentence. Health authorities in the UK, Canada, and Israel recommend including a throat specimen for reverse transcriptase polymerase chain reaction, (RT-PCR), SARS-CoV testing, while the U.S. FDA has only authorized rapid antigen tests for use with nasal specimens and advises against using throat specimens. What a sentence.

Two different things are going on here. Perhaps the honest way to state the truth here is that in the U.S., we only have rapid antigen tests that have been approved based upon evidence supporting their sensitivity and specificity for nasal specimens. We previously discussed that the new variants may be detectable at a slight bit earlier time point using a throat PCR. The question here is about rapid tests. Let's not compare PCR and rapid tests in the same sense. These are results from an investigator-initiated multi-center randomized clinical trial conducted at two public COVID-19 test centers in Copenhagen, Denmark, from February 15 until March 25, 2022.

The participants had four specimens collected. Two health care worker-collected nasal and throat swab specimens for RT-PCR testing. Afterwards, two nasal and throat swab specimens randomized to either self- or health care worker-collected for rapid antigen testing. Flocked nasal swabs from a rapid antigen test kit. We want to know which one. Standard Q COVID-19 antigen test by Biosensor Incorporated were used for both nasal and throat specimen collection for rapid antigen testing in the intervention and control groups. The detection rate was 86.6% for a nasal specimen and 94.2% for a throat specimen.

The median CT value was lower for a health care-worker collected nasal specimen - remember, that means they're getting more - than a healthcare worker-collected throat specimen. They actually compare 16.7 versus 22.8. That's about six cycles there for a single specimen. The mean sensitivity for rapid antigen testing was lower for a self-collected throat specimen than for a health care worker collected throat specimen. It's actually significant here, 53.7. When the health care worker does it, 69.4%. Comparable for self-collected and health care worker collected nasal specimens.

They reported that no difference was found between self-collected throat specimens versus nasal specimens for rapid antigen testing, 53.7%, with a confidence interval of 48.7 to 58.7 versus 57.9, confidence interval 52.9 to 62.9. Not a statistically significant P-value. Then they tell us that in a subgroup analysis of participants with symptoms revealed that self-collected nasal specimens had significantly higher mean sensitivity than self-collected throat specimens, 71.5 versus 58%. Really encouraging was that this particular rapid test, the specificity was greater than 99.5 for the rapid antigen testing of all sample types. Because we've talked about how some of these kits can give us a lot of false positives. You drink a soda, you have juice, et cetera.

Let's pull all this together so that we're not just reading the headlines in the media. The authors point out that these results demonstrated that the throat sample technique is more challenging than obtaining a nasal sample, as they found a lower sensitivity and a higher number of inconclusive rapid antigen tests for self-collected throat specimens compared with health care worker-collected throat specimens.

In contrast, no difference was found when the health care worker-collected and self-collected nasal specimens were looked at. The authors discussed in their discussion section that current tests are only authorized with nasal specimens and that redesigning the current rapid antigen test to include throat specimens will increase medical manufacturer costs and the complexity of home-based rapid antigen testing.

I'm also going to leave in a link in our show notes to the collection instructions in the supplementary material. In short, it is a reasonable bit of science here, and if companies are willing to spend the time to demonstrate that their tests can be validated for throat testing, that is great. As we know, there's virus, there's viral RNA, there's viral antigens in the throat that could be detected. We just need to know what tests do not have a specificity issue so we don't end up with an excessive number of false positive throat tests.

**VR:** Daniel, is there any need to validate a throat test when the nasal swab looks great?

**DG:** The nasal swab works. It's going to show up, 10, 12 hours, sort of same window. I'm not sure there's really a clinical need for this. I think what we're really seeing here is a lot of people, social media, "I've been saying this," and it's like, "And what have you been saying?" [laughs]

**VR:** It's much easier to get a nasal sample than a throat sample, isn't it?

**DG:** If you go and actually follow the links that I put in here, they're sending people mirrors, they've got cartoons, this is where you need to be swabbing. You're swabbing in the back of your throat, you're swabbing on the palatine tonsils, who knows what those are? Yes, it just, you're just making something. We already have an issue, right? People don't want to test. Now we're like, "Oh, we're going to make it more and more complicated."

I guess what I would just say, the FDA has not validated tests for throat samples, right? Don't just go taking one that's validated for the nares and start rubbing the back of your throat and then thinking what to do with a positive test. If you really are high risk and whatever, we can do PCRs, et cetera.

**VR:** The swabs for the nasal kits are pretty short. You'd have trouble getting it back there.

**DG:** Yes, that's also the weird, and they're different swabs, so the ones that we do, like the anterior nares and the throat, they're bigger ones. The ones that we're doing, the deeper brain biopsies are smaller ones. There's actually a lot of, I think we've been putting a lot of challenges on people, and this, I almost worry that we might do more harm than good by just adding complexity to something.

All right. Ventilation transmission. While this came out on December 5, I did want to discuss this article, I was saving this. “Four Methods for Monitoring SARS-CoV-2 and Influenza A Virus Activity in Schools,” published as a research letter in *JAMA* *Network Open*. The cool part of this study that I want to discuss is the air sampling. In this study, air samplers, ThermoFisher AerosolSense, were placed in communal gathering spaces, cafeterias in seven schools. Cartridges were analyzed twice weekly for the presence of influenza A virus and SARS-CoV-2. Influenza A virus and SARS-CoV-2 genetic material captured in air samples and detected using QRT-PCR assays targeting the influenza A virus M gene, SARS-CoV-2 N1, N2, and RNaseP as an internal control.

They found that air sampling provided equivalent results to home-based specimen collection using RT-PCR cause-specific absenteeism monitoring and school-based rapid antigen testing. Kind of cool, you just sort of set these things up and you pull the cartridges out and it gives you a, instead of just trying to find in the wastewater, this might actually even work in communities where they don't necessarily have wastewater, just basically sampling the air.

Moving on to COVID early viral phase. No big movers here. You get acutely ill, you've got that positive test, hopefully you're using the test correctly. High-risk individuals, number one, Paxlovid, remdesivir, molnupiravir, convalescent plasma, isolation for the infected, and avoid doing those harmful and useless things. Second week still very similar, steroids, anticoagulation, pulmonary support, remdesivir, but a little bit new on immune modulation, tocilizumab, but what about baricitinib?

The article, “Efficacy and Safety of Baricitinib for the Treatment of Hospitalized Adults With COVID-19: A Systematic Review and Meta-analysis,” recently published in the *European Journal of Medical* *Research*. Here, the authors searched in PubMed, Embase, and Cochrane Library databases on January 31, 2023, but what about the gray literature, Vincent? They looked closely, they report on 3,010 patients, all included studies were randomized control trials or prospective trials, no difference in 14-day mortality between the two groups.

In subgroup analysis, they found that baricitinib did not seem to improve significantly in 24-day mortality, critically ill patients. There was a faster recovery in shorter hospital stays for folks that got baricitinib, so there may still be a role there, but perhaps tocilizumab is going to be the immune modulator of choice.

**VR:** This is a JAK kinase inhibitor, right?

**DG:** Exactly.

All right, late phase. I found this article really encouraging. It's the article, Symbiotic Preparation (SIM01) for Post-acute COVID-19 Syndrome in Hong Kong (RECOVERY): A Randomized, Double-blind, Placebo-controlled Trial,” published in *The Lancet*. Why was I so encouraged? I feel like we might be pulling on the right thread. These are the results from a randomized, double-blind, placebo-controlled trial at a tertiary referral center in Hong Kong.

Patients with post-acute COVID sequelae PACS-PASC, according to the U.S. Centers for Disease Control and Prevention criteria, were randomly assigned one-to-one by random permuted blocks to receive SIM01. This is 10 billion colony-forming units in sachets twice daily for six months. Now, what is SIM01? The symbiotic preparation, SIM01, is a micro-encapsulated lyophilized powder containing 20 billion colony-forming units of three bacterial strains. There are different Bifidobacterium, so Bifidobacterium adolescentis, Bifidobacterium bifidum, Bifidobacterium longum, with three prebiotic compounds, including Galacto-oligosaccharides, xylo-oligosaccharides, and resistant dextran, which have been shown to promote the growth of these bacterial strains that are also other probiotic strains. Before we get lost in any word soup, I just want to clarify a symbiotic is defined as a mixture of probiotics, those bugs, and prebiotics, basically stuff that's going to improve their survival. The probiotics are the Bifidobacterium species, and the prebiotics, which are described as non-digestible food ingredients, help those grow.

Ultimately, we end up with 463 participants, about half of them get the symbiotic, about half of them are getting placebo. At six months, a significantly higher percent of individuals with SIM01 had alleviations in fatigue, more than twice as likely with a p-value of 0.0001, about twice as likely to have improvement in memory loss, p-value 0.0024, improved issues with concentration, about more than twice as likely to have improvements there, less GI upset, improved general wellness. These are all very statistically significant, they held up adjusting for multiple comparisons.

About 47% improvement in fatigue, 56% memory loss, 62% concentration, 30% for GI upset, 31% for general wellness. Potentially going to become available as a product from GenieBiome, maybe they'll sponsor us or something. [crosstalk]

**VR:** This is a thing you'd take orally, right?

**DG:** Yes, it's basically going to be a pro and a prebiotic, really targeting the disruption of the GI microbiome, and really impressive that it wasn't just GI, but a lot of cognitive, which goes along with some of the earlier preliminary reports we've heard.

**VR:** I just would like to see this done in a different population, because different populations have different microbiomes, right?

**DG:** That's actually, yes, you're right. What works in Hong Kong might not work in Denmark or in the United States.

**VR:** I could use better concentration for sure.

**DG:** Also be nice to sort of do some a dose, like are they just sort of hitting at 10 billion? That's always the challenge, I talk to patients that tell me, "Oh, I'm taking this probiotic." "What dose?" I'm like, "I do not know." "Is it 10 billion--?"

**VR:** Is there any negative to doing this?

**DG:** No, actually, it was really well tolerated. That's nice.

All right. Nice contrast to much of the doom and gloom. We have the article, “COVID-19 Recovery: Consistent Absence of Cerebrospinal Fluid Biomarker Abnormalities in Patients With Neurocognitive Post-COVID Complications,” published in *The Journal of Infectious Disease,* where the authors report they found no evidence of ongoing viral replication, immune activation, or CNS injury in plasma or CSF in patients with neurocognitive post-COVID conditions compared with COVID-19 controls or healthy volunteers, suggesting that neurocognitive PCC is a consequence of events that may have been suffered during acute COVID rather than sort of an ongoing process.

Now, in this study, 31 patients underwent clinical exam, lumbar puncture, venipuncture. They have healthy volunteers included. They look at CSF and plasma, severe acute respiratory syndrome, coronavirus 2, nucleocapsid, spike antigen, looked at a bunch of different markers, did principal component analysis. They didn't indicate any significant differences between the study groups in the marker set cytokines, neuronal markers, anti-cytokine autoantibodies.

All right. I'm going to get ready to wrap us up here with our last article, the “Risk of New-onset Long COVID Following Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2: A Community-based Cohort Study.” A word of warning, a slight word of warning for those who are relying on survivor immunity for protection. Here these investigators estimated the likelihood of a new onset self-reported Long COVID after a second SARS-CoV-2 infection.

They included UK COVID-19 infection survey participants who tested positive for SARS-CoV-2 between 1 November 2021 and 8 October 2022. The primary outcome was self-reported Long COVID, 12 to 20 weeks after each infection. Separate analyses were performed for those less than 16 and 16 and up. The estimated odds ratio for new onset Long COVID compared first, second to first infections, control for sociodemographic characteristics, calendar date of infection, plus vaccination status.

Overall, Long COVID was reported by those 16 and over after first infection, 4%, and after second infection, 2.4%, so an additional 2.4%. The corresponding estimates among those less than 16, quite a bit lower, 1% and less than 1%, 0.6%. The adjusted odds ratio for Long COVID after second compared to first infections was 0.72, so it is a lower risk for those over 16, but it's actually still a risk. You can still get Long COVID if you survived and didn't have Long COVID after your first infection.

I will wrap it up here. No one is safe until everyone is safe. I want everyone to pause the recording right here, go to parasiteswithoutborders.com, click that big ‘Donate’ button. I'm not sure whose donate button is bigger, ours or microbe.tv, I must check. What we're doing right now is we're in the middle of our MicrobeTV fundraiser. Whether a button is smaller or bigger, when you click our button, it doubles your donation up to a potential maximum donation of $20,000 for microbe.tv. If you like what we're doing, if you don't like what we're doing, but you want us to continue, please go ahead and support our work.

**VR:** It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Denise writes, “I would love to hear your input on receiving the COVID vaccine while pregnant after a prior infection during pregnancy. Background. I received my initial two Pfizer COVID vaccination shots in February 2021, my booster in October 2021. I then had a COVID infection, January 2022, have not received any further COVID boosters. I've been exposed to family members with COVID in the house a few times but did not have another infection myself until this past summer while pregnant.

I became pregnant in May of this year, had a very unpleasant bout of COVID in August when I was 13 weeks pregnant, much worse than my first time. I'm now 32 weeks pregnant, due in early February. Would another COVID vaccination be supportive to me and or the baby at this point, even though I had an active infection while pregnant? I'm most interested in boosting the baby's immunity and I plan to get the RSV shot in a few weeks as well. If it's not necessary, due to the infection a few months ago, I'm less inclined. Would love to hear your thoughts.”

**DG:** The timing is ideal asking this question because we really just covered the data here. That prior vaccination doses, the prior infection, these are giving you a certain antibody level. What we know is that a vaccination during that last trimester could really boost those levels and that prior infection boosted your levels. As we saw from the data, you actually have a pretty quick waning.

Ideally what you want to do is get that COVID vaccine during that last trimester. Not only is that going to boost your levels, but as we saw, that's going to boost the levels in your breast milk. That's going to boost the levels in the cord, thus boosting those levels that are going to protect your newborn. We would encourage that. I like that you're also thinking about the RSV vaccine because we have a Beyfortus shortage. Really the best thing, what we've been doing is encouraging moms to get vaccinated during that last trimester. Last thing you want to do is have your baby and then find out you don't have access to the Beyfortus.

**Vincent:** Clark writes, “Would you please tell me the source of the number of weekly deaths in the U.S. from COVID-19? As a physician, from time to time I am asked and would like a reliable URL source to reference and cite.”

**DG:** OK, excellent. Yes. It's sort of a shame during the heyday of the pandemic, right? You had Hopkins, you had so many people reporting for us. Now I've been actually looking at BNO News each week just to get some numbers to go by.

**VR:** Scott writes, “Finally had COVID after many chances. My only symptoms a day after my RSV vaccine, nausea, vomiting, and feeling achy. Took me more than 24 hours before I even thought to test. After the first 24 hours, even before Paxlovid, I felt much better. Interestingly, still on the last day of Paxlovid, I had Paxlovid rebound with cold symptoms and fatigue, evidently not from the Paxlovid.

Question one, you've talked a lot about the five-day course of Paxlovid, but how was it originally decided to treat for five days? Traditionally in medicine, we have guessed on a 10-day or seven-day or three-week treatment, and then often years later, studies are finally done to see what might actually be best.”

**DG:** Yes, so let's start with that. I think that's a great, why five days? Why not 10? Why not 15? When I went to medical school, pneumonia, we told people they had to take their antibiotics for 21 days, and then we would berate them, why are you not finishing it? If you don't finish it, we're going to have antimicrobial resistance, and the world will end. Over time, we've realized, actually, 21 was not great and probably was driving AMR.

We've realized with almost all of our therapeutics, with a few exceptions, that really three to five days is actually the window. What we've seen in a couple things with COVID, for instance, we looked at remdesivir, we looked at five days versus 10 days. Five was actually slightly better than 10 days, interesting enough. We've seen that if we wait till after 10, and viral replication has gone down, you're really not doing very much. Don't be misled by a bunch of sloughing nasal epithelial cells, with a rebound, et cetera.

The five has really been built upon a history of understanding, a history of understanding the viral kinetics, and also a bit of a history of other antivirals that we've used in this disease. I will say there's ongoing trials looking at five, 10, 15 in Paxlovid. We will see, and I'm humble enough to say that when we get that data, I will share it, and whichever way it goes, that's what I will go with.

**VR: “**Question two, I've tried to get an understanding of how and where Paxlovid works, reading some articles, et cetera. Not being a virologist, I keep wondering if it could also suppress the replication of any other viruses.”

**DG:** Yes, no, so that's a great question. Certain antivirals seem to be, potentially, pan-viral, right? If they're working on an RNA polymerase, and it happened to get some interaction with others. This is working on a protease. You'd have to be looking at other viruses that rely on a similar enough protease. What is a protease? A lot of viruses, other organisms will make really long proteins, and then just chop them up into the component pieces.

**VR:** I think this, I think Paxlovid will work on some other coronaviruses, but not as well as SARS-CoV-2, and unlikely other viral families, because the proteases are really different.

**DG:** Yes.

**VR:** Mary Ann writes, “This is a question from my daughter-in-law with an almost 5-month-old. Her sister has COVID, and she got it from her husband. She had to stop breastfeeding at six weeks to go back on a mental health medication she needed, but pumped extra during those six weeks, hoping it might be helpful. Here's her question. What I'm curious about, and I think it's a question for an immunologist, does giving breast milk once a week or twice a month provide any antibodies protection to a primarily formula-fed baby?

**DG:** As we've talked about several times, is there, are antibodies in that breast milk? There's also more than antibodies, right? There's also some cellular immune that gets transmitted across. You think the antibodies are going to be fine with refrigeration, this would be interesting to ask an immunologist about the cellular component.

**VR:** You're an immunologist, aren't you, Daniel?

**DG:** I guess that's true. I do have a PhD in immunology. I'm trying to be humble here, Vincent. No, but I do think that there is some advantage to that breast milk, as much as you're able to provide.

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

**DG:** Thank you. Everyone, be safe.

[music]

**[00:40:33] [END OF AUDIO]**