TWiV 1328 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 1328, recorded on June 4, 2026. 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: It was very crowded here at the incubator on the streets, because there's some kind of basketball game going on.

DG: Oh, and wasn't there something going on last night as well? There's a lot of sporting stuff.

VR: Yes, last night there was a basketball game, and the sidewalks were just jammed. You can barely walk.

DG: Oh my gosh.

VR: I guess that's what makes New York go, all this.

DG: That's part of what, I think, people love about New York. They love the vibrancy, all the people, things happening. Yes, it's an exciting place.

VR: It's like all the homeless people sleeping on the street too, beggars.

DG: That's one of the tough things.

VR: It's terrible. I feel really badly that they can't do something. These people are just - I mean, they're a mess. They probably have all kinds of illnesses that they never get treated. Because most of them are very old, or older.

DG: Yes. There's a tremendous number of people in a lot of our cities who are experiencing homelessness, who have mental health challenges, physical health challenges. The shelters are not safe. Really, it's one of those tasks that, gosh, if someone could really figure out how to do this in a way where the places they could go would be safe, where they would want to go there. I mean, they get abused, they get robbed. It's a disaster, really.

VR: I don't know - Salt Lake City provides housing to homeless people, right?

DG: Yes.

VR: But I'm sure they have fewer homeless people than here in New York. That would cost a lot of money. I do think they should be helped because they have no jobs and they're in great pain.

DG: Yes. It's really tough. Really tough.

VR: [crosstalk] What's on the tie today, Daniel? Is it the same one as last night, all the different waterborne infections?

DG: No, no. Last night, for those who are attending the *Vincent Racaniello Office Hours*, we were talking about the fact that - Though I have over 100 bow ties, I have kind of 20 favorite and really 10 top favorite. I actually choose them thinking about what's going on. Some are getting a little bit of extra attention lately based on what is going on in sub-Saharan Africa. Maybe -

VR: That's an Ebola, huh?

DG: It is. It is. Actually, this might be one of my most favorite bow ties.

VR: It looks interesting. It's got the shepherd's crook, right?

DG: Shepherd's crook, and it's got this pink - It's a beautiful bow tie.

VR: All right.

DG: This artist did a great job. [laughs]

VR: All right.

DG: Let's jump into it. We got a lot to cover today. I should say, Vincent, you actually apparently had come up on rounds right before I went to the ICU.

VR: What does that mean?

DG: I told the intern resident trainee that, hey, I was mentioning her last night about how she was wearing a mask and all about masking and stuff. She said, "Oh, what were you recording?" I said, "Well, it was *Vincent Racaniello Office Hours*." She said, "Oh, we were just talking about Vincent Racaniello and his slide during the virus lecture where he's got a picture of Coxsackie, New York."

VR: Yes.

DG: Apparently, they had a case of Coxsackie, and apparently, you were remembered. That was memorable.

VR: [laughs] Wow, what a thing to be remembered for. That's OK. I don't mind.

DG: She doesn't know the Baltimore classifications of viruses, but she does remember that. OK, anyway.

VR: That picture was taken a long time ago when I had a regular big Nikon digital camera. I was driving past, and I just opened the window, and I held it up, and I took it. I wanted to have the picture for my lectures, and I had it. It's really cool. Coxsackie, New York.

DG: Yes. I think that she remembers quite a bit more than just that, but that was entertaining.

VR: [laughs] Good.

DG: We were just talking about him. OK, I will start off with a quotation, and maybe people understand why I'm bringing this up, but here it is. Dante, "The hottest places in Hell are reserved for those who, in times of great moral crisis, maintain their neutrality."

VR: You didn't say his last name, Daniel. I want to see how you pronounce it.

DG: I'm going to pronounce it wrong. [pronunciation of Alighieri].

VR: [pronunciation of Alighieri].

DG: [pronunciation of Alighieri] [laughs]

VR: No, no, [pronunciation of Alighieri]. It's a smooth transition.

DG: [pronunciation of Alighieri].

VR: Alighieri, there you go.

DG: OK. [laughs] All right. We'll go right into news. Right in here, we have White House published an executive order on Friday, May 29, titled “Realigning United States Core Childhood Vaccine Recommendations with Best Practices from Peer, Developed Countries,” a strategic undermining. The January schedule changes were struck down on process, so the pieces now falling into place look like a rebuild on firmer footing, a formal assessment in the record, a directive aimed at a future ACIP, and language about sorting the schedule into categories.

The administration has even quietly rewritten the ACIP charter to broaden who can serve, a challenge legal scholars read as an effort to seat a new panel that can survive the next court challenge. You don't have to strip a vaccine from coverage to undermine it. Reclassify it from "routine" to "high-risk only," and the recommendation that schools, insurers, and pediatricians follows quickly erodes, while the coverage language lets the administration say nothing was taken away.

VR: This article at CIDRAP is very interesting. They point out this idea, best practices from peer, developed countries. We talked about this months ago. This is nonsense. Denmark, for example, is not even comparable. If you go through all the other countries, country by country, most peer nation schedules track with the U.S., and some even have more vaccines. This whole idea of aligning with peer nations is just nonsense. The other thing that's very interesting is that this was written by two people, Tracy Beth Høeg, a sports medicine physician, and Martin Kulldorff, a biostatistician, neither of whom works in vaccine policy. This is a document meant to look authoritative, but there's nothing here.

DG: Yes. No, and they do point out how this way to subtly do these things, which seem like

not a big deal, but then you realize what they're actually doing, is they're eroding access, they're eroding recommendations, they're eroding vaccination coverage. What we're ending up with, we're going to go through this, you're going to end up with sick and hospitalized and dead children. That's ultimately where this is headed.

We've talked about why would someone possibly do this? There is a lot of money, and some people are willing to sell their souls. I didn't put in here, Vincent, but the last deep dive *TWiV*, the topic you talked about with this document where now politicians are going to decide who gets to do science in our country.

VR: Yes, it's moving away from scientific peer review by scientists to politicians deciding what we can work on.

DG: That's made it into the mainstream press, which I'm glad, it's getting a lot of attention. People, I think, are not happy with this idea that we're going to have this new policy where if a politician doesn't like what you say, maybe you're a guest on *This Week in Virology*, and you say something that they don't like, that they feel "does not align with the agenda of the current administration," then they can just strip your funding. That's it.

VR: There's an article I was reading today about this. I think it was a Harvard guy. He's a genomics person. He looks at evolution. His grants were taken away, and they said, "Your projects are no longer of interest to the American people." What?

DG: [laughs] "They don't align with the values of the current administration."

VR: Right. Has everyone spoken out on that? Most people don't even know, understand what he's doing. Right?

DG: Yes.

VR: That's the nature of science. Sometimes you don't know where it's going to lead. This is all nonsense. Folks, science is being destroyed in this country. Do you understand that?

DG: Yes. We're going to talk about hantavirus. We're going to talk about Ebola. Remember, these are things that they got rid of. They decided, "We really were not interested in having vaccines and medicines and everything we needed for other than the Zaire or maybe the Sudan, but definitely not the current Ebola that we're having an issue with. We're not interested in understanding hantaviruses."

None of this - It's all about basically stripping money from science, no longer being a leader in the world in science, and getting more money into certain people's pockets. It's terrible. OK. Let's move to Ebola. The Ebola Tracker. This is kind of tricky to track what exactly is going on. That's actually the biggest disaster I'm going to point out here. We used to have pretty robust surveillance systems. We talked about last time, a lot of this stuff was cut because, as Elon Musk thought, you don't actually have to be prepared. You just have to be rich.

If you're rich, you can fix anything. Now that we're rich, we're seeing what's happening. I'm not sure we're rich, but there are over 100 deaths that are suspected due to Ebola. So far, 60, so about half of those are confirmed deaths. We're seeing a case fatality rate 25% to 50%. This has to do a lot with which deaths actually are confirmed relative to the number of

cases.

A bunch of different places you can look. Actually, the CDC, right, for this, Vincent? The CDC has this updated as of June 2, where they say in the DRC, we have 363 confirmed cases. We have 15 confirmed cases in Uganda, 62 confirmed deaths in the DRC, one confirmed death in Uganda. One of the biggest challenges, as I'm communicating here, is we're not sure exactly, the numbers here, because a lot of these areas, they're not safe. We talked about this at *Office Hours* that when they try to go to a home because someone they think died from Ebola, it's not exactly a pretty scene. They're not excited to work with the local health officials.

VR: Also, the diagnostics are lacking, so you don't really know who's infected. There's nothing to do, right? There's no vaccine, there's no therapeutics, so it's a problem. These numbers, I've seen over 900 cases estimated by some places.

DG: Some over 1,000. It's very hard to know what the actual number is right now.

VR: Yes. That's bad. That means this could explode at any time.

DG: Yes. I worry that it may have already exploded, and we just don't know. We're just finding now is the problem.

VR: Yes, exactly.

DG: But a little optimism in this pretty dark time. We have a couple of things to share. One is a news - this is an article in the news section of *Nature*, "Race Begins to Trial Ebola Drugs Amid Current Outbreak." There is a positive aspect to this beyond finding out what works, but just the idea that there's actually some reason to get diagnosed. You might get diagnosed, you might be offered a potentially helpful treatment.

What are these drugs that might help with Ebola? One is remdesivir. I thought it was really funny the way they describe it, as if we don't know what remdesivir is. Remdesivir is manufactured by Gilead Sciences in Foster City, California. We're going to keep coming back to California here. They're actually making drugs in California. Imagine that. We got manufacturing jobs in America, making stuff. Remdesivir, that's what we use for COVID. It's one of the antivirals that works.

VR: Yes.

DG: The other is -

VR: The idea with remdesivir is that it was tried for Ebola, but it failed. I don't know what they're going to do with it here. It doesn't work for Ebola.

DG: Yes. They trialed it in the DRC. This was about, I guess we're about eight years back. There was a 2018, 2019 outbreak. This was the Zaire species. There have been trials before, but why not just try it again?

VR: Sure.

DG: [laughs] This other, we've got MBP. This is a mixture of two antibodies, monoclonal antibodies. We've got two antibodies. This is developed by Mapp Biopharmaceuticals in San

Diego, California. Now, this was done in 2022. They've tried this before. This was an outbreak of the Sudan species in Uganda. They did this like a compassionate use, "Let's just give it to some people," so we really have no idea if there was any efficacy there. We tried it, but -

VR: This would be given post-exposure. Is that the idea?

DG: Well, no, this would be given as treatment.

VR: Treatment?

DG: Yes. Someone's sick, they have symptoms, they test positive, you give them. This would be like we did with bamlanivimab or the Regeneron cocktails, things like that.

VR: You need to do it IV, I presume, right?

DG: It is interesting. The monoclonals, though we gave a lot of them IV, some of these you can give subcu. We may even be able to do - Yes, because it's quite a challenge, right? It takes a skilled person to be able to cannulate a vein and give something intravenous.

VR: Someone skilled in the art, as they say.

DG: Skilled in the art. Imagine that. [laughs] Okay.

VR: Can you do that, Daniel? You still can do that?

DG: Yes, I can still do that.

VR: Because you get out of practice because you let everybody else do these things.

DG: Yes. No, it's true, it's true.

VR: It's like the captains let the co-pilots fly and they forget how to fly, right?

DG: Which is a problem. [laughs] All right. From CEPI, we hear CEPI fast-tracks three Bundibugyo ebolavirus vaccine candidates. We're going to get pretty comfortable saying that word after a while here.

VR: It's a good word. I always liked it.

DG: Yes, it's great. It looks like they'll be testing, there's a VSV vaccine platform, and there's an mRNA vaccine, and there's a ChAdOx platform.

VR: Good.

DG: We're going to check different platforms. We'll see how -

VR: I added another antiviral here. Obeldesivir. It's a chain terminator, nucleoside analog. It inhibits the RNA polymerase of filoviruses. It's been pre-clinically trialed in non-human primates, and it's very effective. You can only do a few NHPs. They're expensive, but it has worked well against filoviruses. They are preparing a clinical trial with this. It's an oral pill, which is great.

DG: Oh, which is, yes, it makes more sense than remdesivir, right? Just based on what we know.

VR: Actually, I shouldn't say oral pill. Just the pill. It's redundant, right?

DG: [laughs] I think it's nice to just reiterate. It's oral, right? You put it in your mouth.

VR: It's like saying genetic mutation. You don't need -

DG: There's suppository pills, right? Let's go the other end.

VR: Really? They're called suppository pills?

DG: I don't know. Are they called suppository pills?

VR: No, they're just suppository.

DG: Yes, that's true. That's true.

VR: Yes.

DG: Yes, let's not confuse the two. All right. OK. Hantavirus. You always wonder how currently we are. So far, we're hearing that we're still at the same number, 13 confirmed, 10 symptomatic, three deaths, those people, 26 asymptomatic. Still a dashboard, we're following it. It's interesting. I have to say, I think many people have lost interest,-

VR: Yes.

DG: -but there's still a bunch of people that haven't lost interest because they're waiting out the incubation period in quarantine. This was something that happened that was a bit controversial, a bit upsetting, I should say. We read an *Inside Medicine* substack. "Scoop: HHS Asks Confined Hantavirus Cruise Passengers to Assist in Propaganda." Did you see this before, Vince? This is just outrageous.

VR: It's horrible. It is just ridiculous.

DG: I've got a screenshot here, which may be people on YouTube. I'll read this because this is just beyond. "Greetings, We hope you're doing well. We wanted to reach out with a fun and completely optional opportunity to help us share a glimpse of your experience with the public. We'd love it if you'd be willing to share one or more photos that we could feature on HHS social media.

Photos could include activities you're doing in your room, photos of your room, photos of you packing, photos of yourself, if you are comfortable being identified. If you're open to it, please take a moment to review the following before sending. Please remove or obscure any photos or personal items in the room that could identify you, your friends, or your family members (unless you're comfortable being identified).

HHS does not plan to identify the image as being your room or of you specifically. That said, you are absolutely welcome to re-share the post once it's live and self-identify if you'd like. Please send horizontal photos if possible." Then they go on and give you some stuff; this is entirely optional, et cetera. Then we have a screenshot from this person who left the

quarantine facility. I think it was a nice contrast. I think it's readable. It's not the best handwriting in the world. "Although my stay here was -" [crosstalk] Are you ready for this, Vincent?

VR: Yes, go ahead. Go ahead.

DG: "Although my stay here was involuntary, and in my view, unlawful, I recognize the very difficult position in which NQU staff and rank-and-file federal employees were placed by the outrageous and shameful conduct of federal decision-makers and their spineless lackeys."

VR: I like that very much. I love it.

DG: "To the former, my sincere thanks for your efforts and especially for your ultimately efficacious advocacy for my release." [laughs]

VR: It's crazy. Yes, these federal decision-makers, they know nothing. Bhattacharya and all these people, know nothing.

DG: It's just crazy. OK, here's an interesting -, it's a case report. We'll talk about it, but it's one of those issues, a case report. We don't really know if any of this amounted to anything, but this is the story. In *CMI*, we have the article, "First Reported Case of Andes Hantavirus Cardiopulmonary Syndrome Treated with a Combination of Favipiravir, Ribavirin, Icatibant, and Baricitinib."

This case report, a 69-year-old Spanish man, repatriated following a multinational ANDV, the Andes virus outbreak aboard a cruise ship, I guess at some point in the future this will not be current, was managed in a high-level isolation unit. Diagnosis was established by RT-PCR and serology while he was still asymptomatic as part of a protocol-driven screening.

Under compassionate-use authorization and written informed consent, the patient received ribavirin (initially intravenous, then switched to oral on day four), oral favipiravir, subcutaneous icatibant, and oral baricitinib, with serial clinical, lab, and radiological monitoring. Now, I just thought, for our listeners, let's run through, what are these medicines? We'll talk a little bit about them. Correct me when I mess up, Vincent, feel free. We'll talk about ribavirin first.

For our listeners, think of RNA, think of the A's, the C's, the G's, the U's in RNA. It's interesting, ribavirin resembles the G or the A depending on rotation. We talk about it as a guanine analog, but actually if you rotate it, it can get incorporated as a G or an A. When it gets incorporated, it interferes with RNA, it causes an increase in mutational rate, so you end up with this hypermutation. I think we've talked about the fact that there seems to be a sweet spot for different viruses with the amount of changes.

VR: You know what that's called, Gerald - You know what that's called, Daniel? "Gerald," what am I talking about, "Gerald"? Do you know what that's called, that sweet spot?

DG: The sweet spot? No, what is the sweet spot?

VR: It's called the error threshold.

DG: The error threshold. OK, I like that.

VR: You exceed it, and you're dead, and if you exist too far below it, you can't compete, so you've got to be near it.

DG: I like that, the threshold.

VR: You need mutations to adapt and so forth, but you can't have too many of them. The error threshold is that level you can't exceed.

DG: You were talking, I was listening to *TWiEVO*, you and Nels were talking with Roxanne Khamsi about the fact that mutation has this negative word. It shouldn't, right? We just talked about the fact that if you don't have mutations, you're not going to survive. Sequence variations. Because mutation has gotten this - I was looking through the history of why, with AI, but not Claude, I was talking to Grok.

VR: You like Grok?

DG: It's in the car, I'm driving around talking to - I've renamed it, of course, which we all do. I use a woman's voice, because then when I'm wrong, I get less upset when I get scolded or told that I'm, you know.

[laughter]

DG: No, so you end up, basically -, yes. That's what we're doing. We're messing with the RNA. We're messing with the polymerase. Then we've got favipiravir, which selectively inhibits RNA polymerase. This is also something that might be, you know, no one actually uses it for flu, but I guess you could.

VR: I think it's licensed in Japan for flu, right?

DG: Yes, but not here in the U.S.

VR: No, it's not.

DG: Icatibant, most people have never heard about this, but this is a competitive antagonist selective for the bradykinin B2 receptor, has an affinity similar to bradykinin. Bradykinin is this vasodilator causing this swelling, inflammation, pain. Probably causes a lot of the pulmonary manifestations that we see. Then baricitinib, a Janus kinase inhibitor. These last two, you're basically affecting immune responses, right?

VR: Yes. [crosstalk]

DG: Then they describe the man. Basically, he had hypoxemia, so low oxygen in the blood, bilateral B-lines. This is usually involved with looking on ultrasounds, so extra fluid in the lungs, thrombocytopenia, so low platelets, lymphopenia, low white cells, hyponatremia. This all develops within 24 hours after - Remember, they diagnosed this guy just screening, just testing. They start the therapy day zero. Basically, the guy goes on - he's sort of a rocky course, diarrhea, severe recurrent diarrhea. They're not even sure if that's from the disease or maybe attributed to one of the medicines, but basically goes ahead and goes through this 10-day course of treatment.

VR: He's OK at the end. Do you know?

DG: We think he's OK. I was sort of like, OK, tell me a little bit about follow-up. Yes, sounds like he's OK.

VR: I can't imagine he's not going to have some longer-term issues, right?

DG: That's going to be the big issue with these folks, is let's follow these folks out. Hopefully, we're going to follow these folks out, the survivors, how do they do? Because a lot of folks after the other hantavirus infections end up with ongoing issues.

VR: Yes.

DG: All right, measles. A little bit more on measles this time. Measles are up to 2,077 so far this year. It's another 44 cases just in the last measured week. You go to the CDC, they've got us at 1,983. I wanted to comment about what's going on in some other places. Canada, May 17 to 23, so the 23rd, 2026. They're up to over 1,000 cases in Canada, 1,052 cases so far this year. Measles is raging in Bangladesh with over 1,000 cases. We've got a couple deaths there. Then they say the country's tally. This is just in this one day, basically, pushing us up to a tally of nearly 71,000 infections. 585 fatalities since the outbreak. The outbreak, 71,000. We're seeing here over 1,000 measles cases and two deaths just in one day. Really horrible what's going on over there.

Now, this is another story that we talked a little bit about, and now we have a little more details in the *MMWR*. This was that measles outbreak in a childcare facility, Lubbock, Texas, March through April 2025.

Now, during 2025, the U.S. recorded the highest number of measles cases since measles elimination was declared in 2000. March 21, 2025, Lubbock Public Health in Texas received a report of a childcare attendee aged 3, fever, rash, cough, coryza, you probably knew the diagnosis before they used that word, conjunctivitis, otitis media, and diarrhea, who received a positive test result for measles by real-time reverse transcription-polymerase chain reaction (RT-PCR).

Six additional children who attended the same childcare facility, and the grandfather of one of the children were confirmed by RT-PCR testing to have measles. None of the patients were reported to have traveled. They contacted the pediatric patients' caregivers to conduct case investigations, provide recommendations. The childcare facility implemented measures to minimize transmission. Then there was this, they described the collaboration between public health and community partners.

VR: I presume a lot of these kids were not vaccinated, right?

DG: That tends to be the universal issue, is these kids are not vaccinated.

VR: Of course, sometimes they're too young to be vaccinated, right?

DG: That's that issue, right?

VR: Yes.

DG: In that first year when you're relying on other people to protect your child.

VR: Right.

DG: All right. Flu, the only thing I mentioned in flu is we're still counting the tally of pediatric deaths from last winter. We're up to 174 children died from flu last winter.

VR: Dan, do you ever see influenza over the summer?

DG: We see a little bit, a little bit of particularly flu B. We see a little bit. Then if people are going to travel, we're sort of off cycle. You go down to the southern hemisphere and you see flu down there.

VR: Where it's winter, yes.

DG: Yes.

VR: Who would go to the winter anyway, right? [crosstalk]

DG: It is interesting, right? You leave the summer. Maybe you're going to go skiing down in Chile or something.

VR: [laughs] Well, skiing would be another thing. I could see where people do that.

DG: Yes. There are these ski instructors and they follow the winter throughout the world.

VR: Yes. I think you used to do that, didn't you?

DG: I was a ski bum, yes, yes. [laughs]

VR: Do you regret not continuing that?

DG: No. I basically ran out of money and decided I needed to -

VR: You needed a job.

DG: - get a job. All right. COVID, this is good news, look at our multicolored lines.

VR: Very low.

DG: Yes, very low. Can we just keep following? What is that called when you just extrapolate the line and it goes to [crosstalk]?

VR: Asymptotic.

DG: Yes.

VR: Asymptote, you approach the line, but you never quite get there.

DG: OK. Zeno's paradox. That's why when you shoot the arrow at the target, it never actually hits.

VR: We have a shirt you can purchase. It says, "Life is an Asymptote." You never get where you want to go.

DG: [laughs] OK. All right. In the COVID section, we have big news. I put that in bold. “FDA Approves Oral Antiviral to Prevent COVID-19 After Exposure.” This actually got brought up

on our *Office Hours* last night. People were asking about it. I was criticizing the naming. FDA approved the oral antiviral agent ensitrelvir (Xocova) to help prevent COVID-19 in people ages 12 years or older who are exposed to SARS-CoV-2 virus.

We talked about this SCORPIO-PEP trial, where, basically, they've got these primary contacts. This is the index person. This is somebody who's got COVID. Then what you do is you take this medicine, this pill. It's a pill. We know how you're going to take that.

[laughter]

DG: You're going to take this pill. Then you're, like here you are, 50% less likely that you're going to get COVID from that sick person in your household. Now, Shionogi is going to try to market this in the U.S. I'm going to try to help them. Here's a couple issues I have, Shionogi. Xocova, the whole idea of the X's and the V's is supposed to make it sound powerful, but I think you want something to sound powerful if you're sick, but if you're taking it just to not get sick, you want something that's going to be gentle because now you're more worried about side effects. They should have branded it. This is like Xofluza.

VR: I just realized it's good to say oral pill because you could put pills the other way, right?

DG: Oh, I lost you there for a second. Also, I have this yellow dog coming under the table, licking me and knocking my monitor.

VR: You didn't hear what I said?

DG: No, no.

VR: I said I think it's good to call it an oral pill because sometimes you can put pills the other way, right?

DG: [laughs] OK.

VR: Isn't that correct? I thought that was a thing.

DG: Well, you mean suppositories, [crosstalk] you were saying, but we don't call them pills.

VR: Yes, but you could put an aspirin rectally, couldn't you?

DG: You can. You can even put things under your tongue, so you're not really - It's really in the mouth, but it's under the tongue. We say sublingual. We don't say oral. It's a sublingual pill.

VR: OK. Just want to make sure we get everything right here on *TWiV* weekly clinical update with Dr. Daniel Griffin.

DG: Yes. No, it was interesting talking about that. This morning, Jorge, who has done and continues to maintain that tropical medicine curriculum, he was doing the study of, like, this is when people first start - The first five minutes of your lecture, they're really attentive and they're learning everything. Then in the middle of it, it goes down, and then it kind of somehow comes back at the end. You want to let them know how long your thing is going to be.

Right now, we're at that low point. Then we also tell people like, "Hey, 50% of what you learn in medical school is wrong." Now I'm worried because people only remember 50%. What if they only remember the 50% we taught them that was wrong? All right, throwing that out there.

VR: I think some docs only remember that part.

DG: [laughs] I work with some of those folks. All right. We did hear, right? We talked a little bit about it last year. The next round of COVID vaccines are going to target the Stratus. All right, fingers crossed on that.

Here's a good one. We keep talking about the fact that vaccines don't just prevent you from getting sick. They don't just prevent you from getting that acute viral illness or bacterial, for that matter. We talked about the fact they might protect you from cognitive dysfunctions, dementia. They might protect you from having a heart attack or a stroke.

Here is the article. "Impact of COVID-19 Vaccination on Long-term Risk of New-onset Atrial Fibrillation/flutter After COVID-19 Infection: A Retrospective Cohort Study," published in *PLoS One*. These results come from a retrospective cohort study that used the TriNetX Research Network. They were looking at the potential protective effect of COVID-19 vaccination against long-term new-onset atrial fibrillation or flutter.

They call it NOAF because, of course, we need this four-letter acronym. The 24-month NOAF incidence, getting AFib or flutter, was significantly lower in the vaccine group compared with the control group. They actually give us about an 18% reduction. This protective effect was observed at one month, so about 27% at one month, about 29% at six months. At 12 months, we've got 23% reduction. It's really nice.

Basically, you can see that you can get protection against all the examined subgroups, but the biggest effect is actually going to be the 18- to 60-year-old folks, the folks that people are like, "Oh, I don't know if we really need to vaccinate them." If you can reduce their risk of getting a new arrhythmia by 25% by just giving them a vaccine, I mean, come on. I put in the figures, and hopefully these will be up on YouTube, but you can see basically all these different ways of analyzing the data. I really like if you say, "OK, well, let's look at 18 to 60 years," those folks are getting more than a 30% reduction in new-onset AFib or flutter.

VR: This is a very specific cardiac alteration, right? AFib. Do we know how infection does that?

DG: I don't think we know exactly. We know a lot about the post and the acute COVID effect on the heart. One is, I think, to point out, this is not uncommon. Over 2% of folks are developing this after a COVID infection, in this period of a year following it out. It's one in 50. That's a lot, right? Pretty high incidence. We do know that during acute COVID and post-COVID, there's inflammation. We don't think it's the virus doing it. We think it might be interferon-mediated. I think you guys have actually, on the Deep Dive, talked about a gamma-interferon mechanism of cardiac inflammation.

VR: Yes. There's also one where influenza virus is trafficked to the heart by some monocyte, and it actually destroys cardiomyocytes.

DG: Yes.

VR: I don't know, when you have AFib, is that a destruction of certain cells in the timing area?

DG: It can be, yes. All right. Yes, pretty impressive, right?

VR: Yes.

DG: All right. Then, this, I think, is important because we may be past doing this in COVID, but we still might consider this in the future, so it's really important, when all the data comes in, to keep talking about it. In this section, we have the article, “Convalescent Plasma for People with COVID-19.” This is a *Cochrane Review*. I'm always rather careful regarding *Cochrane Reviews* as they suffer from this idea that if you put all the cow pies together, you put them in this huge pile, then somehow the pressure turns the ones on the bottom into diamonds.

VR: It's Mark Crislip, huh?

DG: He always said gold. Suddenly, you pile it high enough - Yes, pile it high enough, and you get gold. We're going to take a little time here, because the concept of convalescent plasma as an elixir of health and the secret to recovery, it's not only an emotional topic as whether - It's about as emotional as whether something involves airborne transmission or not. Here, early in the pandemic, we had legions of people who were donating their blood hoping to help others. This is like the Survivor Corps and all this other stuff.

We even had some very passionate advocates on *TWiV* talking about the value of artisanal plasma and hyperimmune plasma and why they were certain this stuff was great and why the studies failed to show how wonderful this stuff really was. I'll refer people to *TWiV* 739 with Arturo Casadevall. It's also the stuff that-- it saves everyone's lives in those *Hot Zone* books. We all read those. We got excited. We decided to pursue careers in science, medicine, the field of infectious disease and virology.

We need to be a little careful too in the words of my grandmother and mother, letting the truth stand in the way of a good story. Unfortunately, we may have to do that here. We're bad like that, Vincent. Sometimes we have these wonderful stories, and they're so great. This used to annoy Dickson, right? We're like, "Yes, but Dickson, that's not true." He's like, "Oh, Daniel." [laughs] All right, so -

VR: By the way, tomorrow's his birthday. June 5 is Dickson's birthday.

DG: Yes, I know. I have that on the calendar, and I'll have to drink a little Scotch in his memory. Everyone out there listening, that was always the Dickson thing. All right. In this review, they searched for completed ongoing studies. They searched CENTRAL, MEDLINE, Embase. You ready for this? The Epistemonikos COVID-19 L*OVE Platform, and clinical trial registries to October 24th. First off, what is this Epistemonikos COVID-19 L*OVE Platform, and why are they not searching the gray or the dark web? This platform was established by this foundation with the same difficult-to-pronounce name. How would you pronounce that?

VR: That's a tough one. This is Greek. I'm not good at Greek. [pronunciation of Epistemonikos]. [pronunciation of Epistemonikos]

DG: OK, Epistemonikos. The Epistemonikos Foundation, they create this platform, and it's actually got a repository of over 6,000 pandemic-related articles, including systemic reviews. They say every primary study and all kinds of other articles. I'll leave a link into that because it is interesting. I was not really that familiar. Here we're looking at 42 RCTs that investigated the use of convalescent plasma for 21,393 participants with moderate to severe disease.

Of these 36 RCTs, 20,798 participants compared convalescent plasma to placebo or standard of care, five to standard plasma and one to human immunoglobulin. They break the RCTs into two groups. We've got convalescent plasma versus placebo or standard of care alone, and convalescent plasma versus standard plasma.

Let's start off. Convalescent plasma versus placebo or standard of care. In this group, they report that convalescent plasma did not reduce all-cause mortality at up to day 28, risk ratio 0.96, confidence interval 0.90 to 1.03, 20,798 participants, high certainty of evidence. Also, it has little to no impact on the need for invasive mechanical ventilation or death. Actually, that was a relative risk, 1.03, so a little in the wrong direction, but definitely not statistically significant. We've got a confidence interval of 0.98 to 1.08, so high certainty that it's not reducing the need for ventilation, not reducing your chance of dying.

High certainty evidence here. No impact on whether or not patients survived and got out of the hospital. That was a relative risk of 1, so it was basically the same 13,930 participants. Little to no impact on quality of life. Basically, you can go across it. It's basically not doing anything. Here, I guess I'll close. It probably has little to no effect on serious adverse events. This was not only trending in the wrong direction, but relative risk 1.19, confidence interval 1.02 to 1.38. Actually, not even overlapping with, so actually suggesting it may have been harmful with no benefits.

VR: No love here, Daniel.

DG: No love here for convalescent plasma. Now, we've got convalescent plasma versus standard plasma. Here, they give us, again, you end up with confidence intervals that overlap with one, really, not certain what's going on here when you compare convalescent plasma to standard plasma. One of the things I think is concerning here is we're saying it may not be so innocuous to get plasma to begin with. Whether it's convalescent or standard, it may not be so helpful.

We can dive a little bit deeper, but unfortunately, what's going on here is this is behind a paywall, so you've got to use your academic access. You can look at a nice summary of the findings. What I really like, this is what I'm excited about here, is the funnel plot.

VR: Why is it a funnel plot, Daniel? I don't see any funnels here.

DG: All right, so let's talk. It is a funnel. You're going to understand it's an upside-down funnel is what it is. Maybe people are looking at this on the screen. I'm going to tell you what a funnel plot is because I like forest plots. I really like funnel plots. I want both of them together, to be able to look at both.

VR: How about there's violin plots and volcano plots too.

DG: I like volcano plots. Yes. I actually think this ability to see the data helps you. Here's the deal. A funnel plot, if you're on YouTube, you're probably looking at this right now. You're

going to see there's a vertical axis. There's a horizontal axis. Horizontal axis is easy. This is going to be that risk ratio. It goes to the right, and the risk ratio goes up. Getting the plasma is bad. It's increasing your risk. Going to the left, relative risk is going down. It decreases your risk. If you're two on the right, you doubled your risk of bad outcome.

If you're a 0.5 on the left, you halved your risk of a bad outcome. This is the cool part, is the vertical axis. This shows the study size or precision. What you really care about is not some tiny little study down low, which just has a small sample size and is unreliable. You want to look at what's going on towards the top of the funnel. It's funneling all the really good, powerful, helpful information to the top. If you look at the top, you can see all the powerful, the large sample size, the studies with good precision. They're basically showing no bad thing.

VR: There's no risk reduction, right?

DG: Yes. No risk reduction. Actually, if anything, it looks a little worrisome from a doing harm kind of issue there. Yes, I like this. I like that funnel.

VR: Yes. I think the names are really great. They tell you what's going on.

DG: Yes. It's tough, right? It's convalescent. People are really excited. Probably, people are ready to start talking about maybe we should be doing this in Ebola. This gives me pause when all the data is now in.

VR: You have to know. For Ebola, you have to know if it works because you don't want to give people things that are not helping them.

DG: I think that's the big thing. It's one of these things where we're so sure that it works. If the data doesn't show it, it's that the study was wrong because we know this works. I think we've got to have the humility to say, "We don't know. We might actually be harming people." When you don't know, and you might be harming people, that's the time you keep your hands in your pockets. You design a well-controlled study. You figure out what's going on. Then you act. All right. No one is safe until everyone is safe.

We were talking last night. We're doing our FIMRC Foundation International Medical Relief of Children fundraiser. Very appropriate right now because they're in Uganda, where we've got this ongoing Ebola outbreak. They're there in harm's way. If you're saying, "How can I help?" This is a fantastic organization. Your money basically goes to actually helping people. It's not going to go to some overpaid administrator. Go to parasiteswithoutborders.com. Click on the Donate button. We're going to double your funds up to $10,000. Try to help FIMRC continue to do this great work.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Dania writes. Dania is one of our moderators on *Office Hours*. She had this question last night, and I skipped it.

DG: Oh.

VR: I felt so bad. I said, " Send it. I'll ask Daniel." Do you have any advice and/or tips for a non-traditional starting med school next month, and since you mentioned Montana during *Office Hours*, tips for surviving Montana winters?

DG: All right. I love Montana. My first real job, I guess, after finishing my residency in internal medicine was Helena, Montana. I'd cover the VA. They'd fly me in on Friday night, and I was it, the entire VA, until Monday morning. Isn't that scary? 150-bed hospital. I was the ICU, the ER. They'd come in at noon on Saturday and Sunday, spell me for like an hour. Montana's beautiful. Actually, hey, you've got a little bit of time to do a vacation. What a wonderful time to go up to western Montana if you love to fly fish, if you love to hike. It's beautiful up there.

How do you survive Montana winters? Again, it's cold, so you've got to just dress for it. I used to work up in Alaska. I remember one time, it's minus 30. It's freezing cold. My buddy Joe Lestin and I used to work the night shifts when I'd go up there to work as a hospitalist. It's right before I'm about to go in and work the night shift. We're talking about the importance of layering. I'm a big fan of layering, but as Joe and I pointed out, layering is wonderful, but the most important thing of layering is your outermost layer should be a big, huge down parka.

VR: OK. What about some advice for a non-traditional medical? She's going to medical school in Montana. Non-traditional. She's worked -

DG: Yes, I'm going to actually say take a little time off. Get your head straight. Go into it. The other is don't be intimidated. If you got into medical school, you deserve to be there. Non-trad, that's great. We need more non-traditional. You're going to be that slightly different perspective. Don't get imposter syndrome. You're going to do great. If you start getting imposter syndrome, come join us on *Office Hours*. Tell us what's going on. Write in. Tell us what's happening. No, you're the people. We need more of the round, what is it, square pegs in these round holes.

VR: Just don't learn the 50% that's wrong.

DG: Yes. Only remember the 50% that's true. If they tell you, they say, "OK, listen, because this is a pearl," in my experience, that's the marker for something that will turn out later to be not true.

VR: Daniel, you just said those three words, in my experience.

DG: Yes. Don't forget the three scariest words in medicine are, in my experience.

VR: In my experience. John writes, "Thanks for reading my letter 1326. That did the trick when I asked for Nuvaxovid at my pharmacy. They had it, but I think you're trying too hard to pronounce it. Nuvaxovid, unaccented, is, I think, how it's intended to be pronounced, not Nuvaxovid, which we were -

DG: OK, Nuvaxovid.

VR: Nuvaxovid, that's it. Just let it flow. Susan writes, "Listening since 2020. In March 2020, I was working as an art therapist at a cancer center. Many outpatient staff were sent into the main hospital, which was all COVID to work, and I was one of them. End of April, I was out with COVID, returning in two weeks once I was without a fever. I was vaccinated when it became available and experienced the night of 103 temp plus other symptoms, as when I was initially diagnosed. Symptoms were gone the next day, but every time I receive the vaccine, I expect the night of the same symptoms.

I'm fine with that, but curious as to whether this is a common experience with people who have had the virus before vaccines were available. I'm someone who tends to run high fevers when sick anyway, and also someone who had measles as a kid without being vaccinated. Not sure if this is relevant. Thanks for all these years of listening to intelligent and thoughtful information. All greatly appreciated."

DG: I'm trying to sort through here. The fact that you're having this reactogenicity, this may be something you're getting with the mRNA vaccine. Appropriate to the question right before this, the Nuvaxovid might be an option for you to think about. Let's see. I am someone who tends to run high fevers. What am I missing? No, I think this is a pretty common occurrence, and particularly people, as we saw, people that had COVID before often will have more reactogenicity.

VR: Anonymous writes, "My daughter-in-law recently had a baby, and so when she had a sore throat, she tested for COVID. One test was a very light positive, so she took another, which was negative. Then she got a PCR, which was negative. She then took several more antigen tests of different types, got a bunch of negatives and a couple of light positives. She socially distanced and masked while nursing. No one else in the family tested positive. The doctor said the baby would probably be asymptomatic anyway. PCR negative is negative.

What was up with the three positive tests? She looked online, and it said some tests gave false results if you have rheumatoid arthritis, which she does. Can you discuss this? She never had any other symptoms except a brief sore throat and brief fever, and tested negative for RSV and flu. Thank you for your sanity and expertise." I don't know if we're sane, Daniel.

DG: [laughs] How about expertise?

VR: Yes, that's OK.

DG: We'll leave sanity out of it. Yes, no, this is a challenging issue. When we're developing these tests, there's always going to be this balance between how sensitive or how specific. The sensitive is if you have it, what percent of the time is it going to pick it up? Then the specificity is basically, if it's positive, what percent of the time is that actually really true? Then maybe even more is positive predictive value. When it's positive, you then even add more, like, is there a lot of COVID going on? That'll increase more likely that it is.

Then the other comes, like what's the mechanism? Why do we even get these false positives? Does having something like rheumatoid arthritis, are there things that are somehow interfering with the tests? I'm not sure about this connection with rheumatoid arthritis, or really what the mechanism is for some of these positive tests. Any thoughts from your side there, Vincent?

VR: No. Maybe there are antibodies that are precipitating this reaction that she's getting. Those are a bunch of anti-self antibodies in rheumatoid arthritis, right?

DG: Yes. Even though theoretically you're picking up antigen, and then it's the antibodies in the test that are then causing your line. Yes. Maybe there's something so that you end up with, because the antibodies can bind other antibodies, so that could potentially be a mechanism.

VR: You're testing too much. You remember, Daniel, you always said, don't test too much.

DG: Yes, no, that's a little bit of an issue. It sounds like there was a lot of testing. What do we recommend? Maybe this is a good reminder. We don't know the timing on this, but you have symptoms, there's a concern, you test. If it's positive, it's positive. Again, as we talked about, what's the prevalence? It sounds like it was light, so they weren't sure. 48 hours later, because you're not sure, you test again. PCR is really going to tell you. You get a PCR, and that's going to really clarify the issue. Greater sensitivity and specificity than the antigen tests.

VR: Jeffrey writes, "Daniel, you mentioned the pneumococcal vaccine. I have heard some conflicting information, and I'm now going to the expert for clarification." Jeffrey is an MD. "I understand that the vaccine covers, at most, 21 strains, and that most pneumococcal pneumonia is not covered by the vaccine. Also, I would like to hear your comments on the efficacy of the vaccine in the real world. I would like to know how often you recommend repeated vaccination. Personally, I received the vaccine this past winter. I am 73 and will hit 74 before Vincent.

I'm a cardiologist that wants to give the best information to my patients. The patients are at high risk for the complications of the viral and bacterial diseases. I feel it's my responsibility to address this with them. Your knowledge and communication skills help greatly."

DG: All right. Jeffrey, even though you're a cardiologist, now, a little history on this. My first published paper was on people with CHF, so heart failure, and why they should actually get the pneumonia vaccine. Can you imagine that? This is a very appropriate question. It was a long time ago. It's the last century. Here's the story with pneumococcal vaccines. We've moved on now to these conjugate vaccines, and there's a 21-valent and a 20-valent pneumococcal vaccine. At this point, it's a one-and-done, but we'll see 10 years from now if that still holds.

The different company, one company with the biggest market share makes the Prevnar 20, and the other company makes the 21. It's a market share. Then they go ahead, and they show, "Oh, but our strains cover this frequency, and these cover the other frequency." It does cover pneumococcal bacteria. It doesn't cover viral. It's not a disease. It's a specific pathogen vaccine. It does look like it has great efficacy, and studies have panned this out, so definitely encourage it. We don't recommend repeating. Right now, we've actually moved it down.

Here's the recommendations. 50 years of age, either get the 20- or the 21-valent. It will cover the majority of the pneumococcal pathogens out there causing pneumonia. Also, it's particularly targeted towards the pneumococcal that are resistant. Even if you do get pneumococcal pneumonia, even if you get pneumococcal pneumonia with bacteremia, you're going to be more likely to have a treatable disease. Yes, best information for your patients. Everyone across the board, 50 years of age, time to get that first shot. 10 years from now, maybe we'll have some data if there should be any repetition.

VR: An anonymous writes, "Thank you so much for your weekly clinical update, which I listen to every Saturday since spring 2020. I learned a lot about virology, immunology, and public health. A comment and question. I truly appreciate you discussing HPV vaccine and bringing up that it is possible and likely beneficial to receive this vaccine at a later age. I'm a 48-year-old female. The vaccine was initially approved when I was already older than 26.

When it was extended to age 45, I was in my early 40s, and somehow it did not appear on my radar.

After listening to you discussing the vaccine, I reached out to my gynecologist for some shared decision-making. He was very supportive of me getting the vaccine, but he was not sure my insurance would cover the cost. I went to my small non-chain pharmacy to investigate. They said that because I'm over 45, I need a prescription from my doctor, and with that, my health insurance would pay for the vaccine, minus $30 copay per dose. It worked. I already got two doses and will be getting my third dose soon. I hope this anecdotal information would be useful for other patients older than 45."

DG: Oh, this is great. This is great.

VR: Question. "On TWiV 1324, I was excited to hear a question from Jessica regarding measles vaccination, as I am pretty much in the same boat. Background, I received two doses of Soviet-era measles vaccine." What does that mean? Like the ‘60s?

DG: Yes, sort of. When was that?

VR: "At ages of 10 months and 7 years. Then at age 21, I came to the U.S. for schooling." Maybe she was--

DG: Maybe she was in the Soviet Union, yes. Sovetsky Soyuz.

VR: "Because I did not have a proper vaccination proof and it was not MMR, I was tested for antibodies. There was nothing detected. I was given one MMR shot then and was told it's enough for an adult to just get one dose. I happily forgot about this until last year once measles outbreaks began to increase here in the U.S., and you started discussing how much protection one versus two doses provide. I asked my primary care doctor if I should get the second MMR dose to increase my protection. Really, my fourth measles shot overall. We decided to check antibodies first, and I had nothing above the cutoff again. I got another dose and tested antibodies. Four weeks after the shot, no antibodies detected. How frustrating. My question is what people like me could do as the herd immunity around us wanes. From listening to *TWiV*, I do know that antibodies aren't everything, but measles-induced immune amnesia sounds very scary, and I feel I would like to proactively do something if I would learn that I was exposed to measles virus.

I read that infants and immunocompromised people can get immune globulin injections as post-exposure measles prophylaxis. Is that efficacious? If yes, would such injections be available for those people with documented lack of antibodies after multiple MMR shots?"

DG: Yes, this is a great, great, great email. Great questions. Yes. These post-exposure immunoglobulin injections, they're efficacious. We certainly do them in the context you described. People like you, we're not seeing a lot of people with the described where you have like no antibodies detected, ending up getting severe measles, getting immune amnesia, getting in the hospital. As you point out, as we've discussed, antibodies are not everything. We don't have any great commercially accessible T-cell assays here. I

If there's a measles prophylaxis exposure issue, talk to your doctor. In general, we wouldn't be recommending that, but case by case, discuss what's going on and your concerns.

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

DG: Thank you, and everyone, be safe.

[01:01:12] [END OF AUDIO]