TWiV 1318 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 1 May 2026

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

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VR: *From MicrobeTV*, this is *TWiV*, *This Week in Virology*, Episode 1318, recorded on April 30, 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: Black and white tie, bow tie. Those look like virus particles anyway. I could be wrong.

DG: They are these spherical virus particles with these little spikes that are sticking out all the way around, almost like in a corona formation.

VR: You just gave it away, Dan. You don't have to give me so much information. A coronavirus.

DG: Maybe for you, but maybe our listeners don't know.

VR: OK. Coronaviruses. That's okay.

DG: You got it. I want to point out that I owned this bow tie before 2020 to just feed into all the conspiracy theories.

VR: Coronaviruses have been around. They've been known for many, many years.

DG: I know. Not only that, but weren't we warning people that this was one of the top 10 potential causes of a zoonotic pandemic?

VR: In fact, the big problem was coronavirus 2003 never went anywhere, it was 8,000 people and then it petered out, and so people said, "Ah, these viruses don't have what it takes," and so they stopped paying attention, which is really unfortunate. Some people were doing experiments, and now they're getting in trouble because people say they caused the pandemic. Did you see David Morens, Fauci's right-hand guy, was indicted?

DG: I saw that. Oh my gosh. It's crazy.

VR: I had dinner with him in Toronto at ASTMH.

DG: Oh, did you go to a fancy Michelin restaurant? Because you could get yourself in trouble.

VR: No, no, it was an Indian restaurant. Anyway, we all split the bill.

DG: That sucks.

VR: Yes. Two bottles of wine and a meal, that's it, and Trump gets an airplane from the Saudis and it's OK?

DG: Wasn't Peter Daszak at that dinner?

VR: Yes. Peter Daszak and Angie Rasmussen.

DG: Oh my gosh.

VR: Are we all going to get indicted now for talking?

DG: Probably yes. This is the end. You're going to have to switch from the black turtlenecks to orange. All right, let's jump in.

VR: Yes. Orange is the new black, right?

DG: Oh my gosh. Look, you're all ready. All right, let's jump in with a Rachel Carson quotation. "The human race is challenged more than ever before to demonstrate our mastery not over nature but of ourselves."

VR: Boy, that's a statement, isn't it?

DG: It really is.

VR: We think we know how to run things.

DG: Oh my gosh. Gosh. All right. We've got a lot in the front part here, this is our news update stuff, attacks on science. Very much appropriate. Let's run through this, and then we're going to discuss some literature. In the journal, *Nature,* we read, "'Entire NSF Science Advisory Board Fired by Trump Administration. Members of the National Science Board, which the US Congress founded in 1950, were given no explanation for their termination. All 22 members of the advisory board that oversees the US National Science Foundation," so NSF, "a leading funder of fundamental science, were fired on the 24th of April without explanation."

"Every member of the NSF's National Science Board received an email on Friday afternoon saying that, 'On behalf of President Donald J. Trump, their positions were terminated effective immediately.' Members of the NSB -"

VR: Science Board?

DG: National Science Board, "were appointed by the president and served six-year terms that are staggered, avoiding complete turnover. Asked about the reason for the termination, a White House spokesperson said that 2021 Supreme Court decision United States v Arthrex, Inc raised constitutional questions about whether non-Senate-confirmed appointees can exercise the authorities that Congress gave the National Science Board."

I'm going to leave a link into the *Harvard Law Review* discussion of that Supreme Court decision. Even better, I'm going to leave a link into a five-minute SCOTUS brief podcast that

explains what was going on there.

VR: I tried reading that, Daniel. Boy, lawyers, they make up stuff. They just make stuff up.

DG: I think the whole idea - in a nutshell, and this is just in a nutshell because I want to - as we were talking a little bit, let's cede expert opinion to the experts. I am not a constitutional Supreme Court lawyer as much as you know. There's this whole idea that our constitution gives the president certain authority, they give Congress certain authority. Basically, if Congress and the president choose someone, they can give them a certain amount of authority, but then below that, like a lower level, they can't be making decisions that require both Congress and the president. Something along those lines. Anyway, I think we're going to find out what the real story was. What's the story?

The board meets five times a year and publishes reports on the state of U.S. science and engineering that help to guide the president and Congress. Its next meeting was set for the 5th of May, a few days away, and members, they had this report that they were going to release about the United States ceding scientific ground to China. I'm going to leave a link into the *Nature* article, "'China Could be the World's Biggest Public Funder of Science within Two Years.' China is on the cusp of becoming the world's biggest public funder of research according to a forecast by U.S. academics as stalled growth in government investment in the United States coincides with consistent rises in spending by the Chinese authorities."

VR: I tell you, so many papers we do recently on these podcasts are from China, and they're really good. I'm just not surprised because we're just dropping the ball here.

DG: Yes, we're dropping the ball. Basically, by the time we get our next president, it's over, China will have overtaken the U.S. as the biggest public funder of science.

VR: We can still restore science in the U.S. to what it used to be by restoring the funding and so forth and not doing dumbass things like firing this board of experts because you want to put your own people in. We can reverse it, but it's going to take a lot of time and money. It doesn't matter if we're the world's biggest funder as long as we do good science here.

DG: Yes. If it motivates people. That was the space race with Russia. Basically saying like, "OK, China's increasing its investment in science, that's great, but don't we want to keep up with the Joneses? Don't we want to be up there as one of the leaders in science?"

VR: I don't get this. I thought authoritarian regimes don't like correct science, like the Soviets with Lysenko and the guy in Hungary. China is an authoritarian regime, and they understand the value of science, so why can't this king?

DG: Yes, appreciate the importance of science. No, I'm actually glad that China seems to really value science. It's really interesting how many MDs out of China are MD-PhDs. They do even a little bit of extra training in scientific rigor and investigation. All right, go China.

VR: The science is absolutely impressive coming out of China. It's just almost every *TWiV* we have a paper out of China, or *TWiM*. It's just great.

DG: There seems to be something interesting about their cooperative model over there.

VR: Good for them.

DG: Yes. All right, go China. All right. Just this afternoon, Sara Brenner was elevated to Mr. Kennedy's Senior Counselor for Public Health, a post that, unlike the CDC director, does not require Senate confirmation. Dr. Brenner's background suggests that she is aligned with Mr. Kennedy on some of his signature issues, including skepticism about vaccines and a strong belief in the importance of fitness as she was trained in preventive health at North Shore on Long Island. Oh my gosh. Despite these trainings, she is consistent with the individual choice policy that RFK and others in the administration have implemented, another action weakening America public health.

VR: I'm just going to say it. If you're skeptical about vaccines, you're an asshole. You're a dumbass. Because there's no skepticisms to be had about vaccines, they work, and in most people, they are terrific. I don't understand this. People are now making a career out of being vaccine skeptics. It's so stupid.

DG: The verbiage is the concern here because what is vaccine skepticism? We've always been. This is part of science, is always questioning, checking, rigorous trials to look at safety and efficacy. Skepticism, that's the wrong word here. They're not skeptic about vaccines, they're anti-vaccines, pushing -

VR: Yes. It's just nonsense. There's, "Oh, the COVID vaccine is so dangerous." There's no evidence for this, yet they can advance their careers. I just don't understand it, Daniel.

DG: No, it's the opposite. We covered this study with sudden death. Your risk of sudden death dropped in half. People say, "Oh, but I am certain. This one person got the COVID shot, and two days later, they suddenly died." Hey, twice as many people didn't get the COVID shot and suddenly died. It's tough. We go to school, in a sense, to learn that the plural of anecdote is not data. We have to be taught.

We're hearing it with Roundup, just to put my foot into that, "I knew this one guy, and I can tell you for sure -" We don't. It's really hard to connect cause and effect, and that's what science is, it's a rigorous way of finding out what's actually true as opposed to what we want to just believe. All right. This week was, is World Immunization Week, the purpose of which is vaccine catch-up for more than 100 million children in over 30 countries for routine immunizations, including polio, measles, pertussis, et cetera. Leave in a quote there.

VR: This is, of course, run by WHO, we no longer support. Another dumbass move.

DG: Yes. We're going to get into some issue there. "Despite an anti-vaccine surgeon general and governor, the Florida State Senate refused to debate the DeSantis bill pushing for the loosening of childhood vaccine mandates, which has always been defeated in the state House. Mr. DeSantis has said the bill would promote medical freedom, likening it to the state's ban on mask mandates and other policies that his administration adopted during the coronavirus pandemic."

"Critics have said that broadening Florida's existing vaccine exemptions law was unnecessary and would allow a dangerously high proportion of children to attend school unvaccinated. The House's rejection of the bill was the latest show of Republican defiance toward the term-limited governor."

VR: Good for them. "OK, DeSantis, medical freedom, get rid of the stop lights, get rid of the stop signs, get rid of seatbelt laws. How about those freedoms?" Another moron.

DG: We talked about the biggest freedom is freedom to be healthy and alive and not sick.

VR: Oh, you don't want freedom to be infected, then?

DG: I do not want my neighbor to have the freedom to make me sick. All right. Europe approves the Moderna mRNA combined influenza SARS-CoV-2 vaccine. It's the same vaccine that Vinay Prasad unilaterally rejected this winter. I think that's before they got rid of him. All right.

VR: What's happening with that vaccine in the U.S., I think they're doing some more trials for the U.S.? Is it conditionally approved or something? What's going on?

DG: Hopefully, at this point, it's going to move forward because the staff scientists were on board, but then Vinay unilaterally just said so. All right. What's this next one here, Vincent? The illusion of America First policy.

VR: I showed this slide to my students in the AIDS lecture the other day. Yes, this is U.S. not supporting AIDS prevention and cure in countries like Zambia, where people are just dying as a consequence. You know what Trump said? He said, I'll give you all the aid back if you give me access to your mineral resources. This is the ultimate in disgusting behavior.

DG: Yes. Oh my gosh. That's just horrible. We'll leave a link into this, *MMWR*, but oh my gosh, horrible. All right. "Scientists Esteemed by Public, Vaccine Scientists Seen as Similar to Scientists in General." This was actually interesting. Despite what you might think is going on in the internet, the social media world, the Annenberg survey conducted February 3 through 17, 2026 among 1,650 U.S. adults finds that, "Nearly seven in 10 people say they trust vaccine scientists a moderate or greater amount to act in the best interest of people like you."

This finding is statistically no different from the percentage who have moderate or more trust in medical scientists, 72%, scientists in general, 70%. The level of trust moderate or higher in scientists is comparable to the levels found in earlier Annenberg surveys for trusting police officers, 70%, military, 70%, and is considerably higher than trust in journalists, 49%, religious leaders, 47%, elected officials, 36%, and business leaders, 30%." I'm glad I'm not a business leader. Oh my gosh.

VR: Scientists should be up there. They save your life.

DG: They do. They do. Here is what I was referring to up above. We have the article, "RFK Jr is Holding up $600 million in Vaccines for Poor Countries," in *Politico*. It's just horrible. Basically, again, it's all about thimerosal, and that money might end up going to the evil WHO. We basically have people dying of vaccine-preventable illnesses, and he is somehow getting away with this.

VR: It's basically because of the thimerosal, which is not a problem, but he thinks it is, and so kids will die because of his brain not being able to process information properly. This is just disgusting.

DG: Can we close on a good note? Casey Means's nomination for surgeon general has been withdrawn by Trump. Dr. Means's nomination had stalled in part over her views on vaccines. The president said he was instead nominating Dr. Nicole B Safier, a radiologist at

Memorial Sloan Kettering Cancer Center, Dr. Nicole B. Safier, a radiologist and director of breast imaging at MSK Monmouth, a branch of MSK in Manhattan. He described Dr. Safier as a star physician who has spent her career guiding women facing breast cancer and an incredible communicator who makes complicated health issues more easily understood by all Americans.

VR: Do you know this person at all, Daniel?

DG: I don't, actually. I don't, but I'm about to check her out.

VR: At least she is a practicing physician, unlike Casey Means, and seems to have had a career so far, so that's good.

DG: Yes, it's definitely better.

VR: I read this article, and MAHA movement is very upset that they didn't get Means. Also, the president is very mad at Richard - the guy from Louisiana. What's his name? Cassidy.

DG: David Cassidy, yes.

VR: Richard Cassidy.

DG: Richard Cassidy. *(Bill Cassidy)

VR: Apparently, I didn't know this, Cassidy voted to impeach Trump the first time. Did you know that?

DG: I did not know that. Wow.

VR: He's still pissed about that, of course.

DG: Yes, he's pretty touchy about the impeachment stuff. He doesn't like that.

VR: He thinks Cassidy deep-sixed her nomination by asking tough questions during the confirmation hearing.

DG: Yes, she did not do very well. It was not an impressive -

VR: "Dr. Means, would you recommend birth dose of hep B vaccine?" "It's complicated." I told my class, "If you ever answer a question of mine by, 'It's complicated,' you will fail."

DG: Give an actual answer.

VR: Yes.

DG: We didn't ask a question so that you could not answer it. All right, HPV. We got some good stuff, and we're going to talk about hep B vaccination at birth, but first, hepatitis - no, human papillomavirus, HPV. The article, "Incidents of Human Papillomavirus Infections in Women Aged 27 Years and Older in United States: A Federated Data Network Study," published in the *International Journal of Infectious Diseases.* A problem with these TLAs, these three-letter acronyms, what does each letter stand for?

VR: They start to overlap, I guess.

DG: Figure 1, I posted this in, maybe David will have it up for our YouTube viewers, but it shows the cumulative incidence of human papillomavirus, HPV infection, over these different periods of time. Different databases here. I think most people would expect the first part of this curve up to age 55. We see the highest incidence in younger individuals. What's really interesting, Vincent, and maybe some of us can look forward to this or something if you happen to still be single later in life, but at 55 to 59 is where it reaches its nadir.

Then you go past 70, actually it's like the young people, it's beginning to make me think there must be a lot of sex going on in the senior population here.

VR: I heard that in the nursing homes, it's rampant.

DG: The sex or the HPV, or both?

VR: One goes with the other, right?

DG: One goes with the other.

VR: Daniel, this is interesting. It's like a U-shaped curve. The young people, 27 to 29, it's really high, and then it goes down, and then after 55 it starts to go up again. I can understand why in the older people it goes up because maybe they've never been vaccinated, right?

DG: Yes. Maybe they're not married anymore, they lost their spouse, they're starting to be sexually active. Because all you need is someone in that community with HPV to start spreading around.

VR: They're not vaccinated because they're older. Then the young, the 27-year-olds, they should have been vaccinated at 12 to 14 years of age. I don't understand why it's so high. The peak incidence here is like 20%. It's a lot of people.

DG: It's a failure of vaccine coverage, right?

VR: Yes.

DG: We've got a failure of vaccine coverage, I think, on both ends of the U-curve. We've got a failure of vaccine coverage in younger folks, we got to do better there. It does sort of make you say, let's say you're 60 years old. 60 years old, maybe the discussion with your doctor should be, "Hey, if you're going to have new sexual partners and you haven't had your HPV vaccine, maybe time to get that."

VR: Yes. As you said earlier, it's hard to get over some inertia, and doctors are still not used to giving HPV vaccines to people over a certain age. They have to get past that.

DG: The inertia in medicine and science in general is really tough.

VR: What's the formula? Force equals mass times acceleration or something?

DG: All right. The article "Economic Impact of Delaying the Infant Hepatitis B Vaccination Schedule" was published in *JAMA Pediatrics*. I'm going to hit you with another also in *JAMA Pediatrics*. First article, "Universal administration of hepatitis B, hep B, vaccine at birth has

been a cornerstone of hepatitis B virus elimination efforts in the U.S. In 2025, the reconstituted, defunct, I'm adding some stuff, ACIP, recommended delaying hep B vaccine initiation among infants born to birth parents who tested negative for hepatitis B surface antigen. Here, they modeled the impact this could have.

All delayed vaccination scenarios resulted in more infections, worse health outcomes, higher costs than administering the first hepatitis B dose at birth. Under perfect adherence, delaying hepatitis B vaccination by two months for infants of parents with negative hepatitis B surface antigen led to an additional 90 acute infections, 76 chronic infections, 29 hepatitis B virus-related deaths, with $16.4 million in added costs for infants born during the first year. Delaying to 12 years resulted in an additional 190 acute infections, 50 deaths, nearly $30 million in added costs.

Delaying hepatitis B vaccination among infants of parents with unknown hepatitis B surface antigen status or imperfect adherence to the vaccination schedule amplified all negative outcomes.

VR: This is a modeling study, and I hope it just remains a modeling study because I don't want to see this actually happen.

DG: Yes. Unfortunately, that whole discussion, now this is defunct, these recommendations are not supposed to be followed. We're still supposed to be doing hepatitis B at birth. This just shows you the information. This is the stuff that needs to be before a committee of reasonable people. "OK, you're considering this. This would be the consequence of making that change. It's going to cost you more money. It's going to hurt more people. Little kids are going to die. Stick with what you're doing."

The second article, "Impact of Removing the Universal Hepatitis B Birth Dose Vaccination in the U.S.," also published in *JAMA Pediatrics*, also a modeling study, they suggest that with the current maternal hepatitis B virus screening rate of 86%, the universal birth dose vaccine recommendation resulted in a median of 1,292 neonatal infections. In comparison, the targeted high-dose vaccine recommendation would be associated with 628 additional neonatal infections. Then they go on and look at different scenarios.

VR: The important thing here is you get 1,000 babies now who are going to be infected for life, and they're going to transmit it to other people, so it's going to just keep compounding the problem.

DG: If they follow this new recommendation, that might rise to 2,000, and then just all the snowballing that happens with that. To follow this new idea, screen everyone, not only treat certain people, you'd have to go ahead and another 100,000 additional pregnant individuals would need to be screened, et cetera, et cetera. It's a bad idea. Measles. Measles, the number keeps going up. Johns Hopkins U.S. Measles Tracker has us at 1877. Total case in the US per CDC as of April 23, 1,792. Still getting more cases there.

VR: It seems to me those circles are getting bigger, Daniel.

DG: That's what happens.

VR: What is it? South Carolina, Texas, Utah?

DG: I think the South Carolina outbreak at this point, we believe that has actually ended.

VR: It's over?

DG: Yes. All these are coming from other parts of the country now. Flu, I think we're in good shape. I have a new figure up this time. This is the NREVSS dashboard. This is this respiratory dashboard. What's nice here is you can actually have on this one dashboard, not just what's going on with respiratory season, but this one dashboard for the CDC has all the different pathogens. You got the SARS-CoV-2 in there. You've got the influenza in there with that nice peak. You can see the influenza, we're just coming right off. The common cold, right?

VR: Yes, rhino and enteros. They're up. They're still up.

DG: Oh, yes. That's going to be our summer, you get your summer colds, you're sick for two weeks. If you've got a cold and flu-like symptoms right now, it's probably entero or rhinovirus. There's no such thing as entero-rhinovirus, that's just it comes up positive on the panel there, so just people have created that as a new entity. Alright. Continue to see more influenza deaths accumulate in children. Let's talk a little bit about what we can do about this. We're going to talk about nursing home residents and we're going to talk about pediatric flu shots.

In the *MMWR*, we have, “Influenza Vaccination Coverage Among Nursing Home Residents and Healthcare Personnel, U.S. 2024/2025 Influenza Season.” This should be a slam dunk, right? These are the most vulnerable folks, they're captive audience, we got people taking care of them, so also should be another captive audience. Not great to read that during the 2024/2025 influenza season, flu vaccination coverage was 61.3% among nursing home residents and 42.1% among healthcare providers working in nursing homes.

Then the coverage among healthcare providers varied by employment type. Coverage was highest among government-owned nursing homes, 71.7%, lowest among for-profit nursing homes, 58.5%. In addition, coverage was highest among small facilities, 65.3%. Similar among medium and large facilities, 60.4%. Vaccination coverage was highest among healthcare providers working in non-profit nursing homes, 52.6%. Lowest among those working in for-profit nursing homes, 38.3%. Basically, you don't want to be in one of those big for-profit nursing homes.

VR: Daniel, this is why people get sick in nursing homes because the staff doesn't get vaccinated. This should be 100%, don't you think?

DG: It really should.

VR: Now, I understand that some people, "Oh, I don't have time," but still, there are people who object to it. It doesn't make any sense.

DG: You could offer it at the nursing home. It could be for the patients. It could be for the healthcare providers. They could even be involved in doling them out, so to speak. I think a lot of it is you end up with a population that has been misinformed and told they don't need it, or scared about it.

VR: That's right. I know who's telling them that.

DG: The article, "Pediatric Vaccine Effectiveness Among Influenza Hospitalization and

Outpatient Visits 2021-2024," published in *Pediatrics*. Here, investigators used data from seven U.S. pediatric medical centers within the new vaccine surveillance network. They included children aged 6 months to 17 years who were hospitalized or received outpatient care for acute respiratory illness. They estimated vaccine effectiveness against influenza-associated hospitalizations and outpatient visits among 19,970 children with ARI, acute respiratory illness. 14% were positive, 86% were negative for flu, 43% were vaccinated, 57% unvaccinated.

Vaccine efficacy overall ranged 34% to 60% across seasons. Effectiveness was 53% against influenza A(H1N1), 43% against influenza A(H3N2), 69% against flu B. Overall vaccine effectiveness was 57% against outpatient visits, 50% against hospitalizations.

VR: What's wrong with that? Why can't you get vaccinated?

DG: I think part of it is this whole idea that, "Oh, kids don't need that. Kids are fine. It's just the flu." These are really nice. I'm going to leave in a link. If you go to this article, Samantha Olson, the first author, actually has a video abstract where they walk you through. Kind of nice.

VR: Now to publish papers, you have to be a YouTuber, huh?

DG: (laughter) You could start publishing some more, Vincent. The companion article, "Influenza Vaccine Effectiveness in European Primary Care Pediatric Practices 2022-2024," published in *Pediatrics*. In this study in 2023, 2022-2023, overall vaccine effectiveness against any influenza was 68%. 2023 overall vaccine effectiveness against any flu was 71%.

VR: Good. Slightly better in Europe, huh?

DG: Yes.

VR: It's good.

DG: Yes. They don't have to be YouTubers, right? Because if you've got a good article, we're going to be talking about it right here for you. We'll be your YouTuber. All right. RSV. We've got a couple of things here, one is the all-viral activity, all that lumped together as opposed to the figure we had before.

VR: This is wastewater now, right?

DG: This is the Yale School of Public Health. Let's see the details on this. Yes, let's follow this link. Let's take a look and see what we got here. We have emergency departments by visit. You can look at that. This is interesting. This is actually trends in viral activity. This is not actually wastewater. This is number of positive RSV tests reported by labs participating in the CDC's National Respiratory and Enteric Virus Surveillance System.

VR: Because that first one where you have all-viral activity, it's got different influenza viruses. These are all different surveillance systems, right?

DG: Yes. They're different colors, if people are able to look at this. There's a dotted, which is CDC NHSH (sic), and then there's a solid, purple, which is the CDC NSSP. These are all different data sources, but they pretty much track.

VR: It's interesting. One of them is Google health trends, people doing searches for flu or -

DG: They even do have in there, one of the dotted lines is the National Wastewater Surveillance Program. That's a dashed, slightly purple in there. It's really interesting to see. I think, if anything, this validates our focus on wastewater because it really tracks with positive tests.

VR: Yes. The Google Trends is also good, apparently, right?

DG: Yes. Multiple sources of good data, which is great. All right. In the same, here we are in the RSV section, the article, "Impact of Universal Nirsevimab Prophylaxis in Infants on Hospital and Primary Care Outcomes Across Two Respiratory Syncytial Virus Seasons in Galicia, Spain: A Population-based Prospective Longitudinal Observational Study," published in *The Lancet Infectious Diseases*. These results come from the NIRSE-GAL, an ongoing population-based prospective longitudinal study in Galicia, Spain.

For this study, they included all infants eligible for nirsevimab. That's the passive antibody, the monoclonal antibody shots that the little kids get, 2023-2024 RSV campaign in Galicia, followed up from their first RSV season, 2023/2024, until the end of their second RSV season, which is the 2024-2025. Primary endpoint was RSV-related lower respiratory tract infection hospitalization, and they've got some secondary endpoints. The lower respiratory tract infection hospitalization, acute bronchitis or bronchiolitis hospitalization, pneumonia admission, all-cause hospitalization, primary healthcare outcomes.

Now, of 12,492 eligible infants, 94.4% coverage. Compared with historical cohorts, this is impressive. RSV-related lower respiratory tract infection hospitalizations decreased by 86% in the first season.

VR: Amazing. That's great.

DG: Fantastic. Fifty-five in the second, and they saw a reduction in several other endpoints as well. Some really nice figures where you can see what happened here. They've got this in bright red, predicted events, and then you see this almost flat, black observed events. Just tremendous, 86% reduction in little kids going to the hospital. The article, "First Report on Remdesivir Use for the Treatment of Respiratory Syncytial Virus in Five Allogeneic Hematopoietic Cell Transplant Recipients," published in *JID*.

RSV infection causes substantial morbidity, particularly among hematopoietic cell transplant patients, and lacks approved therapies. Remdesivir demonstrates antiviral activity in vitro, but data in humans are lacking. Here they describe five HCT, these are hematopoietic cell transplant recipients with RSV lower respiratory tract infection were treated with remdesivir and got better. There's no placebo. This is just, "Remdesivir was safe. It was well-tolerated. Everyone got better." We don't know if they got better more quickly. Really just suggesting this might be worth a proper look.

VR: Maybe even in non-transplant patients it could be useful in some populations, right?

DG: As we've talked about, particularly folks who are 75 and older, and then maybe move that down to under 75 but with lung disease, other risk factors. All right. Following our new link for wastewater, we've got our multicolored lines. Pretty much, we're about as low as we've been in five years. Really, really in good shape. I did actually some poor girl I got consulted on that's going to go home today with positive COVID test. I was shocked. What are you doing? Apparently, somehow, her - what is it, there's still like 90,000 new infections per day in the country, so low is relative, right?

VR: Yes.

DG: All right. I hate that we've spent so much time already because this is, in a lot of ways, this is the hot-button discussion of our show this week. Hopefully, people actually read this article. For those of you that did or didn't, I'm going to walk everyone through this. We have the article, "Oral Nirmatrelvir-Ritonavir for COVID-19 in Higher-Risk Outpatients." We have an accompanying editorial, "Same Pill, Different Impact - Reassessing the Efficacy of Nirmatrelvir-Ritonavir," published both in *The New England Journal of Medicine*.

Here we have data from, I want to point this out, it's two open-label platform trials. "Sorry, I've two trials and I'm going to stick them here together." One, because we're going to try to pull them apart and talk.

VR: Open-label means everybody knows what they're getting.

DG: Everyone knows what they're getting. We've got PANORAMIC in the UK, and we've got CanTreatCOVID in Canada. These trials enrolled what they describe as higher-risk adults. These are greater than 50 years of age or greater than equal to 18 with coexisting conditions. Just to point that out, these are just either you're over the age of 50 or you're equal to 18 or over and then you've got a coexisting condition. We're going to talk about how high-risk that actually is.

The participants were randomly assigned to receive usual care plus nirmatrelvir/ritonavir twice a day for five days, so Paxlovid for five days, or receive usual care alone. Primary outcome was hospitalization or death from any cause within 28 days after randomization. The first thing I thought we would start with doing was looking at these groups because the baseline risk will impact the number needed to treat and how big a study we will need to see a statistically significant difference. We have a nice Table 1, baseline characteristics. Basically, what you can see is the average age of folks in this study, the mean was 54.7, 54.8, 55. Pretty young, right?

VR: Yes.

DG: Median age, 55, and then women. They were mostly women, 65% to 69% women. In general, we're talking about a low-risk population, maybe like a 1% or so, or less risk of ending up with one of these endpoints. You can follow a few more characteristics. For the CanTreat Canadian population, they break down into people who are wealthier and people who are below a certain threshold. 78% of the folks were wealthier.

VR: Mostly white, also.

DG: Yes. They're young, white, wealthy, healthy women, and highly vaccinated. By highly, if you look at it, not just, "Oh, I got my first dose, my second dose," 98% of these individuals had multiple vaccinations. More than two.

VR: These are healthy people, they take care of themselves.

DG: Yes. These are healthy, wealthy, white women who take care of themselves and get their vaccines. They even have good wellness scores. Now, there are some coexisting conditions that you can see. It's interesting. You could have high blood pressure. You could have lung disease, but that might be asthma, which we realize is not really actually increasing your risk of ending up in the hospital. There are 50 pages of supplemental material where you can look more into detail about what exactly, which comorbidity, who has what.

About a quarter get in for lung disease, but as mentioned, this potentially is asthma. Maybe up to 20% get in for hypertension. 20% have listed other as a comorbidity, it would be nice to have 50 pages, what are the others? Then I think this is really interesting. [clears throat] PANORAMIC trial. We're talking about young, healthy, wealthy, white women, multiple vaccines, take care of themselves. The time to start treatment in PANORAMIC was a median of four days. They almost missed the window, and in the CanTreatCOVID trial, it was three days. Maybe the CanTreatCOVID, we'll get some better results there, but four days.

Now, from December 8t 2021 to September 30, 2024, a total of 3,516 participants in the PANORAMIC trial, and only 716 participants in the CanTreatCOVID trial underwent randomization. In the PANORAMIC trial, 0.8% and 0.7% in the usual care end up hospitalized or died. Sort of as predicted, we're looking at a population that had a baseline risk of less than 1%, and getting Nirmatrelivir or Ritonavir started on day 4, did not really move anything. This is actually right in line with the molinupiravir study with the numbers in highly vaccinated, low-risk population.

Now, in the CanTreatCOVID Trial, this is thrown in the same paper. Here, we have 0.6% in the nirmatrelivir/ritonavir group, and twice that, 1.2% in the folks that did not get the Paxlovid, and that's the hospitalized or died. That's a greater than 50% reduction, so a relative odds ratio, 0.48. A greater than 50% reduction, but not reaching statistical significance in this lower-risk population with only a little more than 300 participants in a trial that was stopped early and did not reach its recruitment target. All right. Keep going here.

In both trials, the incidence of early sustained recovery appeared to be higher in the Paxlovid group than the usual care. In the PANORAMIC trial, early sustained recovery was reported in 33% of participants that got Paxlovid, but only by 22% in the usual care group. That's an adjusted odds ratio of 1.74. It would be about 74% more likely to feel better sooner.

In the CanTreat trial, early sustained recovery was reported by 69% and 53%, so about twice as likely to feel better sooner, and to sustain, like be better and stay better. The time to participant reported recovery appeared to be shorter in the Paxlovid group than in the usual care group. We've got a nice curve where you can see, like, hey, if I'm hoping to feel better sooner, about twice as likely by day seven to feel better if you got your Paxlovid. What do we mean by feeling better? What symptoms are getting better? More likely for the fever to be gone, more likely for cough to go away, shortness of breath gets better, the fatigue gets

better, the muscle aches get better, dizziness, the headache. You can go through whether you're looking at time to alleviation or time to sustained alleviation. All those things are going to be maybe gone away twice as soon.

Now, what does that actually translate into? I'm just going to pull this together. Here we find two studies. In a lower-risk, highly vaccinated, wealthy group of mostly white women, [chuckles] they're about twice as likely to feel better more quickly. In the UK group, this translated into feeling better, on average a week sooner, and a half a week sooner in the Canadian group. If your chance of ending up in hospital or dying is already less than 1%, it's going to take a larger sample size to get that to be statistically significant.

In the editorial, they have several comments, and they point out that it is important to note that the CanTreatCOVID trial was stopped early, owing to slow recruitment, and because the supply of nirmatrelivir/ritonavir was discontinued. Although secondary endpoints are not usually highlighted when the primary endpoint has not been able to be adequately addressed, it's worth noting that the nirmatrelivir/ritonavir group had a shorter median time to early sustained recovery than the usual group, 14 versus 21 in the UK, six versus three in Canada.

VR: I think people ought to relax about saying Paxlovid is finished. This trial is not such a great trial for reasons that Daniel has pointed out. I am 73. If I got COVID tomorrow, I would take Paxlovid. No question about it. I want to feel better quickly, and I want to reduce hospitalization, even if it's really low. I had COVID after the first ASTMH five years ago in Seattle.

DG: I remember that, yes.

VR: You prescribed Paxlovid for me, the next day, symptoms were gone. That works for me, folks. I cannot imagine not taking Paxlovid. Now, I understand the cost is high. It's $1,200, right? Insurance is not going to cover it.

DG: Yes. I wish they could get that cost down. Let's say it was $50, $60, just nudging it.

VR: I'd get Daniel to pay for it.

DG: [laughs] I will.

VR: I'll do an extra clinical update. I would take Paxlovid, for sure. No question about it, notwithstanding these results.

DG: I do wonder, like a lot of the people commenting about this study, have you actually really looked at the data? We've said this all along. If your risk of ending up in the hospital, or dying is less than 1%, you're going to have to treat a lot of people to move that needle, but if your risk is more substantial -

VR: Still, you feel lousy when you have COVID. Look at all these things that they put on the list here, right?

DG: Isn't that amazing? Like your fever, your muscle aches, your fatigue, your headache could go away a week sooner. Oh, yes, but my chance of dying wasn't impacted in a statistically significant manner. I mean, come on. [laughs] Alright. We got two more to go, I think it is. Yes. One, two, I think it's two more. We'll see. We'll count as we go.

We're in the Long COVID section here. First article, "Acute COVID-19 is Associated with Altered CD8 T-cells Indicative of Impaired Ability to Control Epstein-Barr Virus *R*eactivation," published in *Medical Microbiology and Immunology*. This is in the Long COVID section because increasing evidence suggests that reactivation of latent EBV in patients with COVID-19 might be linked to the development of post-acute sequelae of COVID-19 on COVID.

Now, the reason for this co-occurrence of primary infection and reactivation of latent viruses remains elusive. During the first wave of COVID-19, this research group assessed major immune cell populations by flow cytometry in a cohort of 61 patients with moderate to critical COVID-19 at the time of hospitalization. Additional blood samples from these patients were biobanked for later analysis. Using these biobanked samples, they evaluated the co-occurrence of CMV, EBV, as well as HHV-6A and 6B by qPCR. EBV was found to be reactivated not only in patients with critical or severe COVID, that was 72.72%, but also, in patients with moderate COVID-19, that was 68% at the time of hospital admission.

In contrast, HHV-6A was not detected among any patients, whereas CMV and HHV-6B only occurred in low frequencies, that was about 10% to 15%. In COVID-19 with EBV reactivation, the degree of expression of the T-cell co-stimulatory CD28, and co-expression of CD28, and the integrin CD11A were diminished on CD8 T-cells. In contrast, the frequency of CD8 T-cells expressing the proliferative exhaustion marker CD57 increased.

Gobbledygook, unless I think you follow these markers. I was realizing as I was reading this, I was like, yes, I bet a lot of people are, "Dr. Griffith, what are you talking about, basically?" [chuckles] These surface markers collectively point to an altered activation phenotype of the CD8 T-cells and higher replicative senescence associated with EBV reactivation suggest an alteration in the CD8 T-cell compartment with impaired ability to control the EBV reactivation in the COVID patients. All right, now I'm going to vent a little here, Vincent.

VR: Go for it.

DG: I was telling you before the show, my wife always says the first person to lose their temper loses the argument. Well, alright. [chuckles] I thought we had learned something during the pandemic. There was that great idea of giving people hydroxychloroquine that resulted in 20% more people dying than if we had a little humility, and people were actually not publishing fraudulent research promoting this misstep. We still have all those people eating the chocolate-flavored horse paste, apparently now for everything from CHF to cancer. We also saw and still see such widespread use of antibiotics for viral illnesses that 80% of COVID patients got antibiotics. Now, so many microbes are resistant to the good old Z-Pak, and all our other antibiotics. What could go wrong with giving everyone rapamycin to keep them young forever, and treat Long COVID? Some people are so sure that rapamycin is such good stuff that no one wants to be in the placebo arm of a rapamycin trial. Here's this post on X from an unnamed researcher, but people can probably figure this out. "We received feedback that folks are not so eager to enter a placebo-controlled trial for fear of being in the placebo arm. For our trial looking at low-dose rapamycin for Long COVID, we now have an open label extension added to the trial so everyone gets to try it. Reach out." [chuckles] All right. We have the article, "Exercise and Weekly Sirolimus (Rapamycin)-" Got to remember that, sirolimus rapamycin. That's the same stuff. "-In older adults: RAPA-EX-01 Randomized, Double-Blind, Placebo-Controlled Trial." Published in the *Journal of Cachexia, Sarcopenia, and Muscle*.

VR: Wow. That's some name.

DG: Yes. Now, I was not familiar with this journal, but apparently, this journal has a current impact factor of 9.1. It is a high-impact, peer-reviewed, open-access journal covering research on muscle wasting, aging, and fat metabolism with a five-year impact factor of 10.8. You got to start reading this one, Vincent. There was a bit of optimism going into this as pre-clinical models suggest that alternating activation and inhibition of mechanistic target of rapamycin complex 1, that's mTORC1, could enhance adaptation to exercise. This is the cycling hypothesis. This exploratory trial assessed whether once weekly rapamycin 6 milligrams would enhance or inhibit functional gains from a home-based exercise program.

Here, we have the results of a randomized double-blind placebo-controlled trial where 40 sedentary adults aged 65 to 85, that's about 47.5% female, they were assigned one-to-one to rapamycin 6 milligrams or matched placebo once a week for 13 weeks. Both groups performed a standardized home-based resistance, so they did chair stands, and endurance, they did exercycle program three times a week. The primary outcome was the change in 30-second chair stand repetitions at 13 weeks. Complete case and per-protocol analyses were pre-specified sensitivity analyses.

Secondary outcomes included grip strength, six-minute walk distance, the SF-36 physical and mental component score, C-reactive protein, and several epigenetic age measures. Safety was assessed through adverse event monitoring and laboratory tests. People probably get a sense of where this might be headed, but with all this optimism, both groups improved chair stand performance. The primary intention to treat analysis showed an adjusted mean difference of negative 2.13 repetitions. Sensitivity analysis favored placebo, oh my gosh, and reached statistical significance.

VR: Look at that graph. The placebo did better.

DG: The placebo does. Well, this is going to be a recurrent theme. Secondary functional outcomes also favored placebo. We looked at the SF-36, again, favoring placebo. This is the 36-item short-form survey. It's a self-reported measure of health-related quality of life. To top it off, 17 participants, 85% in each arm, had one or more adverse events, but 50% more in the rapamycin group. One person in the rapamycin group ended up with pneumonia, which is felt to be related to the immune suppression that comes with rapamycin. Yes, look at them figures. All right. Let's bring this all together, all you folks that want to be in the rapamycin arm of that Long COVID trial. Once weekly, rapamycin, 6 milligrams, did not enhance, and in sensitivity analysis, it may actually attenuate short-term functional improvements from home exercise program in older adults.

Also increased the burden of minor adverse events and may have even contributed to one serious infection. Putting this in the Long COVID context, here are people struggling with fatigue, struggling to regain the ability to do activity, get in and out of a chair, maybe walk upstairs. Here we have rapamycin actually appears to be harmful in that effort. Little humility. This is why we do science.

VR: It's why we do clinical trials.

DG: Yes, because this whole idea that we just know what is true. We don't. We don't know what is true until we actually properly look. Alright. This is going to come out right as we're moving into our next fundraiser, right? We're going to be moving into our next. We're finishing off Floating Doctors. If you're listening while we're recording, which you're not, then you could send in. We're going to be starting our AS, is it? No, it's FIMROC. Foundation

International Medical Relief of Children. That's going to be our May through June fundraiser. Everyone, go to parasiteswithoutborders.com. Click on Donate. We're hoping to get up to that $10,000 to give to FIMROC.

VR: It's time for your questions for Daniel. You can send yours to daniel@microb.tv. David writes, "Quite some years ago, a local chiropractor offered to give me, a lung specialist, a two-ounce bottle of oxygen drops to place under my tongue to help me breathe. I pointed out to him that, to the best of my knowledge, the lung was the sole organ of oxygen exchange. To this, he replied that this concept was merely Guyton's Physiology, and couldn't possibly be correct. I'm guessing that he was referring to the fourth or fifth edition of Guyton, written long after lung function and gas exchange were codified. I went through PennMed from '73 to '77 using all five to six pounds of the 13th edition of Mountcastle's Physiology, 1974, as did almost all of my classmates. This was and still is an elegant book, much as Vincent's book on virology is elegant. The elegance of science and physiology, obviously foreign to this gentleman who has gone on to direct all of the Trump campaigns in Syracuse, New York. Vincent, please avoid Syracuse the next time you have a sore neck. David, PennMed, 1977."

DG: [chuckles] Oh my gosh.

VR: This is just idiots. Philip writes, "We have a three-week trip to Spain, Gibraltar, Portugal, and France. As I understand it, a polio booster is recommended for those countries. I'm well vaccinated for polio. My wife grew up in Colombia but has no memory of polio vaccine. I think there's a very high probability she was vaccinated. She's 72. She asked her doctor during her recent visits, and her doctor dismissed her concerns. 'That's for children.' We tried to get it along with a COVID vaccine at our big chain, but they don't do polio vaccines. We're going to try our big chain pharmacy. Polio is rare these days, so one would have to be unlucky to get it and really unlucky to suffer its effects. What do we know about vaccine durability for those vaccinated in the '50s and '60s, IPV and OPV? In my case, I've had both. I remember the sugar cube with the purple stain. When I was a child, I received OPV in '91. When my company was sending me to Colombia, I had a more recent IPV series. I tell people catching polio and its complications is like winning a lottery but with a prize you don't want."

DG: [chuckles] All right. Let's run through a few things here. Yes, that is one of these recommendations. Oh, if you go to these areas, they recommend a polio booster, but just a couple bits of background, high vaccine coverage in a lot of those areas. I'm not sure that most of us are actually aligned with this idea that everyone who got their polio shots needs to get it. Vincent, did you have a comment, another recommendation?

VR: I think if you have had IPV and OPV, the immunity is thought to be lifelong. If you've had the complete series, so you, he has gotten both, he should be fine, but if his wife doesn't remember -

DG: Yes, if she doesn't remember, you can actually go ahead. I know it sounds like maybe this might be that not the doctor is going to do it, but you can actually order the IPV and go ahead and get it.

VR: Your physician has to do that, right?

DG: Yes. It is funny. He mentions the - I thought it was pink. He says purple. Wasn't it pink

on the -

VR: Yes, it was pink.

DG: We were talking ahead of time about the fact that Vincent was practically perfect in every way, and that's a quote from Mary Poppins. [chuckles] The spoonful of sugar makes the medicine go down. Actually, that was a reference to the sugar cube polio.

VR: It was. Oh, I didn't know that.

DG: It actually was.

VR: Philip writes that polio is rare these days. Well, it depends where you are, right?

DG: Yes.

VR: Polio virus is not so rare. It's in wastewater in many parts of the world. That's why you need to be vaccinated to prevent acquisition of the virus.

DG: Paralytic polio. We don't want you to get paralyzed.

VR: Virginia writes, "I'm writing to seek your guidance regarding my COVID-19 treatment plan. As a 74-year-old with a history of pulmonary embolism in 2019, unknown cause, I currently take 5 mgs of Eliquis twice daily for long-term anticoagulation. In light of the recent study you cited, *TWiV* 1316, regarding the effectiveness of molnupiravir, I am concerned about my current plan. I had previously assumed that molnupiravir would be the appropriate treatment if I contracted COVID. Given my medical history and the results of the study, what treatment would you recommend I pursue if I test positive for COVID?"

DG: Yes. We haven't left this link in for a while, but I'm going to go ahead and leave in the www.covid19-druginteractions.org/checker. This is the Liverpool. You can also just Liverpool COVID-19 treatment interactions. They actually go through. You can put in the COVID drug, nirmatrelvir/ritonavir. You could put in the anticoagulation. That's apixaban. That's the Eliquis name. You've got to know that. Then they actually go through and they break it down. Let's say we make it easy, but then we're going to get harder. We start off with the low-risk. The low-risk group is somebody who say, OK, you're on the Eliquis. It's for AFib. You're on 5 mgs. Just drop that down to take a half a pill twice a day for the time you're on the Paxlovid, and then go back to your 5 mgs twice a day.

If you were on the low dose, sometimes people are already on the 2.5 twice a day. Just keep doing this. Then they have this other. For patients at high risk of venous arterial thromboembolism. Now, you have a history of it in 2019. In a situation like this, this recommendation would be reasonable. If it was high-risk, if it was more recent, then we actually sometimes will bridge people with a low-molecular-weight heparin. This one, have a discussion with your doctor. Find out exactly for you, are you high-risk for the pulmonary embolism or can you just do this, just take half the dose for the time you're on the Paxlovid?

VR: David writes, "With respect to high prevalence of respiratory infections among people dying in hospital. Another factor you didn't discuss is in-hospital infection. Pre-COVID, most healthcare institutions had a pretty cavalier attitude toward respiratory spread of infections. Crowded waiting areas, shared rooms, lack of masking, and inadequate ventilation all made for a high risk of in-hospital infection. It's possible that what this study showed is that

acquiring a respiratory infection on top of whatever else caused the patient to be hospitalized, may have contributed to their mortality. I found the resistance of healthcare institutions to accept airborne infection at the outset of the COVID pandemic to be very disturbing, and many hospital infection control boards are still resistant to the idea that poor ventilation could contribute to the spread of infections among patients."

DG: Oh, my gosh. Maybe I'm just in a mood. David, this is upsetting. I know we've talked about this several times during the pandemic. We're going to just rant a little bit here. There's a history about transmission here. It started off with this idea of the miasma, and then the idea that you actually have to get in contact with the germ to get sick. There was this 100 years ago, this real distinction that if you're going to get flu, or entero rhinovirus, or any kind of illness, you had to actually physically get hit with these, like, ballistic viral infectious particles. Then it took years and years to basically reset the needle and be like, no, no, measles, you could just enter the room after that person already left, that it's in the air. Tuberculosis, it can linger in the room, you can breathe it in. Even if it's flu, if you're in an area with this poor ventilation, let's call it that 5%, can start to accumulate.

Then we saw this with SARS-CoV-2. Early on, there was like, OK, it may be that majority of the transmission as we're seeing from people within three to six feet and the coughing and sneezing, but in poorly ventilated circumstances, we see transmission of flu, we see transmission of SARS-CoV-2.

I was optimistic at some point that there would be a real modernization of the concept of infectious respiratory particles, and we would start to understand that you need good ventilation, you need good air changes. We seem to be stuck, still fighting about droplet versus airborne, aerosol, whatever you want to call it. Still stuck with this antiquated physics of the five microns. It is disturbing because, yes, if you're sick and you're in the hospital, incredibly vulnerable time. You really should be in a single occupancy room. It should have good ventilation. People taking care of you should be vaccinated. People coming to visit you should not be coming when they're sick, potentially infecting you. I think it is really disturbing. We are maybe moving at a high level. New facilities have standards for how to keep people safe, but you're definitely correct. If you're sick enough to be in the hospital, the last thing you need to do is get infected on top of that.

VR: Susan writes, "First, thank you for the important service that you both have consistently and selflessly provided. I have faithfully listened to every weekly clinical update episode since the early days of the pandemic, and then have taken it on as my mission to share your evidence-based guidance with the people in my life, at least those who are willing to hear it. Unfortunately, sometimes well-read, but non-scientifically trained friends only hear the data you've presented as that coming from one source, and they believe it prudent to skeptically weigh it against differing other information, often misleading opinion pieces that they've read elsewhere. So frustrating."

This is all you need to listen to, folks.

"I'm writing now for two reasons. I want to share my experience with obtaining Gardasil vaccine. I'm 77. A few years ago, I had an HPV-involved squamous cell carcinoma on my thumb. As a result, I've had to be followed and screened regularly for HPV recurrences in several organ systems. After you alerted me to the study showing that vaccination with Gardasil in people with previous HPV cancer significantly lowered cancer recurrences, I've tried to get the vaccine despite my being well above the recommended age of 45. CVS

couldn't even process my prescription for Gardasil from my primary care physician. However, I found a local non-chain pharmacy that did obtain it for me. I'm having to pay $350 for each of the three shots, but at least I can get them. I thought you and your audience might like to know about this option.

I have a question for you on a different topic. I know you recommend a June and October schedule for twice-yearly COVID vaccinations for people over 65 in order to acquire maximal protection during the late summer and winter COVID peaks, but I'm wondering if the timing of the peaks differ in different parts of the world. My husband and I are going to Jamaica in early June, so just by virtue of the fact that we will be traveling to a third world country, we will get our COVID vaccine in May. We are curious if you know whether other places, such as the tropics, have COVID peaks at times that differ from those in the U.S. Thanks again for all your good work."

DG: Yes, Susan. The flu epidemiology, the COVID epidemiology, it varies by region. It is a little tricky to figure out. Yes, if you're traveling to a place where you feel like, hey, it may be low where I am, but it might be higher where I'm going, reasonable to get that vaccine before you travel.

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

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

[music]

[01:08:46] [END OF AUDIO]