This Week in Virology

TWiV 1180 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 4 January 2025

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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 1180, recorded on January 2, 2025. I have to get used to saying that. I'm Vincent Racaniello, you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Very colorful bow tie.

DG: Thank you. I'm doing my flu one again, just to remind people that-- we'll get into it. The respiratory season, it was a little late, but it is definitely going. I'm going to start with a quotation from, I will say, one of my favorite individuals. Now that they have passed, they're getting mostly lauded, but some people have been critical, interesting enough. Here's a quotation. "Whether the borders that divide us are picket fences or national boundaries, we are all neighbors in a global community." That's Jimmy Carter.

VR: Did you meet him, Daniel?

DG: I did, actually. He was interested in neglected tropical diseases, particularly Guinea worm. When they did the presentation at the Museum of Natural History there in New York, I'm some kind of patron or something at the Museum of Natural History, I was there and I was with Jimmy Carter, but I was also with the head of his Guinea worm program and hanging out with him and his wife. Jimmy Carter, he really was a sharp individual. What a lot of people said, he did so many tremendous things. He did more after being president than any president probably did.

The Guinea worm is a thing. The Guinea worm, the fiery serpent of the Israelis. When he was president, when he finished his time as president, there were 3.5 million new cases every year of this Guinea worm. What a horrible disease. It's this parasite that we've talked about where it actually gets in through the intact skin. Then over the course of about a year, it grows to be about three feet in length. It's under the skin. At some point, usually it's the lower extremity, but sometimes it can happen on the face.

The uterus will actually release a substance that causes this burning blister. Then people, just to try to do something about it, will put their feet in the cool water to cool it down. Then out come all the larval stages, which then infect copepods, which then people consume. Then the next person gets infected. We're down to very few numbers, maybe some cases in Chad or Sudan. It's almost gone, which is just tremendous.

VR: In an old episode of *TWiP*, we have a picture of you with this thing in your mouth, which I think you used to filter the water.

DG: I have that somewhere around here. Oh.

VR: There it is.

DG: Jimmy Carter actually gave me this. When I was upsetting my wife because I gave Jimmy Carter the father-in-law handshake, where you check the lymph nodes. I can never stop being a doctor, even when I'm hanging out with Jimmy Carter. Our book, our parasitic disease textbook, the last few editions have been dedicated to Jimmy Carter. You can't just put a dedication there. He's got to reword it, make sure it's exactly - Really a man who cared about details.

VR: He knew the book is dedicated to him.

DG: Not only that, but he made sure the wording of -

VR: That's great.

DG: Exactly.

VR: I like it. Very good.

DG: Actually, Chuck Knirsch spent a bunch of time with Carter because he worked on a lot of the sub-Saharan African neglected tropical diseases. He referred to Chuck as the Pfizer guy. What does the Pfizer guy think? [laughs]

VR: Very good.

DG: Jimmy Carter, it's a tremendous loss, but tremendous that you made it to 100. We're going to start off with winter vomiting disease. I don't know if you've partaken of any winter vomiting disease so far. This is quite a problem. Norovirus activity is high, lots of vomiting. Actually some of these folks are ending up in the hospital. The big thing is guidance for people on norovirus, is you can't just use that alcohol, unless you're at Chipotle where they have a

high alcohol concentration. Really get in there with the soap and water. If someone's vomiting, this is a very easy thing to get. Lots of soap and water. Spreads very quickly.

VR: Is this current outbreak unusually big. If so, why?

DG: There are lots and lots. I think there's over 90 outbreaks so far, so there's a lot of outbreaks going on. I'm not sure why, what is driving it to just be so much. The cruise ship, right? With more cruise ship norovirus outbreaks than in history. I don't know if it's because people are not getting the respiratory viruses, so they're able to get together, feel well, and then this is spreading.

VR: Maybe if you get a respiratory virus infection, it induces interferon that protects you against norovirus infection.

DG: That's interesting. I know that's been coming up on some of the episodes. You got that innate immune system turned on.

VR: There's some epigenetic innate memory that can last a few months and it will protect you against other infections.

DG: The opening of the chromatin, and the turning on of the interferon-stimulating genes. Really interesting stuff. Avian influenza. A bit this week. There's a letter and an article. There's the letter, "Critical Illness in an Adolescent with Influenza A(H 5N1) Virus Infection." That was published in *The New England Journal*. Also the article, "Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in Humans," published in *The New England Journal*. Then there's an editorial. I'm going to leave links into everything. The editorial in *The New England Journal of Medicine* is, "The Emerging Threat of H5N1 to Human Health."

There's a lot here. I'm going to go through this. Then, Vincent, I'm going to sort of ask you to hopefully jump in and put this in some context. They start with a nice summary. Let's start here. Highly pathogenic avian influenza A, HPAI A, H5N1. I like to call this highly pathogenic avian influenza in birds and cats, just to put this in some degree of context. We'll see here. It emerged in 1997, so almost 30 years ago. This has been around for 30 years. You read the news, you almost think it just arrived this year. In a sense, we'll talk about what happened just this year.

Since 30 years ago, since 1997, it has spread globally by migratory birds, resulting in infections in animals on every continent. The HPAI, so the highly pathogenic avian influenza A, H5N1 clade 2344B, emerged in 2021 and resulted in fatal infections in poultry as well as terrestrial and marine animals. Now, here's what did happen about a year ago. In early 2024, influenza A infection was first recognized in dairy cows with mastitis. That's inflammation of the areas where the udders are, breasts, basically, of the cows. They're not in that location. They're where they are in cows.

Infection in dairy cows is now widespread in the U.S., affecting more than 875 herds in 16 states. Most of the cow infections are genotype B3.13, whereas most outbreaks in wild birds and poultry are genotype D1.1. How are people going to remember this? I have a mnemonic, Vincent. For a mnemonic, think genotype B for bovine and maybe somewhat benign, and genotype D for ducks or directly from birds, or D for deadly. To date, the bovine variant

infections have been mild for people but deadly for felines, and the D, the direct variants have been deadly for birds and also pretty deadly for people.

We'll talk about that. Now that we have our mnemonics, in Canada, a 13-year-old girl with mild asthma and obesity presented with conjunctivitis and fever and had progression to respiratory failure. She ended up intubated. She actually required ECMO. She was treated with oseltamivir, amantadine, baloxavir. She did recover, but you can see, quite sick, quite a lot of supportive care. If we think about our mnemonic that she got this really deadly directly from a bird, it was the genotype D1.1. Sequencing of one isolate from the lower airways collected eight days after symptom onset showed three changes, mutations, potentially associated with an adherence, virulence, and human adaptation.

There were mutations that led to amino acid changes. Those amino acid changes were E627K, so an E to a K in the polymerase basic 2 gene, an E186 to D, and a Q222 to an H in the H5 hemagglutinin gene. It's unclear, as we read in this article, whether these changes were present in the infecting virus or emerged during the course of illness. Here's the stuff that hopefully we can talk a bit about.

The current vaccine candidates that we have neutralized these circulating strains in vitro, and these strains so far are susceptible to the antiviral agents. Studies have shown the safety and immunogenicity of these H5N1 vaccines. These are two-dose. These are prime and boost approaches that use adjuvants. Studies are ongoing looking at messenger RNA-based H5N1 vaccines, other novel vaccines. As mentioned, the current isolates are susceptible to our drugs.

VR: I don't understand the emerging threat. What if we had one severe human case, one? All the cow-associated cases are mild. What is the emerging threat? I would say 2009 H1N1 influenza, we didn't have any clue that was coming. Boom, it comes out of nowhere, been reassorting for years and so forth. Here we're watching this. By the way, 1997 were the first human infections with H5N1. The virus actually emerged earlier than that in poultry in China. This has had many years to reassort. It's been in many animals. Yes, it's in more now. This is what people are worried about. As you said, we have vaccines. We have antivirals. What more could you want?

DG: I think a lot of it is if your concern is for humans versus what we're clearly seeing is this is really impacting the poultry industry, right?

VR: Oh, yes. It always has.

DG: Millions of birds.

VR: There used to be outbreaks on poultry farms and they would kill all the birds to stop the infection. This always happened. This is nothing new. You can go back in the literature and find these kinds of culls in the U.S. and other countries for years. I appreciate people were being worried, but I think these articles are getting people over worried, right?

DG: You and I think we're on the same page here because there are a lot of these, we'll call them talking heads. These folks who may have MD degrees but they don't necessarily, like,

do research or treat patients. They're, oh, we're making the same mistakes we did in the early days of COVID-19. I don't think we're making the same mistakes.

VR: That's nonsense. These viruses have been around a long time and nobody paid any attention to them until now because they're more widespread. I appreciate the fact that there is more potential. These changes, the amino acid change that you mentioned in this young lady in Canada, it's not enough for transmission. We know that. It's not enough for transmission. Could be that the changes you need for transmission in humans make the virus less fit. In ferrets, actually, when you add amino acids that allow transmission, the virus is no longer virulent. It's less fit. You have to think about that possibility as well.

DG: It's an interesting concept, the whole what is gain of function. If something becomes innocuous, but it can do something it couldn't do before, you become less concerned. That is the big thing. What will it take for this H5N1 to be able to go from person to person, that human-to-human transmission? We've been watching this for 30 years and so far it hasn't happened.

VR: The only hemagglutinins that can infect people, H1, H2, and H3. We've never seen anything else. This is an H5. Maybe there are problems with other H numbers infecting people.

DG: We will keep an eye on it. The sky is not falling. Acute respiratory illness activity. This is a map that was just updated about a week ago. These things are always a little behind. We have some more updated wastewater things. Updated on Christmas Day. Somebody was working on Christmas Day updating this map, I guess. Lot of parts of the country with high. What is that? New Hampshire is very high. A lot of the country has moderate. Really moving into moderate and high across the country. I did want to talk about an article right up here.

It reminds me, COVID-19 is bad. Comparing it to flu is worse. I enjoyed that headline. Here is an article, "In-hospital Outcomes of Healthcare-associated Coronavirus Disease 2019, (Omicron), versus Healthcare-associated Influenza: A Retrospective, Nationwide Cohort Study in Switzerland." The headlines were interesting. I'll jump in a little bit. It's an article in *CID*. Here the investigators conducted a retrospective cohort study of patients with symptomatic healthcare-associated COVID-19 or influenza reported to the nationwide hospital-based surveillance system in Switzerland.

Here you've got folks, patients, adults. They've got to be 18 or older. Hospitalized for at least three days or more in tertiary care, large regional hospitals. They end up looking at almost 3,000 patients with symptomatic healthcare-associated COVID-19, 868 patients with symptomatic healthcare-associated influenza from nine hospitals. I really want to point out these numbers. They found a similar case fatality rate between healthcare-associated COVID-19 Omicron, of 6.2%.

It's a pretty big number, 6.2%. Trying to do the math and it's more than one in 20 people, or about one in 17 people are not surviving. Seems like a lot. The same, so 6.2 for omicron, COVID-19, 6.1% for influenza. After adjustment, patients had a comparable subdistribution hazard ratio for 30-day in-hospital mortality. A similar portion of patients were admitted to

the ICU. About 2.4% and 2.6%. They have a nice graphic abstract. We can actually see these pretty high percentages.

VR: I don't know, Daniel, this could be also related to the quality of healthcare.

DG: In Switzerland. [laughs]

VR: This could be a good number. Maybe if you went somewhere else, it would be worse.

DG: I think of the healthcare in Switzerland as being very good. You go to another place. We've talked about what's going on in the DRC where you get COVID, you get flu, and you're not well-nourished, and you don't have the supportive care that can be provided in these places. You're going to see even higher.

VR: I just want to caution people to thinking that this is not a property of the virus. This is in part a property of the healthcare system.

DG: Speaking of influenza, influenza activity across the country is, we are now high. That's based upon some wastewater data. We can actually look at the wastewater data across the country. Lots of areas where it's very high or high across the country there. Lots of flu-A activity, really only a few places where it's not in the high. If you look at a map where we're looking, and this is a little bit behind the wastewater data, that fiery red of high activity across much of the country. This is something we followed in the last couple of years. Right around this time of year, things go from that green up to this fiery red high activities across the country.

Plenty of folks in the hospital. Maybe this is a reminder, I should just point out. We say that in the outpatient setting, if you go and you see the doc and you're not doing well and it's been more than 48 hours, there's really minimal benefit to antivirals in the outpatient setting. Some studies we've discussed previously, if you end up sick enough to be in the hospital, in that context, even if you're beyond 48 hours, we're actually seeing reduced mortality, shortened stays, morbidity impact to getting that antiviral started. Just a reminder for our clinicians out there.

RSV activity, it's also high. That's an updated wastewater activity. Then if you look across the country, not maybe quite as bad as flu, but actually New York City, Vincent, is terrible. People, can you imagine this, they're discussing the recommendation of masking for RSV. Interesting enough. One of the hospitals where I work, they've decided that RSV is not really a transmissible pathogen, so you don't need to isolate for that if you're admitted to the hospital. Meanwhile, in New York City, they want people to wear masks walking around.

SARS-CoV-2, our COVID update. Then I'm going to jump right into the wastewater data. You can actually see a little bit later than we were last year, but we are exponentially rising across the country, really getting pretty high already in the Midwest. The rest of the country, we're seeing folks passing right through the moderate to heading right into the high, heading towards the very high levels.

VR: Why can't we have poliovirus on these wastewater charts? Why not? I think we should see the data. People should see. They shouldn't hide it from us. I want to see every state

wastewater. If it's zero, that's fine. It's not going to be zero. If it's high in some places and others, I want to see it. I think it's ridiculous that the CDC is hiding it from us.

DG: I agree with you, Vincent. I think that if people knew that the virus was out there, that it was circulating, that they kept seeing, it's in your environment, there are people around you who are shedding this, who if they didn't wash their hands and they handled your food before they served it to, you could end up - your unvaccinated child could be at risk. I think in coming days, having that data is actually going to be helpful.

VR: I just think maybe it would blunt this idea of de-licensing the polio vaccine that a certain individual has. If people saw that there's virus everywhere, they would say, hey, you can't do that. Right now, most people think it's eradicated.

DG: If they saw that, no, there it is. We've got it popping up in wastewater periodically in different areas.

VR: There was just an isolate in Australia.

DG: I saw that.

VR: Came from someone who came into the country who had gotten OPV somewhere else and they're shedding it. You think that doesn't happen in the U.S.? Give me a break.

DG: It happens in the U.S. Speaking about testing, remember to stock up. The flu, RSV, and COVID are all very high. The only way to tell what viral syndrome you have is to do that test. Moving into COVID early viral phase, we still have our treatment guidelines. Number one, Paxlovid is recommended. Oral treatment, 86% reduction in progression in the RCTs early on in the unvaccinated. Now we have over 800 real-world efficacy studies. The time of Omicron in highly vaccinated population was still about an 80% reduction in progression. Remember, we averaged last year over 1,000 deaths a week, so save actually 800 lives per week, which I will suggest is worth doing.

Number two, remdesivir. Number three, molnupiravir. Actually, I'll share, molnupiravir, the redheaded stepchild. Another real-world effectiveness study, "Real Clinical Effectiveness of Molnupiravir against 30-day Mortality amongst 74,541 SARS-CoV-2-Positive Patients: A Nationwide Cohort Study from the Czech Republic," published in *Open Form Infectious Diseases*. This is a population-wide retrospective cohort study in the Czech Republic. They analyzed all 74,541 patients with an officially registered diagnosis of SARS-CoV-2 infection between 1 January and 31 December 2022, aged 18 years or older, treated with molnupiravir.

It's amazing to have a healthcare system where you can just get this data. The primary outcome was 30-day all-cause mortality. Secondary outcome was 30-day COVID-19-related mortality. Here, they report that the use of molnupiravir in adult SARS-CoV-2 positive patients was associated with a lower risk of both 30-day all-cause mortality, and we have a 42% reduction there, and a 50% reduction in the 30-day COVID-19-related mortality. This effect was highly significant regardless of sex, the severity score, the hospitalization status, the vaccination status, whether they were older or under 65 years.

Remember, this is an easy lift. This is a medicine with no kidney adjustments, no drug-drug interactions. Just go ahead, take your four pills twice a day for five days. We still have convalescent plasma for some folks. Yes, you still get sick from germs. Still a big believer in germ theory. Particularly during those first five days, you can spread COVID to others. Keep those isolation guidelines in mind.

Then the early inflammatory phase, we're still seeing people where they start to get through that first week, and then they get that cytokine storm, that early inflammatory phase. This can be that bad week. People feel rotten. They might end up in the hospital. We're still seeing folks end up in the hospital as our numbers are rising. Steroids, right patient, right time, anticoagulation guidelines. It was interesting. It was a paper. I didn't include it here, but I'll just make this discussion. We very quickly in the pandemic moved from no anticoagulation to anticoagulation. Then there were some studies looking at, should this be full-dose anticoagulation? Should it be prophylactic-dose anticoagulation? A lot of those studies that were done early on showed a benefit of a full-dose anticoagulation in the general hospital patient.

A lot of us have moved to just a prophylactic anticoagulation dose. If we still see those patients who are basically laying there and not moving, very high risk, there is some clinical judgment there. Just comment about that. Pulmonary support, remdesivir, immune modulation.

Then we'll close this out with late phase, PASC and Long COVID. There was an article here that I read through and decided not to include. It was an article, another one of these articles demonstrating rehab and cognitive behavioral therapy used in this setting, which I think we've learned from ME-CFS and other studies.

You really have to be careful to select the appropriate patient population, not trigger that post-exertional malaise. Then again, balance that with all the harms of deconditioning that we see. I will say, as we've been saying for a while, no one is safe until everyone is safe. I want to thank everyone who really come out and really supported us, particularly this last month. I do want everyone to pause the recording right here. Go to parasiteswithoutborders.com and click Donate. We are doing our microbe.tv fundraiser where for November, December, January, we will double your donations up to a potential maximum donation of $20,000 for *MicrobeTV.*

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Javone writes, "I was watching CNN Sunday, December 29, and saw Laurie Garrett seemingly contradicting the information about bird flu that I've read and heard from scientists. She said there is already human-to-human transmission. What's up?"

DG: I think we already covered this, but Vincent, unless I missed something, there's no human-to-human transmission of bird flu.

VR: Years ago, there were some cases in Southeast Asia where it was suspected to have a little local, but these were always in cases where there's a lot of poultry around and you couldn't rule out that multiple people didn't get infected from the same source.

DG: I think I remember that. It was maybe Vietnam and there was the main person. Then there was a younger girl.

VR: This virus has not become human sustainable, human transmissible. There's no question about that. Debby writes, "Could you keep us abreast of the progress of the norovirus vaccine trials? This unpleasant virus has been quite a problem in my senior community this month, leading to a lot of illness and a lot of social isolation. I'm excited to see more than one vaccine is in trial."

DG: Most of us at this point, there's, what is it, 90 different variants of norovirus that you can get over your lifetime. This is something you can get many times. We'll keep you updated. As soon as there is some good data on norovirus vaccine, not only will I share it, but I will try to figure out when I can get that.

VR: I was looking at Instagram today and a post comes up for Moderna's norovirus trial, mRNA vaccine trials. They're recruiting people into it. There's an mRNA and other platforms as well.

DG: Actually people, if you're interested, sign up, volunteer to be in these trials.

VR: Ian writes, "With respect to your comments about home flu, RSV, and SARS-CoV-2 at-home antigen tests in Episode 1178, I was in Germany this summer and found these tests in the pharmacy." Ian sent some photos. "They're over-the-counter and get this, they cost €2. So cheap. SARS-CoV-2 tests alone were €1.1. I bought a bunch of the triple tests, brought them home with me. I agree that these should be available in the U.S., but I fear they could be expensive. You can get a flu and SARS-CoV-2 at home test here in the U.S., but they are relatively expensive at $8 to $10 per test.

Do you think that adding RSV to the test would have any meaningful clinical impact, given that there isn't a treatment for RSV? Overall, I think the cost of at-home antigen tests in the U.S. is too high and potentially a barrier to people using them. In addition, why doesn't health insurance reimburse for these at-home tests? Insurance would cover them at a PCP or urgent care visit, so why not at home? They're the exact same test." Ian sends pictures. This is great to have. It's a pretty big card. You're used to the small ones. It's got COVID-19, flu AB and RSV. Beautiful, isn't it?

DG: I like it, actually. I got emailed directly from people after our comments with photos of this, and Germany, it was Germany where this was. There's a couple great points here. Let's talk, what's the clinically meaningful impact? As we talked about with poliovirus, if you don't know about this, it's just not maybe something you think about. When people start realizing, oh, I got RSV and was I really sick? Then next thing you know, maybe someone's going to get a vaccine, because now there are vaccines. It helps with awareness.

It also helps that, oh, you've got RSV, why don't you take a Z-Pak and some unnecessary antibiotics? A diagnosis like this can hopefully help make sure you don't get something harmful that you don't need. I agree. This is an interesting - why are these tests so expensive? You could potentially save that urgent care visit, maybe even turn it into a telehealth visit, maybe even work from home and address things another way. Actually, a big fan of accessible testing.

VR: Now, the next topic, we had several emails, but I picked this one. Lauren is part of a “large and active still-COVIDing online community, a worldwide group. We're doing our best to minimize risk of infection and transmission. This includes keeping ourselves up to date on the

latest research." She is writing about our discussion in 1176, around 43 minutes, a listener question. "You mentioned that transmission has changed over time and that early on, 50% of transmission was from asymptomatic and pre-symptomatic. Now you said it's much less." Lauren would like to know, what are the data that lead to this conclusion?

DG: I'm glad you sent this in, because Vince and I talked a little bit about this after the show last time. Then I spent some time, really going through the data. Vincent, you made some points even just in our discussion about how good is the data we have right now. We were spoiled early on. I was going through this data in part for our paper, also in part for this question.

Early on, you had all this contact tracing, and you had the relative risk of which day you were exposed to the contact person. We had all these in-home. Now people aren't testing. I have to say that the data when I went through this, is in no way, the quality that we saw before. Even though this has been suggested, I'm not sure how confident I can be in that statement that I made.

VR: I think that the lack of testing and so forth really makes it difficult to make that a conclusion. Then, lastly, Barb writes, "I'm a pediatric subspecialist looking for advice for management of COVID isolation in my personal home. I understand that there was no change in knowledge for which the CDC based its updated isolation guidelines, but rather a sense of isolation fatigue. That being said, it would seem that for people who still care, it would be nice to have updated data with information that might include prior infection, recent vaccination, time from last, severity of illness, perhaps, and if possible, a rapid antigen test, negativity repeatedly.

I know the data has not really supported the use of rats, rat negativity to imply lack of infectivity, though many knowledgeable and well-meaning people still rely on this. I think it stems from a desire to have some objective measure by which to end what seems to still be a very long necessary period of isolation. By way of practical example, my spouse, early 40s, had one day of fatigue, malaise, two nights of fever, no URI symptoms. Rapid antigen test was just barely positive. In fact, there was a discrepancy between us as to whether it was really positive.

Recent, a month ago, vaccination with Novavax, one prior infection. As I read the data, isolation at home should last a minimum of seven days, based on this *CID* paper and more confidently 9 to 10 days. Even as someone who has been particularly careful for much longer than many around me, this seems like a long time for someone who was sick for such a short period and had such a recent vaccine, not to mention the data, less equivocal rapid antigen test. You have any updated data or practical advice?"

DG: In a lot of ways, Vincent, this ties very well into the discussion we just had about when transmission happens. Early on we had all this really good data. Then as you mentioned, just at some point in time, and maybe it was because of this isolation fatigue, early on when they recommended 14 days, we had about a 2% acceptance rate. From a public health messaging standpoint, that was honest, but not particularly useful. When they shortened it and made a suggestion of 10 days, a little bit more of an uptake, maybe 8% to 10%, but again, not much going on.

I'm not even sure with the five days, if that idea that that was a better public messaging as a result in much better uptake, because I think it's really just most people have taken that as the, I'm not going to isolate at all and I'm not going to test because if I test, I might end up getting penalized with this five days. I don't think there is a lot of recent great data that helps with this. I think we're still stuck with the data that we had from early on.

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

DG: Oh, thank you. Everyone, enjoy the holidays. Happy New Year, and be safe.

[music]

[00:38:20] [END OF AUDIO]