This Week in Virology

TWiV 1166 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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Vincent Racaniello: Support *MicrobeTV*. It's time for our annual fundraising drive. We depend on your support to produce high-quality science videos and podcasts. Now is the time to help us. If our programs have appealed to your science interests, or if they have helped you in some way, please record a brief audio or video with your phone and tell us about it. Let us know how we empower your inner scientist. We'll use it for our fundraising efforts. Send it to incubator@microbe.tv. For more information on how you can give us your support, go to microbe.tv/contribute.

Daniel Griffin: *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 1166, recorded on November 13, 2024. I'm Vincent Racaniello. You're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

DG: Hello, everyone.

VR: I can't really tell. It looks like you have a virus on your tie.

DG: It's Creutzfeldt-Jakob. These are misfolded proteins.

VR: It's too far away. I can't see it.

DG: Yes, people zoom in, I think, and then they can see.

VR: Creutzfeldt-Jakob. OK.

DG: I've actually seen some - Occasionally, I watch our YouTubes, and sometimes the production people do a zoom-in on the bow tie and you can really -

VR: David likes to zoom in. That's good.

DG: Good job, David.

[chuckling]

DG: Hello, everyone. I've got a lot to talk about today. I don't know if this will be a trend. This will be the second time where I do two quotations right up front. They're from the same

author. They're actually, I think, from two different books in his trilogy. I am working my way gradually through, probably about 120 hours of reading here. First quotation. "To effectively contain a civilization's development and disarm it across such a long span of time, there is only one way. Kill its science." We'll talk about that. "Weakness and ignorance are not barriers to survival, but arrogance is." That's Liu Cixin. I don't know how that's actually pronounced. C-I-X-I-N. Maybe people can tell us. That's from *The Three-Body Problem* and *Death's End*.

VR: Civilization is a big thing. It's not like hunter-gatherers, right? Because they didn't have any science.

DG: There's an interesting idea behind these books. If people have either read the books or watched the Netflix series, the first of the trilogy, they pull stuff from other books, but the first Netflix season is a way maybe some people have accessed this. There's a lot of suggestion that the books have a science fiction discussion about the way things are different in China and the United States. Some interesting ideas there. All right. Let's jump into first thing that maybe our listeners may have heard about. Bird flu. I just got an update on this.

Our listeners may have heard even a little bit more. BC teen, British Columbia teen, in critical condition in hospital with first presumptive human case of bird flu, in Canada. We heard from Dr. Bonnie Henry, who's the BC provincial health officer, that there's a teenager in children's hospital with, at this point when it first came out, they were saying presumptive case of H5N1 avian flu in critical condition. The patient was admitted late. This is going to be last Friday, about eight days before our episode drops. Condition varied over the weekend.

Just Tuesday, we're recording here on Wednesday, just yesterday had taken a turn for the worse. Now, interesting enough, the symptoms started, not surprisingly, with conjunctivitis, as we hear from Dr. Henry. When initially it comes out, they say, here we did a PCR at the British Columbia CDC lab. Needs to be confirmed at the National Microbiology Lab in Winnipeg. Yes, we have an update. This was confirmed to be H5N1.

Even a little bit more information, we have sequence. Based upon the sequence, not only is this H5N1, but it actually looks like it's closely related to the H5N1 viruses that are circulating in the British Columbia poultry, meaning it belongs to the 2.3.4.4b clade and to the D.1.1 genotype. Let me translate that. What that means is this is a different genotype from the B3.13 virus that has infected U.S. dairy cattle.

VR: I guess we're following in the tradition of SARS-CoV-2 variants.

DG: People should be all familiar with all the variants. This isn't really like an offshoot. I'll also point out that the U.S. Department of Agriculture, Animal and Plant Health Inspection Service, I don't know if people are familiar with APHIS, also a little bit of updates here, five more H5N1 outbreaks on poultry farms, including a massive layer farm in California's Kern County that has over 2 million birds. Two other outbreaks in California, a large broiler facility in Fresno that has about a quarter-million birds. A turkey breeder farm in the same county with about 40,000 birds. Then also seeing an H5N1 in Montana's Missoula County, as well as a turkey farm in Utah's Piute County. Lots of bird flu. What are your thoughts here? I'm trying to make sense of this, Vincent.

VR: This probably came from a bird of some kind. It's not the same clade that's going through cows.

DG: We're thinking migrating birds. They're following the -

VR: Could be migrating birds. I don't know if the kid had any contact with farms, poultry or anything like that.

DG: They're doing the investigation. So far, no. So far, it doesn't look - so far, no known poultry exposure.

VR: It could be from a poultry source. It could be from wild birds. It's interesting. When humans have gotten H5N1 from wild birds or poultry, it tends to be virulent, right? The infections are severe. I'm not surprised that this child has problems. The cow virus in the U.S. doesn't seem to because very serious infections in people, as you know.

DG: I think that's actually the important point that you think about. Right now, I think there's nine cases of H9 influenza over in China. Usually, when we're seeing that direct avian into humans, people have been pretty sick, 20%, 50% mortality. Almost all the cases that we've seen are either asymptomatic or maybe some conjunctivitis.

VR: We've had 14 human cases since April of the cow-adapted H5, 238 herds in 14 states are positive, and that's just going to increase. The interesting thing, it infects other animals, foxes, bears, seals, sea lions, cats, dogs, mink, and goats. It's not good that it's infecting so many things, because the more things it infects, the more variation it can undergo.

DG: It's mammal-adapted, and once you're in these mammals, then that's the opportunity.

VR: I think we have to keep our eye on it. I have a paper for the next *TWiV* where they have an isolate from a Colorado guy who got it from a cow. The guy's OK, but the virus is lethal in ferrets, and it also transmits among ferrets.

DG: I saw that. I'm looking forward to that.

VR: What does that mean, that ferrets are not people? Oh, we know that already. I don't like the fact that it's transmissible, but on the other hand, maybe ferret transmission isn't the thing. I just don't know.

DG: Concerning that it's getting this opportunity for selection pressure.

VR: Sure. I think we should be ready. We have an email about that, so we can talk about that later.

DG: Excellent. Marburg, some good news. Rwanda begins countdown to declare Marburg outbreak over. Kigali, Rwanda, has discharged the last Marburg virus disease patient, kicking off this mandatory 42-day countdown to declare the end of the outbreak. Good job, Marburg. Good job, Rwanda, on containing Marburg. The country has reported no new confirmed cases since the 30th of October, 2024. As mentioned, the last patient was discharged on the 8th of November 2024. You do this thing where, once they're basically cleared, then you start this.

Contacts of the last patient, along with those previously discharged, will be followed up until they finish this 21-day observation period.

Then the outbreak can only be declared over if no new infections arise 42 days after the last confirmed case test negative. Hopefully this will be over by Christmas. We're starting to see just a slight rise in cases of the flu. We did have our first death in a child this season from influenza. There's a couple different ways of looking at that, the large overview where we can see what's going on. Then you can actually do a close-up. You start to see a little bit of an increase there. Still plenty of time to get that flu shot, but not so much time. I don't know if you ran across this, but I put this into our human flu section, but it's a bird flu thing.

This is this *MMWR*, "Serological Evidence of Recent Infection with Highly Pathogenic Avian Influenza H5 Virus among Dairy Workers - Michigan and Colorado, June-August 2024." I want to point out, highly pathogenic avian influenza in birds, not as we're seeing in people. This is -

VR: No cows. Cows. don't get very sick.

DG: Yes, cows don't get sick either. They don't get very sick. It's hard to know, Cows are not very -

VR: They're not very loquacious.

DG: No. It's like talking to a two-month-old. It's April 2024. Sporadic infections with the H5, we call it the cow-adapted virus, have been detected among dairy farm workers in the U.S. To date, infections have mostly been detected through worker monitoring and have been, as we keep repeating, mild. Usually some irritation in the eyes, maybe some mild symptoms. During June through August 2024, so this summer, the CDC collaborated with the Michigan Department of Health and Human Services, the Colorado Department of Public Health and Environment to implement cross-sectional serological surveys to ascertain the prevalence of recent infection with the cow-adapted H5N1 virus among dairy workers.

In both states, they did a convenience sample. They didn't get everyone. They were able to get the people they could get. They collected blood samples. A little bit of a selection. Maybe a few more people are getting infected and we're just missing the diagnosis. We don't know. Among 115 persons, 7% had serological evidence of recent infection. All reported milking cows or cleaning the milking parlor. People have been in a milking parlor. It's not a parlor as you might think. Among persons with serological evidence of infection, when you actually asked them, you said, by the way, about half of them said, yes, I was sick when the cows were sick.

Symptoms began before within a few days of the H5N1 virus being detected in the local cow herds. I have a context here. They give us a context. They have this nice discussion where we read that before the emergence of the clade 2.3.4.4b viruses, seroprevalence among workers exposed to infected poultry were really low, 0, 0.6 globally, 4.6 in Egypt after the emergence of this 2.3.4.4b virus in poultry. Here we have a new type of bird flu that seems to be different in that it affects a significant number of people. We're not seeing, as we mentioned, that 50% mortality, that severity disease we see with a lot of the H5N1 bird to human avian flu reports.

I'm going to leave in a link with all the genetics so people can follow that. I'm sure no one will do that.

VR: Earlier this year, a virus went into a cow somewhere and a variant emerged that has since spread to cows everywhere else in the U.S. It's all the same virus. As I said, it's on 200, let's see, 238 dairy herds so far. As you might expect, when so many cows are infected, the people working with them get infected. That's why we have 14 cases and probably more because people are not getting very sick. It doesn't seem to transmit among people. This is all good.

DG: It's all good, except the more people that get infected, the more opportunity for some selective pressure.

VR: You have to be vigilant.

DG: Mpox. Last week, I was heading to the city to meet my dad, my daughter, Daisy, and my cousin, Peter Daytz. Sometimes he's my cousin, sometimes he's my honorary cousin. We were going to have dinner and I've taken the train in. I get my email, my CIDRAP update shows up in my inbox. The headline that caught my attention was, "Cases Top 50,000 in Africa's Mpox Outbreak." What's happening? Our listeners are aware that this clade of the monkeypox virus that causes the mpox disease is mainly affecting children. Immunizations haven't yet started for children, which really the hardest hit groups.

This has to do with regulatory and supply issues. Currently the Bavarian Nordic JYNNEOS vaccine is only approved, only recommended for adolescents and adults. We hear from the Africa CDC that they're working with Japan to try to get three million doses of the LC16 vaccine. They're also going to do a trial, which is actually opening up to look at getting approval, looking at safety of doing the Bavarian Nordic in the youngest kids. Hopefully we'll get some movement there.

All right. RSV. What is going on in Maryland? I got the map up here and maybe David will show that if people are watching on YouTube. You can see, sort of low minimal activity in most of the country, starting to see that moderate activity in Georgia. What is that, Alabama or Mississippi? I can't tell the two apart. Which one is next to Georgia? Do you know, Vincent?

VR: It's Alabama.

DG: If you say so.

VR: That's my guess, actually.

DG: At some point I need to learn. That's the one state I've never been to. I never really -

VR: Which one?

DG: Alabama. I've been to all 50 states except Alabama.

VR: Alabama borders Georgia to the west.

DG: It's Alabama and Georgia that are starting to see moderate - That's usually the way RSV starts in the Southeast and then spreads upwards. Just, if we see our traditional pattern,

which we've been seeing for many years now. For some reason, Maryland has very high RSV activity. I don't know, let's see what happens there.

VR: You know how you can tell that's Alabama and not Mississippi, because Mississippi is the state over. That contacts the Mississippi River, which flows through Louisiana and Mississippi is right next to Louisiana.

DG: I got it. I'm never going to get that wrong again. COVID. How are we doing with COVID? In general, doing pretty well. Minnesota and Virginia actually are still in that 2% to 4% of deaths due to COVID in the past week. What's going on with our wastewater? We're still down pretty low. there's always a little bit of a lag. I put up for David to share on YouTube the CDC, but there's also a more real-time wastewater monitoring, which I leave a link into as well, wastewaterscan.org. Still, activity is pretty low across the country for SARS-CoV-2 at the moment.

Active vaccination. We've spent a little time on vaccines, if that's still allowed, Vincent. We talk a lot about vaccines. We've discussed how they work, how safe they are, how effective they are. When rare safety issues come up, we make sure to discuss those. Unfortunately, it appears that after reading the article, “Trust in the Science Behind COVID-19 Vaccines as a Driver of Vaccine Acceptance in the United States, 2021 through 2023,” published in *Vaccine:X*, it looks like at least one-third of Americans don't listen to *TWiV* or watch our show on YouTube, because you don't have to listen, you can watch us.

Here, these investigators used stratified random samplings for key demographic variables. They're looking at age, gender, race/ethnicity, region, education level, and they're going to analyze data from a series of cross-sectional surveys that were conducted in 2021, 2022, 2023. They found that trust in science actually has remained relatively stable over the study period and actually continued to be a strong predictor of vaccine acceptance. I'm going to pause there for a second, Vincent, because you almost get the sense that that's not the case, that people are losing trust in science. Apparently, according to surveys, people still trust science.

VR: I guess politics have made us think that there's less trust. I don't know.

DG: It looks like there still is a lot of trust. It looks like the trust in science is strong. There are a couple things I'm surprised by. One, they say trust in science was higher among male respondents. That surprised me. That's the data. Those with university degrees, so those that maybe have had more exposure understand what's under the hood. Those with higher median income.

Interesting, they point out, and this makes sense, experience of personal loss was significantly related to an individual's trust in science and vaccine acceptance. If you're asking a question about do you trust this vaccine relative to a certain disease, if a person has experienced the horrors of that disease, then they seem to be more willing to accept the vaccine. I was listening to Neil Young earlier this week on one of my runs, a very pro-vaccine individual, because he had his personal experience with polio as a child.

VR: In Figure 1, Daniel, even though over 80% have trust in science, 26% in that one column will take recommended future boosters. 26% of the people don't have no trust in science

behind COVID vaccines. Those who received one dose, 56% have no trust in science behind the COVID vaccines. It's a lot. They're doing it anyway.

DG: They're like, you know what? I really don't trust it, but I'm going to do it anyway.

VR: I wish I understood where the lack of trust comes from. I would try and fix it. I think it comes from these pundits who are trying to sell their own products, and so they spew misinformation. We cannot reach these individuals because we don't have big enough reach.

DG: I think that's the challenge. Just maybe go ahead. When someone starts, spewing anti-science, anti-vaccine, just ask, so what are you trying to sell me? As we discussed last time, maybe they're trying to sell you their pandemic preparedness pack. Maybe they're trying to make $1 million a month off you on their Substack subscription. If someone is making money off misinforming you, just ask. What's here for you?

VR: I would like if they had included *TWiV* listeners.

DG: We could redo this.

VR: What fraction of people have trust in science who are also *TWiV* listeners?

DG: I feel like I know the answer, but you still got to do the science. They follow it over time. Trust in science, actually, it's holding pretty strong over time. There's a nice Health Day companion article, “COVID Vaccine Mistrust Levels Aren't Budging, Study Finds.” Here they report, the study found that more than a third of Americans continue to express mistrust in the science behind COVID vaccines. That's really different from trust in science in general. Actually, the level of mistrust in the vaccine has always been about 30%. Which is interesting to me.

Because early on, when people weren't sure about the COVID vaccines, things like, I don't know, they're so new, it's this new technology. It's now been, four years. All those years have gone by. All those original arguments about, oh, I don't know, let's see, we've had four years, we've had great experience, we have all this safety and efficacy data. It's interesting, those people, they're not budging. People do not like to change their minds.

In the spirit of we talk about when there's concerns, the U.S. FDA had paused for a while. Now the FDA lifts the clinical hold on Novavax's combo COVID-flu shot. What happened here is Novavax is doing a trial with a - it's a one shot, get your COVID-flu vaccine all at once. They had a participant who had gotten the combination vaccine and reported symptoms of motor neuropathy or damage to nerve cells that control muscles or movement. They investigated this, turns out the participant's symptoms were found to be due to ALS, amyotrophic lateral sclerosis. This is a condition that affects nerve cells in the brain and spinal cord. Not related to the vaccine trial. Vaccine trial is moving forward. Just gives you an example of how much we all focus on safety. If there's a concern, we stop, we pause, we clarify before just moving forward.

VR: It also shows that rare things can happen that have nothing to do with the vaccine.

DG: I remember the child that swallowed the marble in one of the COVID vaccine trials. There was this whole like that's in the potential adverse events. I really don't think the vaccine triggered the child to swallow the marble, but all right.

Just as we like to remind people, we have a guidelines. People still are getting COVID-19. We have ID Society guidelines, we have NIH COVID-19 treatment guidelines, and number one, Paxlovid. Let's talk about this. This article I'm going to mention reminds me of several of the Osler quotations that feel like I already went here. How once a person makes up their mind, they stop thinking because there's something human about not wanting to be wrong. All those people that I don't trust these new vaccines. Will you trust them when they're not new? No, I don't trust them. I made up my mind. I'm done.

I don't know if people remember last week's quotation, "One special advantage of the skeptical attitude of mind is that a man is never vexed to find out that after all he's been in the wrong." That was William Osler. Many physicians and non-physicians made a decision about Paxlovid a few years ago, and they actually seem unwilling to revisit this despite the now over 700 publications since that RCT, that randomized control trial. These publications have refined our understanding of the benefits of this medication. This week we got two more to throw at you. What is it? Who's the astronomer guy? People will not think themselves out of a position that they weren't - didn't think themselves into. Neil Tyson -

VR: Isaac Asimov?

DG: I think he also said it. Yes. Isaac Asimov.

VR: Arthur C. Clarke may have said it. I don't know.

DG: People can write in and they can let us know. Yes. I was talking about a publication on the *ID Puscast* where the people quote Aristotle, except it wasn't actually a quotation from Aristotle. It was in a peer-reviewed journal. We've got the article, "Real-world Effectiveness of Nirmatrolvir-Ritonavir and Molnupiravir in Non-hospitalized Adults with COVID-19: A Population-based Retrospective Cohort Study, Cohort Study." They've got sort of in there twice. These are results of a retrospective cohort study. They use data from the municipal data of public health services, Vienna, Austria, to identify non-hospitalized adults with confirmed SARS-CoV-2 infection between January 2022, May 2023.

Nirmatrolvir-ritonavir, Paxlovid, users were compared with untreated controls, and molnupiravir users compared with untreated controls. Outcomes were hospitalization, all-cause death within 28 days. They identified 113,399 eligible cases. You've got 90,481 untreated controls, 12,166 in the Paxlovid, 10,752 in the molnupiravir group. Just to give this our current context, over 96% of the patients were immunized or previously infected. Remember Omicron's been here since when? End of 2021. This is all immune infected with Omicron.

Mostly immune, 96% infected with Omicron. In the Paxlovid analysis, the estimated risk of hospitalization was 0.57%, so about half a percent. In the people that didn't, so the untreated, it was over 1%. You're cutting that in half. What about deaths in the Paxlovid group? Nobody died. There were deaths in the untreated group. There's actually a really nice sort of Meyer-Kaplan curve where you really see that separation as far as terms of hospitalization. You see

everyone who got Paxlovid survived, but then you can see the people dying who did not get Paxlovid.

A couple comments. The statistically significant reductions were restricted to the subgroup of patients 60 and over, hospitalization and death. We really didn't see significant benefit in the molnupiravir group. They wrap it up with their conclusion among outpatients, 60 and over with COVID-19 in Omicron dominant era, treatment with Paxlovid was associated with a lower risk of hospitalization and all-cause death.

Now we also get another article. People like, oh, but again, that's a cohort, it's retrospective, I want another phase 3 randomized trial. Here we've got it, "Alleviation of COVID-19 Symptoms and Reduction in Healthcare Utilization among High-risk Patients Treated with Nirmatrelvir/Ritonavir (NMV/R): A Phase 3 Randomized Trial," published in *CID*. These are the results from a phase 2/3, double-blind, randomized one-to-one study that assessed Paxlovid versus placebo given for five days, people, in high-risk, unvaccinated, non-hospitalized symptomatic adults with COVID-19 from 343 sites across 21 countries. In testing the primary endpoint of COVID-19 related hospitalization and all-cause deaths.

They also have some secondary endpoints, including symptom duration and COVID-19-related medical visits. What do we find here? Randomization involved enrollment from July, 2021 through December, 2021. We end up with 977 in the Paxlovid group, 989 in the placebo group. They have to have symptom onset within five days, no monoclonal antibody treatment. What did we find? Paxlovid significantly reduced times to sustained alleviation and resolution of symptoms. Couple days, we moved from 15 down to 13 and complete resolution.

I always worry about the binary, but complete resolution instead of 19 days, 16. You feel better in two to three days. You also get a significant reduction in the number of COVID-19-related medical visits and the proportion of the patients with such visits. Hospitalized patients with Paxlovid, so let's say you end up in the hospital. It's not a binary there. The people that ended up in the hospital had shorter stays. None of them required ICU admission. None of them required mechanical ventilation. All were discharged to home and self-care. Fewer of the Paxlovid treated patients required any additional treatment.

No Paxlovid treated patients died through week 24 compared to 15 that died in the placebo group.

VR: It works.

DG: Not only does it make you feel better quicker, it does make you feel all better quicker. Not only does it reduce your chance of going to the hospital, but if you do go, you're going to have a shorter and easier stay. Just with a group here at 989 versus 977, you actually have 15 deaths in the placebo group and we prevented all those with Paxlovid.

VR: Tell me again why some physicians will not use it.

DG: I think it's the Osler thing. They decided three years ago and they stopped reading the literature.

VR: I see. It's not helping their patients to do that, Daniel, right?

DG: What's that?

VR: Their charge is their patients and it's not helping their patients by not reading.

DG: That's the challenge. You got to take this oath seriously. We take an oath. How do we take care of our patients? With evidence about what actually works. There's nothing mysterious under the hood with science. Basically something like this. We say half the people get the drug, half the people don't, none of the people got the drug died, 15 of the people that didn't get the drug died. People in the hospital, people on ventilators, if they didn't get the drug.

Number two, we have remdesivir. Number three, molnupiravir. Also convalescent plasma in certain contexts.

Remember, if you got COVID-19, you're contagious. Then the COVID, the early inflammatory phase. We have that initial phase with the viral replication. Usually have that viral syndrome. That's where you do your risk calculation. You don't say, how are you doing? You don't wait and see, because people can then end up in the early inflammatory phase. That's where they might end up in the hospital. They might have a low oxygen saturation. They might end up on steroids, anticoagulation, might require pulmonary support. There still may be a window for remdesivir and then immune modulation.

I'm going to wrap us up with some really interesting stuff here in our late phase, post-acute sequelae phase. The article, "Post-acute Sequelae of SARS-CoV-2 Cardiovascular Symptoms are Associated with Trace-level Cytokines that Affect Cardiomyocyte Function," published in *Nature Microbiology*. We've discussed individuals with PASC that have effects on their heart. Here, these investigators took blood samples from three groups. They looked at recovered individuals, those with prolonged PASC cardiovascular symptoms, so PASC-CVS, and SARS-CoV-2 negative individuals, apparently still out there.

They found those with PASC-CVS, so that's post-acute sequelae of SARS-CoV-2 with cardiovascular symptoms. They found that they actually had a blood signature linked to inflammation. Trace-level pro-inflammatory cytokines were detected in the plasma from these folks with the PASC-CVS 18 months post-infection using, you ready for this, nanotechnology, which apparently is cooler. Importantly, these trace-level cytokines affected the function of the primary human cardiomyocytes. Plasma proteomics also demonstrated higher levels of complement and coagulation proteins in the plasma from patients with the PASC-CVS, PASC with cardiovascular symptoms.

There really are some, I will say, interesting figures, draw people's attention, and maybe David will put this up for folks if they're watching on YouTube. In Figure 2, you can actually see a really nice heat map where folks with the PASC-CVS have this humoral immune response or heat signal, this neutrophil degranulation reactome heat signal. Then you can even see a lot of upregulation with platelets, platelet activation, inflammatory molecules, things that affect homeostasis, complement, and other things. I'll let people take a look at that. Then, of course, Figure 3, where you get to see the nanotechnology results, where they look at a number of cytokines.

There's a little bit of an overlap, but I'm going to say a little bit of an overlap because you almost start to see separation with IL-6 levels, IL-1 beta, maybe some overlap with IL-12, but interesting stuff there. I will wrap us up before our emails by saying no one is safe until everyone is safe. I want everyone to pause the recording right here, go to Parasites Without Borders, click Donate. The donations, they need to come in for us to keep doing this work. Every small amount helps. We are doing our *MicrobeTV* fundraiser where November, December, January, we're going to double those donations. We're going to get up to a potential maximum donation of $20,000 to support *MicrobeTV.*

VR: It's time for your questions for Daniel. You can send them to Daniel at microbe.tv. Susan writes, "Have you seen an increase in NTM, MAC, and bronchiectasis since COVID? I am a 65-year-old female who has all my vaccinations, COVID-19 twice. I've also had another respiratory virus that wasn't identified. I've been recently diagnosed with NTM, MAC, and bronchiectasis."

DG: Interesting, Susan. For listeners, so these are the non-tuberculosis mycobacterium, so the mycobacterium other than TB. I have to say I've seen more of these in my practice than I did pre-pandemic. That's anecdotal. I'm not sure if they've actually been reported that there's been an uptick in cases. Actually I saw two just yesterday in clinic, which is a lot to see.

VR: Charles writes, "I saw this today and it fit with my previous two emails. I'm sending you a link. This is a *MedPage Today* article. I really would like to understand why the IDSA guidelines on the treatment and management of patients with COVID has the following: Nirmatrelvir/ritonavir - conditional recommendation, low certainty of evidence. Remdesivir, same thing. Molnupirair, same thing.

Convalescent plasma, same thing. Conditional recommendation, very low certainty of evidence. I'm a computer programmer, not an MD. When I look at the evidence for the first three, I don't see a low certainty of evidence. In the large well-run, (ie treatment given early) studies, I see a high certainty of evidence. What do I have wrong, or why is the IDSA being so conservative?

DG: I don't know if it's conservative as much as the way they grade evidence. There are certain rules about how evidence is graded. What do you really want? The highest level of evidence - and people are a little critical of this - are placebo-controlled, randomized, prospective trials. Let's go through. What would you want with Paxlovid, nirmatrelvir/ritonavir? What you're going to want is you're going to want several prospective, randomized, controlled trials.

You're going to want to see them in the current viral variant. You're going to want to see them in vaccinated. I have to say, the last time we published our American Society of Hematology Guidelines, we've got all our guidelines, we looked at all these studies, we end up saying low certainty of evidence. I think it's something to do with the way we communicate in science. When you look under the hood, you see that we are basically willing to accept that we may learn, there may be more information that comes in.

VR: Lis writes, "Could Daniel add the required reporting data that starts November 1 to clinical updates? See below. On April 30th, some federal reporting requirements for hospitals and critical access hospitals expired. This resulted in voluntary data reporting, which led to

reduced visibility. The Centers for Medicare and Medicaid Services has issued a new rule requiring hospitals and critical access hospitals to report information about COVID, influenza, and RSV starting November 24th." She provides a link for that.

DG: I will add that to our updates.

VR: Mike writes, "Given the mRNA vaccines don't seem so durable, is there a possibility that J&J actually wasn't as ineffective as people thought if it had been compared over a longer time period? Are there any studies on this?" Mike, who got a J&J vaccine and had all his friends make fun of him."

DG: Mike, I'm sorry that all your friends made fun of you. Yes, that's an issue. It's crazy how excited people got about the mRNA vaccines. Now we're learning more. We're learning issues about why it seems that we have to keep giving these boosters all the time. Are you going to find that J&J vaccine that will make your friends stop making fun of you, that J&J vaccine study? I'm sorry, Mike, you're just going to have to live with that.

VR: This is the paper where they reported no bone marrow memory, long-lived health.

DG: Show them that, Mike. Not only will they laugh at you.

VR: For mRNA vaccines, they did have a couple of people who got adenovirus-vectored vaccines and had the same results. It's not a lot of data, but it's out there. Hat writes, "Should we be treating asymptomatic congenital hep B patients with etecavir/tenofovir to delay onset of liver disease, A/O cancer?"

DG: That's a good question. We have certain guidelines. I have to say, some of the experts in the field - and you were remotely at that hepatitis B conference?

VR: Yes, I was.

DG: I think Rich went in person. A lot of the experts are wondering why, particularly in the U.S., we're so conservative. We wait to address congenital hepatitis B treatment. Again, this is a question like, we need the data to go forward with the recommendations. I guess that's what I'll leave it. This is an excellent question. A lot of people are curious, why we are so conservative? Why are we waiting to treat hepatitis B patients?

VR: Connie writes, "Thank you for your invaluable show, which has gotten me through COVID. Do you have any information on what steps the government or industry are taking in developing a vaccine for avian flu? It doesn't seem far-fetched that the virus will mutate to be dangerous to humans. Could the mortality rate really be 50%?"

DG: Connie, actually, this is good though, because we covered this quite a bit today. We've seen this 20% to 50% mortality when the avian flu goes directly from birds to humans, which is quite different than what we're seeing with the cow-adapted. Yes, there are vaccines, there's lots of research. We've got to keep doing this because it's not far-fetched. Just because the virus became adapted to do well in cows and currently is not causing severe disease in humans, there's no reason that it can't have selective mutations and end up making people really sick. Vincent, any thoughts?

VR: There is a vaccine stockpiled. Others are in development.

DG: Tamiflu, we've got antivirals -

VR: The antivirals work. We can never predict virulence and transmissibility, we can just talk about it, but you can be ready. I think we're pretty ready for this one, don't you think?

DG: I feel like that was the problem with COVID-19, is everyone has been ready, is ready for the flu pandemic, and we got a coronavirus one. Now everyone's like, can we be ready? That's always what people are predicting is it's the next big flu pandemic. It's not far-fetched to be worried about this. Yes, government, industry, science, we're all keeping an eye and trying to be prepared.

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

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

[music]

[00:46:19] [END OF AUDIO]