This Week in Virology

TWiV 1112 Clinical Update

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Guest: Daniel Griffin

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

(Music)

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1112, recorded on May 9, 2024. 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: Can I see your tie? Yes, I can see your tie. It's poliovirus.

DG: Yes, especially. I was thinking of you, Vincent, when I was picking out my tie last night.

VR: It's the one thing I can recognize.

DG: It's got the rotary stuff on there. What I did is, now we're seeing a few more COVID cases where we have to wear the yellow gowns. My socks have the blue and then the yellow of the gown to bring it all together for the workday.

VR: Nice coordination. They should have you at the Met Gala next year.

DG: Yes, maybe next year. We'll see if we can get an invite. All right, let's jump right into it. We got a lot to cover today. I will start with a Charles Darwin quotation. I think that this quotation, it really serves to put things in context, because I think people often get Darwinian theory a little bit off. As Charles Darwin is quoted as having said or having written, “It is not the strongest of the species that survives, not the most intelligent that survives. It is the one that is the most adaptable to change.”

VR: Good. I like it.

DG: All right. We're going to start right off with the article, “Highly Pathogenic Avian Influenza, A (H5N1) Clade 2.3.4.4b Virus Infection in Domestic Dairy, Cattle and Cats, United States, 2024,” which really point out highly pathogenic in avian influenza. I guess I'm not allowed to put the little "in" there. Here's the story. What is going on? In February 2024, veterinarians were alerted to a syndrome occurring in lactating dairy cattle in the panhandle region of

northern Texas, nonspecific illness accompanied by reduced feed intake, and rumination and an abrupt drop in milk production developing infected animals.

The rumination in this case is not the deeper considered thought, but the action of chewing the cud, that partially digested food that is returned to the mouth for a second round of chewing. Yuck. The milk from most affected cows had a thickened, creamy yellow appearance similar to colostrum. On affected farms, incidents appeared to peak four to six days after the first animals were affected and then tapered off within 10 to 14 days. Afterward, most animals were slowly returned to regular milking. Clinical signs were commonly reported in multiparous cows during middle to late lactation, about 10% to 15% illness.

Minimum death of cattle was observed on affected farms. In early March 2024, similar clinical cases were reported in dairy cattle in southwestern Kansas, northeastern New Mexico. Deaths of wild birds and domestic cats were also observed within affected areas in the Texas panhandle. Then in the one or more dairy farms in Texas, deaths occurred in domestic cats fed the raw colostrum and milk from sick cows. March 21, 2024, milk serum and fresh and fixed tissue samples from cattle located in affected dairy farms in Texas.

Two deceased cats from an affected Texas dairy farm were received at the Iowa State University Veterinary Diagnostics Lab. The next day, similar sets of samples were received from cattle located in affected dairy farms in Kansas. Milk and tissue samples from cattle and tissue samples from the cats tested positive for influenza A screened by PCR, which was confirmed, characterized as the highly pathogenic Avian Influenza (H5N1) - that's the name - virus by the U.S. Department of Agriculture.

A good point here is not all, but most commercial assays used for human influenza virus testing are likely to pick up this HPAI A (H5N1), so that H5N1 virus, because they actually target conserved genes coding for conserved proteins. It was funny in that report, they say they target conserved proteins, but that doesn't always necessarily mean the sequence is going to be conserved. Remember, PCR is going after the genetic material. Now, the authors conclude after extensive analysis that these findings suggest cross species mammal to mammal transmission of H5N1 virus and raise new concerns regarding the potential for virus spread within mammal populations.

Don't worry, Vincent and I are going to talk a little bit about this. We're not saying the sky is falling. Horizontal transmission of the H5N1 virus has been previously demonstrated in experimentally infected cats and ferrets and is suspected to account for large die-offs observed during natural outbreaks in mink and sea lions. Further experiments of H5N1 virus in dairy cattle should seek to confirm cross-species transmission to cats and potentially other mammals. Maybe we pause for a second there, Vincent.

VR: We don't see extensive transmission in humans. That's the key here, that for some reason it's being restricted to non-human animals. There was a case of a human infection by a cow in Texas. If there are more, they're mild and we're not noticing them. In fact, when I talked to an expert, Ron Fouchier, back at a flu meeting last year, he said he was more worried about non-human animals than humans. Already we knew about the outbreak in mink and sea lions. He said it's likely to spread to others. We're seeing that happen. Why it's not in people, we don't know, but it's good so far.

DG: No, and I think when we say mammals, I think everyone gets ready to - on social media, there's certainly a lot of people who are quite worried, but let's sort of carry this a little farther. There's actually a nice article in *CNN Health* by Brenda Goodman. I'll leave a link to that. “H5N1 Bird Flu was Circulating in Dairy Cows for Four Months Before it was Detected, USDA Scientists Say”. That actually links to a preprint, spent a little time discussing, “Emergence and Interstate Spread of Highly Pathogenic Avian Influenza A(H5N1) in Dairy Cattle.”

There's a lot in this rather sophisticated preprint, but ultimately they're going to suggest that in North America, these highly pathogenic Avian Influenza A(H5N1) viruses related to the goose/Guandong 2.3.4.4B hemagglutinin phylogenetic clade have infected wild birds, poultry, and mammals. In this preprint, their genomic analysis and epidemiological investigation supports that a reassortment event in wild bird populations preceded a single wild bird-to-cattle transmission episode. Then we just got lots of cattle-to-cattle transmission.

Remember, this is a preprint, so the story suggested that in late January, 2024, production veterinarians observed dairy cattle displaying unexplained reductions in milk production, which we talked a little bit about, decreased feed intake, changes in the milk quality, that whole chewing the cud issue. Members of the National Animal Health Laboratory network identified influenza A virus in milk, a few nasal swabs from a Texas dairy, forwarded samples to the National Veterinary Services labs for confirmatory testing as epidemiological investigations continued.

The testing revealed the presence of this (H5N1) clade 2.3.4.4B genotype B3.13. Shortly after the identification of this genotype in Texas, it was confirmed in additional Texas herds, herds in other states. They have sort of a nice figure where you can see a little bit of how this, at least, is purported to have spread within the cattle populations. Remember, cattle, we're not actually talking about this spreading within humans.

Then I thought this was sort of a nice one, and I think one of our listeners will appreciate this before we get to COVID this week. The article, “Comparative Effectiveness of Baloxavir Marboxil and Oseltamivir Treatment in Reducing Household Transmission of Influenza: A Post Hoc Analysis of the BLOCKSTONE Trial,” actually published in an open access journal, *Influenza and Other Respiratory Viruses.* Quite a name for a title. I've sort of read that a couple of times. It's not influenza, it's influenza and other respiratory viruses. Despite some rather, I will say, poor marketing of baloxavir or XOFLUZA, it might have some qualities we are ignoring.

The transmission of influenza virus in households, especially by those pesky children, is a major route of infection. Prior studies suggest that timely anti-viral treatment of ill, so symptomatic cases, may reduce infection in household context. The aim of the study was to compare the effects of Tamiflu to XOFLUZA, treatment of index cases on the secondary attack rate of influenza within household. The abbreviation for that secondary attack rate is SAR, S-A-R, a terrible three-letter acronym. Anyway, a post-hoc analysis was done for the BLOCKSTONE trial, which was a placebo-controlled double-blind post-exposure prophylaxis study, 185 index cases.

We've got 116 treated with the XOFLUZA, the Baloxavir, 69 treated with Tamiflu, oseltamivir, 410 household context, 201 from the trial, 209 by questionnaire were included. The

secondary attack rate, those treated with XOFLUZA was 10.8%, while with Tamiflu, almost double that, 18.5. We get an adjusted relative risk reduction of 41.8% when you get the XOFLUZA. Considering that the whole box of Tamiflu and the limited dose of the XOFLUZA is really about the same price, maybe those folks need to do a little better job of marketing. All right.

VR: Bob Krug will be happy to hear this.

DG: I think it's Shionogi or somebody. Maybe they're listening and they could work a little bit on marketing, so ask your doctor about XOFLUZA.

VR: If you were asked by a patient, would you be able to get it for them?

DG: Yes.

VR: Would you? The question is would you?

DG: Yes, sure. Both are underutilized and part of it is a timing issue, unfortunately. I don't know if I shared it with any of our listeners, but there was a great program that we had during the pandemic for the Medicare Advantage folks. This whole idea it's really critical to get the antivirals in there as soon as possible and really probably both these agents really want to get it within the first 48 hours. We took this program that they were getting ready to ramp up for flu.

We converted it to COVID where people that thought they had COVID, originally it was supposed to be flu, would get carried out these little at-home tests and it was a molecular test by LUCIRA, right, which is now - I bought a bunch during this window when LUCIRA went bankrupt and now Pfizer is selling them for $40 each, which is, dare I say, more than I paid. They would get tested and if it was the flu, they had a little Bluetooth box which had Tamiflu in it and the doc with the telehealth could push a button and out would come the Tamiflu and they could start.

If it was positive for COVID, then we would send someone out to do monoclonals in the home. Just, yes, time matters. All right, we'll get into COVID now. Looking at the map, things look pretty good across the country as far as percentage of provisional deaths. The wastewater is looking great, really getting down to like June 2023 levels of last year. We are starting to see a few folks locally in the hospital but not really seeing that pick up on the wastewater. I will keep people up to speed with that. Let's just run through where we are. Active vaccination, the recommended booster.

Passive vaccination, waiting for more word on PEMGARDA to use. The early viral phase. Number one, Paxlovid, remdesivir, molnupiravir, convalescent plasma, isolation guidance. It's now OK to go out and infect others.

The article, so is Metformin the poor man's antiviral? More information from the COVID-OUT trial. I think my buddy, David Boulware, is just getting a lot of publications out of this one trial. Anyway, we have the article, “Favorable Antiviral Effect of Metformin on Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load in a Randomized, Placebo-Controlled Trial of Coronavirus Disease 2019,” published in *CID*.

As a reminder, the COVID-OUT trial was a 2 x 3 randomized, placebo-controlled, double-blind trial that assessed metformin, fluvoxamine, and ivermectin. End up with about a thousand participants self-collecting these anterior nasal swabs on day one, day five, day ten. Viral load, RNA copy number, was quantified using reverse transcription, basically, qPCR, RT-qPCR. The mean SARS-CoV-2, I'm going to keep replacing viral load here with RNA copy number, was reduced, as they say, 3.6-fold with metformin relative to placebo. They give us some curves to look at. They say that the metformin effect was consistent across subgroups, but neither ivermectin nor fluvoxamine showed any effect over placebo.

VR: Daniel, is that 3.2-fold reduction in RNA copy number clinically significant?

DG: One is, I really don't know. Two is, I really don't think so. Three, I think if I showed this at like a lab meeting, Steve Goff, who I was just hanging out with earlier this week, would sort of roll his eyes.

VR: I would like them to do the study that was in the previous paper, the transmission, household transmission.

DG: That would be good, yes.

VR: To see if it makes a difference, but I doubt it would, because it's not much of a - Anyway, this is RNA. You don't know really how much it relates to infectivity.

DG: Does it really affect clinical outcomes?

VR: How will this result be, what's the word I'm looking for? How would it be used in clinical practice?

DG: Yes. I think where they're going with this is just this suggestion like, is there an antiviral effect of metformin. If there is, what's the mechanism? Maybe metformin as a molecule, we've got our chemists out there, they can tweak it and figure out maybe ways to increase that. Again, this is this whole idea of, maybe there's areas of the world, which is, I have to say, interesting, I'm going to say, because this is sort of a, Paxlovid in Germany, what is it? $60 for a course of Paxlovid and the government pays for it.

Maybe metformin is a little bit cheaper, but this is really sort of complicated, gradual ramp up. There's parts of the world where you would want to have a cheaper, less-effective option instead of Paxlovid. I'm not really sure where you go with this.

VR: It's cheap, but it may not work.

DG: What was that like, the guidance about transmission? It's simple, it's easy, it's cheap, it doesn't necessarily work.

VR: It's crazy. If you wanted to do all the additional chemistry that you were suggesting to make something better, then it wouldn't be cheap anymore.

DG: Yes, that's right because then someone would have a patent and they would - I'm not really sure, but put it out there. One of the things about this early period is that perhaps what

we do during the acute viral replication phase might impact long-term sequelae. The question, the article, “Association of Nirmatrelvir–ritonavir,” so Paxlovid, “with Post-acute Sequelae and Mortality in Patients Admitted to Hospital with COVID-19: A Retrospective Cohort Study,” was recently published in *The Lancet Infectious Diseases.*

As we've heard with COVID-OUT, there's this idea of maybe if you can get an antiviral in there early, maybe it can have some positive impact on a person's risk of post-acute sequelae of COVID. Now as authors point out, we have hundreds of studies that have established the short-term efficacy of nirmatrelvir/ritonavir in managing COVID-19, but what about post-COVID conditions? These are the results of a retrospective cohort study that used real-world territory-wide inpatient records, vaccination records, confirmed COVID-19 case data from the Hong Kong Hospital Authority and Department of Health, the government of the Hong Kong Special Administrative Region.

The treatment group included patients prescribed nirmatrelvir/ritonavir within five days of symptom onset, excluding those prescribed molnupiravir within 21 days. The control group had no exposure to nirmatrelvir, ritonavir or molnupiravir. The outcomes were post-acute inpatient death and 13 sequelae. The 13 sequelae congestive heart failure, atrial fibrillation, coronary artery disease, deep venous thrombosis, chronic pulmonary disease, acute respiratory distress syndrome, interstitial lung disease, seizures, anxiety, post-traumatic stress disorder, end-stage renal disease, acute kidney injury, and pancreatitis.

At first, that's a long list, but these are rather objective outcomes. These outcomes were evaluated starting at 21 days after the positive RT-PCR in each respective cohort constructed for the outcome. We've got 50,055 eligible and included in the analysis; 15,242 who were prescribed nirmatrelvir or ritonavir during the acute COVID-19 and 23,756 patients were included in the control group. Pretty significant.

The patients were followed for a mean of over a year, a median of 393 days. In the Paxlovid group compared with the control group, there was a 38% statistically significant lower hazard of post-acute inpatient death, 30% lower risk of congestive heart failure, 37% lower risk of atrial fibrillation, 29% lower risk of coronary artery disease, 32% lower risk of chronic pulmonary disease, 29% lower risk of acute respiratory distress syndrome, and a dramatic 83% lower risk of interstitial lung disease, and a 63% lower risk of developing end-stage renal disease.

Pretty impressive looking at, not just are you going to end up in the hospital, are you going to die within 30 days, but how are you going to do in the future? Just more, dare I say, compelling evidence that it's worth getting your hands out of your pockets and treating.

VR: I think it's a mechanism for this, Daniel, because this is given at the right time after infection. Why would this impact long-term? Because we have a lower viral load, do you think?

DG: I think, yes, and it would be great if you put all these pieces together. I think the idea is you shut down the viral replication as soon as possible, you reduce that inflammatory response. This is common. Mark Crisler was always harping on this, how people don't

necessarily die of the acute infection, they die of all these sequelae, all this, inflammatory sequelae, your risk of a heart attack, atrial fibrillation, heart failure, all these other things.

VR: I don't know why it isn't better than. The one interstitial disease, 83%, that's great, but why aren't the others all similar?

DG: Yes, why can't we get heart failure even farther down? All right. Another study. I like to say this is a compelling study, but there's also a commentary in the same edition. The article, same edition of *The Lance Infectious Disease*, "Oral Antivirals for Acute Symptoms and Post-Acute Sequelae in SARS-CoV-2." I think in this article, they do a good job of putting forward several critical caveats, context for understanding the results. First, this is sort of interesting, commenting about the study we just went through, is patients had to survive the first 21 days after the COVID-19 diagnosis to be evaluated.

Perhaps results are even better if each outcome is death or the specified because we know that there's an acute benefit to the Paxlovid. Second is patients needed to have no contraindication to the nirmatrelvir/ritonavir use. There's certain drugs that they might not have been on. Also, there was a number of patients that were excluded. I'll leave a link to this commentary as well.

Now, we have a couple more. It's the same. It's an article with a commentary. "The Effectiveness of Nirmatrelvir–Ritonavir for the Prevention of COVID-19–related Hospitalization and Mortality: A Systematic Literature Review," published in the *American Journal of Therapeutics*, along with what I think is really a nice editor-invited commentary. Now, perhaps I like the commentary because I wrote it. The article begins with an introduction that highlights the tremendous experience we now have using this medication with over 12.7 million treatment courses prescribed since it became available in the end of 2021.

The article also points out that Paxlovid is recommended as the preferred outpatient COVID-19 treatment for individuals at high risk of progression of severe disease. They mention the pivotal randomized, double-blind, placebo-controlled, multinational trial evaluation of protease inhibition for COVID-19 in high-risk patients, EPIC-HR, with that 86% reduction in the combined endpoint of COVID-19 related hospitalization or death. They also comment on the EPIC-SR standard risk, where we saw a 62% decrease in COVID-19 related medical visits relative to placebo.

In this review, they ultimately include 18 studies with a total of 343,197 folks that received Paxlovid treatment. The analysis revealed a Paxlovid effectiveness of 21% to 89%. We have a bit of a range for the prevention of all-cause hospitalization and 24% to 60% for COVID-related hospitalization. The analysis revealed that this impact was regardless of vaccination status. The two studies that they had where they looked at all-cause mortality, Paxlovid effectiveness was 66% and 85% against all-cause mortality. I'll leave a link into this study and that really wonderful commentary.

VR: I wonder if the variations, because they get it at different times, right?

DG: Yes, that is one of the challenges. All right. Then COVID, the early inflammatory weeks, steroids, anticoagulation, pulmonary support, remdesivir, immune modulation. Unfortunately, we're still seeing some folks end up in the hospital. I've got a few people in

now, so we had that sort of brief day or two and things were a little bit better. All right. COVID, the late phase. I always leave a link into *TWiV* 1088, where I did a bit of a clinical update on post-acute sequelae of COVID. A few articles this week. The first article, "Cognitive Profile in Multiple Sclerosis and Post-COVID Condition: A Comparative Study Using a Unified Taxonomy," published in *Scientific Reports.*

This is a cross-sectional study that included 218 patients with post-COVID conditions, PCC, and 218 with MS, matched for age, sex, years of education. Patients were evaluated with a comprehensive neuropsychological protocol. Fatigue and depression were also assessed. They reported that cognitive profiles of post-COVID conditions and MS largely overlapped, with a greater impairment in episodic memory in MS. The most salient deficits in both disorders were in attention and processing speed. The severity of fatigue was greater in patients with post-COVID conditions than MS.

The correlations between fatigue severity and neuropsychological tests were more prominent in the case of MS. Ultimately, they report that the study found very similar cognitive profiles in post-COVID condition and MS. Fatigue more severe in post-COVID conditions, but was more associated with cognitive performance in MS. Now, our listeners may notice I often talk about biochemical and physiological abnormalities consistent with PASC. We have the very low serotonin levels, the post-COVID decreased AM cortisol, the evidence of EBV reactivation with detectable EBV during acute COVID, and IgG levels off the scale after the acute period.

I'll just share a recent Long COVID, acute COVID story before I mention this next article. I had a gentleman come in. This is his third acute COVID episode. What he reported to me is after his second acute COVID, he really went on to develop sort of a characteristic Long COVID clinical picture. We had a little bit of a discussion. Here's this opportunity. He's now in the hospital again with acute COVID. We actually went ahead and did EBV DNA. He actually had detectable EBV DNA in the serum. Sort of nice to catch in real time, really high serological results suggesting that reactivation.

Here, we're catching it right there during the acute. He and I will be chatting in the future. He's now out of the hospital, through this acute COVID, but now he and I will be talking about what to do about his Long COVID. I also talk about the physiological abnormalities, such as the abnormal nasoline test, the tachycardia, are there evidence for autonomic sequelae. Here we have the article *"*Unravelling the Mechanisms Behind Exercise Intolerance and Recovery in Long COVID," published in *The American Journal of Medicine*.

As an aside, in this *American Journal*, they have two L's in unraveling, which is the British English spelling. I don't know why that bothers me. This study investigated the relationship between heart rate recovery at the first minute, HRR1, terminology that's maybe new to some of our listeners, a proxy for autonomic imbalance and exercise intolerance in patients with Long COVID. Additionally, the study aimed to assess the effects of a 12-week, home-based inspiratory muscle training program on autonomic modulation in this patient population.

These are the results from the INS COVID trial, single center, randomized clinical trial with blinded assessors wandering around with their sticks. Sorry. That enrolled 26 Long COVID patients. It aimed to investigate a 12-week home-based inspiratory muscle training program compared to usual care in a one-to-one ratio. The heart rate was evaluated at rest, peak

effort, and then the first minute of the recovery phase. You end up with this HRR1 defined as the difference between that maximal exercise heart rate and the heart rate at the first minute into recovery.

First off, the results showed a significant association between this baseline HRR1 and exercise tolerance. They suggest that actually the HRR1 is a practical, cost-effective, and easily collected surrogate for assessing autonomic nervous system function, exercise tolerance, and guiding simple therapeutic interventions. They also report a significant association between the baseline HRR1 and responsiveness to an inspiratory muscle training program, which they make a point of contrasting with other exercise training approaches.

They suggest that this diaphragmatic breathing and strengthening through inspiratory muscle training could modulate arterial baroreflex sensitivity, consequently improving sympathovagal balance. Lots of interest in these non-pharmacological interventions. I would have liked a little more detail on this diaphragmatic breathing, this inspiratory muscle training. How similar is this to some of the box breathing and other breathing interventions that we've been recommending for folks to do? Just more interesting. I'm going to move into an article in the low and middle income countries this week.

There seems to be this idea that things were really so much better in places like Africa during the early years of the COVID pandemic. People even take this to the next level, coming up with ideas of why this might have been the case. Maybe there was some protective benefit to being infested with parasites. I think one of our colleagues has suggested that. We won't mention which one. Here we have the article, “Epidemiology of SARS-CoV-2 in Kakuma Refugee Camp Complex, Kenya, 2021,” published in *Emerging Infectious Diseases*. This is not just Africa, but a description of what was seen in a refugee camp complex.

The United Nations High Commissioner for Refugees estimated that as of December 2020, there were 20 million refugees, 4.1 million asylum seekers globally, numbers seem low, most of whom were living in low- and middle-income countries. As of December 2021, Kenya hosted over half a million refugees in urban and camp settings. The number of refugees in Kenya increased steadily 2019 to 2022. During the COVID-19 pandemic, the Kakuma Refugee Camp Complex was home to almost half of all the refugees in Kenya. Where is this camp? The camp is located in Turkana, West Subcounty, which is in Turkana County in northwestern Kenya.

It shares international boundaries with Uganda, not far from where my cows are, to the west, South Sudan to the northwest. That's about 600 kilometers from Nairobi. Here these investigators conducted a descriptive analysis of routinely collected data from March 2020 through March 31, 2021, on demographics, SARS-CoV-2 testing results, clinical outcomes of COVID-19. The first positive SARS-CoV-2 case was detected March 22, 2020, in a refugee camp two months after the first case of SARS-CoV-2 was reported in Kenya. From there, as one can imagine, the number of confirmed cases only increased.

In general, for context, this is a young population with the median age being 25, 51% were male. How did these people do? Median age 25. If we were here in the U.S., I would not be too worried. Here in Kenya, under these conditions, the overall case fatality rate was 2.25% for the camp, 1.83% for Kenya. Of the deaths in the camp, a lot were reported among

refugees, and we're actually going to see more in the refugees compared to the host community; 2.86%, so almost a 3% case fatality rate in the refugees, about 1% in the host community. Just sort of pointing out, that's not rosy. That's not a great picture. That's not, I wish I was in sub-Saharan Africa when I got my COVID.

VR: It's not good to be in these crowded camps.

DG: Crowded camps and all the other things that come with it. I thought I would mention. During the pandemic, thanks to time zones and a bit of an aversion to wasting my precious time sleeping, I was able to actually do some global consultations. As part of this, I would do these regularly scheduled consultations with the clinicians working at Cox's Bazar Rohingya camp for displaced Myanmar natives.

I don't know if you knew this, but I'd get up at like, I don't know, 5:00 or 6:00 in the morning before like other people are awake, and I would get on these telehealth consultation calls with the clinicians in Cox's Bazar camp. Despite the terminology that the Bangladeshi government requests or requires, we use a camp for displaced natives. The place, in reality, is probably the largest refugee camp in the world, with over 1 million refugees packed into these tight, overcrowded conditions.

Consulting with these physicians at 1.2 days per week, it really gave me a very different picture than this rosy, things are so much better in limited resource settings. The reality was more, if you don't count, then you don't count. We never had, and we never will have great numbers on the number of deaths outside of such studies as the one we just discussed. It just was obvious that COVID-19 in a part of the world where nutrition is less than ideal, crowded conditions, limited medical resources, not a formula for good outcomes.

VR: You used to always say that. We would say during the pandemic, what's with Africa? There are a few cases. You would say, I bet it's a reporting issue, and here confirms that.

DG: It really does.

VR: People use this as an excuse not to vaccinate or not to bother about it, and if you don't have the right data, you can't make those conclusions.

DG: Yes. It's really critical, really critical. All right, as I've been saying for a while, as we've been saying for a while, no one is safe until everyone is safe. I'm hoping everyone will pause the recording right here. Go to parasiteswithoutborders.com, click on the Donate button. That's how we continue to do, hopefully, this important work. We are now in the middle of our Floating Doctors fundraiser. May, June, and July, we'll be doubling those donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to danielatmicrobe.tv. Karl writes, "I wonder if you would share your thoughts on a product called Nozin, a nasal antiseptic that has quietly become part of my hospital network's MRSA nasal decontamination protocol. This product is showing up on the routine order sets for my patients in ICU when they arrive. I've done a cursory search and have found no convincing evidence to support its use. Only an FDA letter from 2022 that objects to the company's

claims. I've attached the link. I'm having trouble wrapping my head around the idea of using this product in hospital without FDA approval. Please help."

DG: I usually don't get a chance, but I had a little extra time, so I was able to read this email ahead of time, and I actually popped in a link to the FDA objection. On the bottle, if you actually look at it says homeopathic.

VR: My gosh.

DG: The FDA actually warned this company, stop with this misleading claims, and so what is your hospital doing? Who made this decision? How did this end up on a routine order set for patients in the ICU? It's just wrong. This is not an evidence-based intervention. This is snake oil, and so really sad to see that whatever this hospital is, is adding this to the order sets.

VR: Anonymous writes, "I have type 1 diabetes and Hashimoto's disease, both confirmed by tests to be autoimmune disease. I have yet to contract COVID as my husband and I are very careful. We get boosted once two times a year. I'm under 60. I feel confident knowing Paxlovid is available if and when I contract COVID. However, I have heard on your show and other places that Paxlovid is not as readily available in other countries and I am traveling to Europe this fall, my first major trip since 2019.

We will, of course, mask on the plane and in the airport. I'm hoping my doctor will give me a prescription for Paxlovid so I can take it with me in case I contract COVID while traveling. However, if she declines and assuming I cannot obtain Paxlovid in Europe, of the patients you have seen with type 1 diabetes who are also vaccinated, what percentage of them end up in the hospital? I have trouble finding data on type 1 diabetes and COVID as most of the diabetes articles are written for type 2. I appreciate your expertise about my concern."

DG: Yes, so you can do these, they should have these calculators like they do for like your risk of a heart issue or things like that. Having the type 1 diabetes is going to increase your risk by about 40% above your baseline risk. Then we sort of need to know a few things like what's your body mass index, is it above 25? You say you're under 60, but are you above 50 when we start to see a little bit of an increase?

It's not a zero number so that's why I commend thinking about the Paxlovid, having that and test with you. Last thing you want to do is realize like, "Oh yes, I've been sick for seven days and I only just tested now." You want you want to have those tests with you as well as talk to your physician about what meds you may or may not be on and potential interactions with Paxlovid.

VR: Russ writes, "Do we know if COVID-19 vaccinations or contracting the disease confer any resistance to SARS-1 or MERS? I'm just fishing for a silver lining from the pandemic maybe the next coronavirus that comes along will be less likely to start a pandemic. I'd love to hear your thoughts."

DG: Over the last few years, there have been some studies here or there suggesting that there might be something maybe at the t-cell level but I'm going to keep my fingers crossed that there's a silver lining and maybe this is going to help us in some way in the future.

VR: Charles writes, "Hello, real doctors from *MedPage Today:* Sherri Tenpenny, DO, the Ohio physician who claimed COVID vaccines can magnetize people had her medical license reinstated last month according to the state medical board of Ohio. What are state medical boards function?"

DG: Charles, what it is, is that that magnetism effect it finally wore off so she's now allowed to be - No, I'm joking. Oh my gosh, yes, I have the same."

VR: Lori writes, "I was listening to the question last week from the 47-year-old NOVID who was wondering about the continued efficacy of her three SARS-CoV-2 vaccination regimen. She wasn't too bullish about getting vaccinated if not necessary given her age and low prevalence of the virus. Your response seemed to indicate she probably wouldn't benefit from a booster. However, I wondered if you could revisit this question specifically in terms of data about continued efficacy of the three-dose series for those of us NOVIDS, particularly for those of us in the older but not 'elderly elderly' or severely immunocompromised age category.

"My guess is that most of the NOVIDS are people like me, mostly older who took precautions and now wonder how protected we are compared to our hybrid counterparts. Is our t-cell immunity still holding strong? Every article I read talks about generally healthy people now being at low risk from severe disease given the high rate of both vaccination and infection but what about the rest of us?

I'm 64, in good health, no comorbidities and was vigilant about COVID precautions likely reason I have never contracted the virus. My last vaccination summer of 2022. How do you think this in general compares to say my spouse same age, same health given the three primary series of vaccines but then got COVID spring of 2022 sparing me from infection? Bottom line, do you think older-ish NOVIDS are at higher risk from severe COVID than matched hybrid counterparts? Do we need to keep up regular vaccinations to keep us on par with everyone who has been vaccinated and infected?"

DG: I'm glad you sent this email because it allows us to revisit this issue. I think what I was trying to do last week, and I'll try to do it again, is the whole discussion about whether or not to get a booster has to do with the audience to some degree and a couple aspects of the audience. Is this an individual who is bullish on vaccines? Someone who is leaning towards getting a vaccine or is this someone who's a little bit vaccine hesitant already and what we don't want to do is over promise and under deliver to that population.

Let's take you for instance. You're 64, you're in good health, so your issue is the age. Good health, no more comorbidities. Hopefully, that BMI is that less than 25 in the ideal zone. You're starting off with a certain risk and then you've been vaccinated over time. We've talked about the evidence for those different boosters and the reduction that can come with those. It was a broad recommendation across the board for vaccinations in the fall. It was sort of a little bit more of a discussion this spring about the degree of benefit that a person might get.

We talked a little bit about that idea that the booster with the bivalent back a year ago did that loss of protection. Was it related to the fact there was a new variant or was it really time and we won't know that answer for a little while? Most of us are not really trying to push a

vaccine-hesitant person into getting another booster at this point, just explaining what we do know, what we do not know. Now, one of the thoughts over time is we do think that this three-primary series gives us this 90% reduction, probably relatively durable but then what we're really comparing over time is people that get a boost on top of that.

What can we do with that remaining because we do still see 100 people a day are dying of COVID. We see thousands of people still end up in the hospital and then as you bring up people who are immunocompromised people who are 'elderly elderly,' not everyone has the same risk so the discussion with a healthy 24-year-old is quite different than a discussion with a 64- or 74-year-old. Now, you also bring up the issue about someone who's had COVID before.

We were maybe hesitant a little bit early on to count an infection as a boost, as an exposure and there were a lot of reasons why. Part of that was a mixed issue. There were certain people that were going out and on purpose getting themselves infected. There was a famous musician who did this and then didn't survive, so it's sort of a mixed idea of, is the science there? What's the public health messaging relative to that? Someone who got an infection in the past, I think of that as basically getting a shot, getting an exposure to the antigen and the immune response that comes with that.

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

DG: Thank you and everyone, be safe.

[music]

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