This Week in Virology

TWiV 1114 Clinical Update

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

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From MicrobeTV, this is *TWiV, This Week in Virology,* Episode 1114, recorded on May 16, 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: Look, I think you have another icosahedral virus on your tie.

DG: I do, yes.

VR: It can't be polio again because you just had it last week.

DG: No. You never really know with these artist representations. It's supposed to be HIV, I think. That's just quite a popular one for the artist when it comes to bow ties, but -

VR: It doesn't look like HIV to me, but OK. It's art. As they say, it's art [crosstalk].

DG: It is art. It is art. What do you think? Are you thinking like, an adenovirus? What would you go with?

VR: No, I was thinking of an enterovirus or -

DG: You would be thinking of an enterovirus.

VR: Yes, I dream about them. Yes.

DG: [laughs] OK. When you see a shape, you're like, "I know what that is."

VR: Yes. When you hear hoofbeats, what do you think, horses or zebras?

DG: I think zebras. Yes.

[laughter]

If it's a horse, I'm disappointed, but let me start with our quotation. We've got a lot to talk about today, and part of it is we've got a number of letters, so we're going to make sure we respond to those email letters. I guess we still call them that. Did I ever quote Jack Kerouac before. I was recently out in San Francisco, and unfortunately, my son does not know who Jack Kerouac is. Here's the quotation.

"Great things are not accomplished by those who yield to trends and fads and popular opinion." I must say, that's one of my favorites. I wonder, have I used that before? You have one like that, and I think that's one of the big things in science. You're not just like, "What does the mainstream media tell us we should be believing?" The other thing when it comes to fads, which actually made me think of that particular quotation, was, I don't know if you know about this, Vincent, but the latest fad appears to be drinking raw milk in an attempt to get H5N1 immunity. I'm going to leave in a link to an article.

VR: Is this like a measles party or something like that?

DG: No, this might be worse, I'm going to suggest. I'm going to leave in a couple links, so a different title. The first title, “Raw Milk Enthusiasts Demand Milk Infected with H5N1.” The second, and I think this is even better, the title of an article in the *LA Times*. “Despite H5N1 Bird Flu Outbreaks in Dairy Milk, Raw Milk Enthusiasts Are Uncowed.”

VR: That's clever.

DG: You like that? [laughs] The title's clever, but I'm not sure how I feel about this. Let's talk a little bit, because I know it's easy to just shake our head and say, "What crazy people." Apparently, there is something called the Raw Milk Institute. I assume for most of our listeners, is the first time you've heard of this, but the whole idea behind the institute is to provide guidance, so you make sure that the milk does not contain the pathogens for which we normally pasteurize the milk, thus mitigating the potential risks.

One might ask, why are we worried getting milk? Why are we pasteurizing to begin with? What are these organisms? Let's go through the common standards. The common standards are, I'm going to put my glasses on to - because I'm reading from the Raw Milk webpage. Have a risk analysis and management plan for raw milk production. What are you going to do? Test for coliform bacteria at least monthly. The testing frequency is going to depend on each farmer's individual RAMP. That's our risk analysis and management plan.

The target is a rolling three-month average of below a certain threshold, which is 10 coliforms per ml in raw milk, so actually pretty darn low. Then you're going to do this test for standard plate count, at least monthly. Basically, to make this intelligible, raw milk, as per these standards, should not contain pathogens, including which are the big ones, salmonella, E. Coli 015787, campylobacter, listeria.

The whole idea is we're doing all this testing and this a little bit small farms and farms who do not have access to pathogen testing labs may rely on coliform and SPC testing as a general indicator of milk hygiene and safety. An interesting thing here. There is sort of an idea that in a small farm, maybe you've only got the one cow, a little bit safer, but when you get up to these larger settings, really kind of jumping in with the testing. Now, they're suggesting that

you should only sell raw milk that meets the standards as intended for direct human consumption, really only coming from your own farm.

Don't go just getting milk from other people and then co-mingling the raw milk from other dairies. That's not permitted. Also providing documentation, it's going to bring us to the history of pasteurization. Documentation insurance that herds are tuberculosis-free, and tested one time per year, or they meet the local TB requirements and provide documentation and assurance that herds are brucellosis-free.

VR: Let me understand, Daniel. They do not pasteurize. They just check to make sure that certain bacteria are either below a certain level or not there, and then they release it. If these things creep into the milk chain, if you will, they should be throwing that out.

DG: What would happen is that if, for instance, it turn out that your herd has brucellosis or TB or your herd has these pathogens, then you don't give that milk to people until you get your herd clear of these. The whole idea here is, let's make sure the bad stuff that we're pasteurizing for is not in the milk to begin with. A lot of our problems have come as this has become this big industrialized complex.

I don't know if you've ever been to one of these dairy farms, Vincent, where they've got all the cows rammed in together. They can't move. They're attached to these machines. Actually, not exactly for an animal lover, the most wonderful situation versus the dairy cow we think of maybe in Laura Ingalls Wilder out there on the prairie. It's just the one cow, and the kids are milking it with their hats probably off because they're not good at keeping them on.

I will say for full disclosure, Vincent, and this may be news to you and all our listeners. My family and I have actually consumed chilled raw milk, and all my children actually know how to milk both cows and goats.

VR: Do you, Daniel?

DG: My kids are better. There's a motion, and I think if you learn it when you're young enough, you get kind of better at it. I think Eloise and Daisy started the youngest. Actually, Barnaby probably started pretty young, too. Yes, they can milk cows and goats, but when we've done this, it's always been at a place where there's just the one cow or just a couple goats. Not been in a large production, and also, actually, they have adhered to these standards.

Here's why I'm a little bit worried about what we're hearing here, and hopefully, Vincent, you could maybe tell me if my fears are warranted, or you can just push me farther to the ledge. I'm going to leave a link into the article, “Avian Influenza A(H5N1) Viruses can Directly Infect and Replicate in Human Gut Tissues,” published in *JID* a number of years back. Human and avian influenza A viruses use different receptors for cell entry. Talked a little bit about this.

Human-adapted influenza A viruses preferentially bind to human-like sialic acid, α2,6-galactose-terminated saccharide. Think of these as sialic acid decorated with sugars in a certain way. We've got the α2,6-Gal for the human ones. Now, the avian influenza A viruses prefer receptors with avian-like α2,3 linkages. α2,3-Gal. Now, this article teaches us the absence of avian sialic acid α2,6-Gal receptors in the human upper respiratory tract may be one of the key factors for limiting human-to-human transmission of H5N1. In this study,

though, the investigators demonstrated that human gut tissues actually express those sialic acid receptors with that α2,3 linkage, preferentially used by the avian influenza viruses.

VR: There are a couple of things here. First of all, yes, the α2,3 are in the gut, but many of these H5N1s can switch to α2,6. That's one of the sentinel changes that we look at, because if it combined α2,6 then we worry more about it. Beyond α2,3, α2,6 in the gut, normally in the respiratory tract, there's a protease that cleaves the hemagglutinin of influenza viruses.

You need that cleavage for infectivity. That protease is not found outside the gut. That's why most influenza viruses, of humans anyway, reproduce in the respiratory tract and not the gut. But H5N1 has a different cleavage site. It has actually a furin cleavage site. [chuckles]

DG: Oh, no. Oh, my gosh.

VR: Oh, my gosh.

DG: How did that get there, Vincent?

VR: I think someone must have put it there.

DG: [laughs]

VR: Furin is the proteases that furin cleavage sites are ubiquitous, so they're in the gut. That would be important for having multicycle replication. The other thing is, of course, that in many birds, influenza virus infection is a gastrointestinal infection. This is not too surprising. The real issue is very few humans are being infected. There are less than 1,000 known human H5N1 cases. We don't know how frequent gut replication is and we don't know if it's shed in the feces and whether it's transmissible. There's a lot of questions there.

DG: Yes. Do we worry? I guess this is the concern. Do we worry if we've got all these people making a point, so to speak, of drinking milk that might actually have replication-competent avian influenza with this certain preference for receptors we have in our gut? Is this a bad idea? Should we be worried? Is the sky falling? What do you think?

VR: Well, I think I'm not worried about the virus getting in the gut. I'm worried about when you drink milk, you aerosolize it. It's going to infect your upper tract. You're swallowing it, but as you know, Daniel, your nose is connected to the back of your throat and it goes down there, separate tubes, but for a while, they're in the same area. It's easy to imagine you drink milk, you aerosolize it, and then you infect yourself in the upper tract. That's what - [crosstalk]

DG: When someone is drinking milk, if you make them laugh and it goes up their nose, you could [crosstalk].

VR: Oh, yes, don't do that.

DG: [laughs] Not to make too much fun, actually, that was one of the things that people were concerned with, like cats and stuff. Well, maybe the cats aren't so much drinking the infected milk and getting sick. Maybe cats are messy and they're aerosolizing it as they're lapping away

and maybe if you giving this raw milk to your children and they're splashing it all over, maybe they're going to actually aerosolize it so sort of some interesting.

VR: Daniel, can I ask you?

DG: Yes.

VR: What is the reason for wanting to drink raw milk? Does it taste better? Is it better for you?

DG: There is this whole microbiome idea that it's out there. We got this pasteurized stuff, this sterile environment and so part of some of the ideas that people have is that the unpasteurized milk may actually help you maintain a more healthy gut microbiome so trying to accomplish that.

VR: Daniel, humans don't need milk.

DG: [laughs]

VR: They don't need cow milk most of their life. They need breast milk for a year or so when they're born, preferably from their mother, if not from another mother, but they don't need cow milk. This is something that has been pushed on us, and it's made a whole industry. [laughs]

DG: Well, yes, it is. It is a whole industry. [laughs]

VR: We just don't need to do. We have other sources of protein, but people like milk. OK, fine, but you don't need it.

DG: All right, well, I will just finish off this section with the preprint, "Virome Sequencing Identifies H5N1 Avian Influenza in Wastewater from Nine Cities." Seems to be getting a lot of people's attention. We read here that sequencing reads uniquely aligning to H5N1 covered all eight genome segments with best alignments. Two are one of interest so to clade 2.3.4.4b. Notably, 19 of the 23 monitoring sites had at least one detection event, and the H5N1 serotype became dominant. Now, a variant analysis suggests avian or bovine origin.

They do say, we can't exclude humans, but just the bulk of evidence here suggesting we're just getting this avian and bovine stuff into the water. So far, other stuff just even though I put the preprint up here, if you want a really great - I have to say, I really enjoyed this Vincent. The *TWiV* 1113 with Richard Webby. This was, "Influenza Virus H5N1 in Cows' Milk with Richard Webby." People are interested in the highly pathogenic avian influenza H5N1. This is a great and enjoyable and very accessible *TWiV.*

VR: Yes, I thought he was very good and it's timely. You ought to listen to it. It's not so hard. He does a good job of explaining things.

DG: He's an excellent science communicator, so just hats off. All right, COVID, update. Just put this in context. Look, across the country are we seeing any hotspots, any bump in the percent of deaths due to COVID? Really, less than 2% across the country and the wastewater is down to those levels June of last year. I do want to point out we're still seeing COVID. It

didn't go away. It didn't go to zero. Still a few people get admitted to the hospital. A couple of people out at one of our local Long Island hospitals. We had some people at Columbia, just finished my attending stint yesterday. That was nice. Really enjoyed it. Mixed that it's over.

COVID's still out there. I like the wastewater data because a lot of people are not testing. "I feel a little crummy. I just got a cold. What, am I going to test every time I get a cold?" People have to make a decision on that. Still out there, but at low levels for the moment. That touched a little bit on testing. How do we figure out when to test? Pretty tough. How do you know whether it's a cold or COVID, testing is really the only way.

All right, COVID active vaccination. I got a little bit here, so keep reminding folks of that CDC-recommended booster, ages 65 and over.

This was a bit of news this week, actually, we were talking about it today, the end of AstraZeneca vaccines. The giant AstraZeneca has requested that the European authorization for its COVID-19 vaccine be pulled. According to the EU medicines regulator, I'll leave in a link, but in an update to the European Medicines Agency's website, the regulators say that the approval for AstraZeneca's Vaxzevria. I don't know if anyone remembers that was their name, has been withdrawn at the request of the marketing authorization holder.

VR: Daniel, was that the adenovirus vector vaccine that caused clotting?

DG: It is. I'm glad you said because, yes, there was a concerning signal for the clotting, so we have safer options out there. This makes sense. All right, the article, "COVID-19 Vaccines and Adverse Events of Special Interest: A Multinational Global Vaccine Data Network, (GVDN) Cohort Study of 99 million Vaccinated Individuals," was published in *Vaccine* last month. It got enough attention. People have been emailing me questions about this. It was highlighted in Doximity. Let's spend a little time putting this in context.

Really robust. These results come from an observational cohort study that compared observed with expected rates of 13 selected adverse events of special interest, AESIs, across neurological, hematological, and cardiac outcomes. Expected rates were obtained by participating sites using pre-COVID-19 vaccination healthcare data stratified by age and sex. Observed rates were reported from the same healthcare datasets since COVID-19 vaccination program roll out.

These AESIs, these adverse events of special interest, occurred up to 42 days post-vaccination with the mRNA vaccines, the adenovirus vector vaccines included in the primary analysis. Let's go through. How many vaccinated individuals: 99,068,901 vaccinated individuals. We had 183,559,462 doses of the BNT vaccine, 36,178,442 doses of the Moderna vaccine, 23,093,399 doses of the ChAdOx1. Risk periods follow-up contributed, right, for this 23,168,335 person-years of follow-up.

Really huge data set here and we did see a signal for some adverse events. They confirmed a signal that we've discussed before for a few adverse events of special interest such as Guillain-Barré, the cerebral venous sinus thrombosis following the first dose of the ChAdOx1 vaccine, acute disseminated encephalomyelitis, myocarditis, and pericarditis. That was fine. The abstract gives you the relative risk. I want to have a little bit of a discussion because I really

felt like this article could have communicated things a little bit better. If you dig into the discussion section, you start to get some context here.

Let's take acute disseminated encephalomyelitis. Here is this event where you end up after the vaccine having this inflammatory response where actually have damage to the myelin. They're talking here about incidence above background of one in a million. I just want to give people a context here. We've talked about these things before. Guillain-Barré is something we see after infections.

It's something we see after vaccinations, myocarditis, and pericarditis. We've certainly talked about in the past, we've really compared the incidents with vaccine to the more severe incidents with infection without the protection of vaccines. If anything, I know this is being taken by the anti-vax, the anti-science side, but really what we're seeing here is we're tracking, we're keeping track of these things, but still the incidents of serious adverse events continues to be very low, but it is there and we are detecting it I know. Vincent, do you have any comments.

VR: Daniel, these events, are they also associated with infection with SARS-CoV-2?

DG: That's a problem, yes. They're associated with infection and the severity can be quite a bit worse. We saw a fair number of cases with acute COVID triggering at that three- to four-week period of time. We certainly saw a really severe myocarditis and pericarditis with COVID. You compare that, apples to oranges, what we saw with these numbers for the myocarditis, pericarditis in the adolescent boys was a 24 hours of discomfort, which would then resolve. I have patients post COVID who have ongoing months and months of continued cardiac dysfunction because of the COVID induced cardiac inflammation.

VR: It's always about a risk benefit determination between vaccines and getting an infection, right?

DG: That is true. That is true.

VR: People complain that, oh, the vaccines have these side effects. They do, they're very rare. You're taking a risk, but you have a greater risk if you don't get vaccinated and you get infected.

DG: Yes, and I think this article just supports that conclusion. All right. We will move on to the to the early phase, you test positive, what do you do? I know we have a letter, so we'll talk a little bit about who gets treated, who didn't. Talk a little bit about it here, but then we'll circle back. The guidelines we have, the IDSA guidelines, the NIH guidelines, which we keep in here, is we're not talking about treating everyone.

If you're talking about that 22-year-old, completely healthy, no medical problems, ideal body weight, those people are considered our standard risk baseline. Once your age gets above 50, you start developing cardiac issues, pulmonary issues. There's a whole list on the CDC of what those issues are, but smoking, obesity, et cetera. Then we start talking about number one, Paxlovid, remdesivir, molnupiravir, convalescent plasma in certain contexts, and all those wonderful isolation guidelines.

As I explained today, I'm not making these up. It's the biology. All right. Number two, COVID the inflammatory. That's that second week you get all this inflammation. We've talked about steroids, anticoagulation, pulmonary support, maybe remdesivir if you're still in the first 10 days, immune modulation, but what about colchicine? What happened to colchicine?

Do you remember all the excitement about colchicine? I certainly do. Now, the article, "The Role of Colchicine in the Management of COVID-19: A Meta-analysis," was recently published in *BMC Pulmonary Medicine*. First off, what is colchicine? Why do people think this might be a good idea? Colchicine is an alkaloid drug that is used in many autoinflammatory conditions, so gout. Remember Ben Franklin? Franklin had that and probably from eating too much meat and drinking too much good wine. Familial Mediterranean fever, a genetic issue there, Behcet's syndrome.

Now, colchicine inhibits the production of superoxide, the release of interleukins. That leads to stimulation of the inflammatory cascade. Colchicine decreases the differentiation of the myofibroblast and the release of fibrotic mediators. That's also including TGF-β1 that are related to fibrosis. Moreover, colchicine has been used to treat viral myocarditis caused by CMV, EBV, also interstitial pneumonia and pericarditis resulting from influenza B infection.

There's a bit of a literature, there's a bit of an experience here, so what do we have? A comprehensive review of the literature was done till May, 2022, yielded 814 articles. After ranking the articles according to authors and year of publication, it started thinning down to only eight clinical trials and cohort studies fulfilling the inclusion criteria. This meta-analysis then involves 16,488 patients, 8,146 patients in the treatment group, 8,342 in the control group.

In their pulling it all together, the results show that colchicine actually resulted in a significant reduction in the mortality rate among patients that receive colchicine in comparison with placebo standard of care. You see a decrease in the need for oxygen therapy. Now this all sounds great, man. Why isn't everyone getting colchicine? Well, then they actually, you dig a bit deeper and you say, well, you got these studies, but what about the people that actually had COVID?

You got studies, you include people with probable, maybe, but if you look at people that actually had COVID, so PCR-confirmed, among the PCR-confirmed COVID-19 patients, colchicine just barely makes the P value cutoff. We see colchicine had no effect on mortality and the need for mechanical ventilation when we look at that subgroup that actually had confirmed COVID-19.

It's always good to put things in context. I went back to the IDSA guidelines. What did they say? This is great stuff out here. Well, if you look at the IDSA guidelines, you can actually see that they do not recommend colchicine. Their concern is that when you look through these studies, their analysis raised concerns about risk of bias, inconsistency, and in precision.

VR: When would you give this to a patient?

DG: Well, it is not recommended for acute or inflammatory phase of COVID at this point. Even though we've got this analysis here, there's a lot of concern about risk of bias, inconsistency, and precision link. Do we really trust this data? The IDSA is saying when they looked closely

at this data, not really seeing that we trust it and we have a lot of other therapies which we do trust. That first week, we're jumping in with an effective antiviral. During the second week, if we need to, we might jump in with something like steroids.

Now, we will wrap things up. I'll say a little bit of exciting news. A little optimism here. The COVID late phase, PASC/Long COVID section and some more clinical trials. We heard on Wednesday May 8, that was actually a little bit about a week ago, so right before we were recording last time, “NIH to Open Long COVID Clinical Trials to Study Sleep Disturbances, Exercise Intolerance, and Post Exertional Malaise.” I'm going to leave links in, but four new trials are going to open.

The first two are the RECOVER-SLEEP clinical trials. The first of the two, they're going to test modafinil and solriamfetol. These are drugs that are approved by the FDA, basically to help people stay awake. Modafinil is a non-amphetamine central nervous system stimulant with this wakefulness-promoting properties. The solriamfetol is a norepinephrine dopamine reuptake inhibitor, binds to dopamine transporter and the norepinephrine transporter also keeping you more awake and alert. The other trial is actually going to test melatonin and light therapy.

All right. We also have the RECOVER-ENERGIZE clinical trials. We've got two here. Just got to be careful about these. The first is a trial to test a program that combines exercise training, strength and flexibility training, education and social support collectively known as personalized cardiopulmonary rehab. Now, I want to point out all participants in these RECOVER-ENERGIZE trials are going to be screened for post exertional malaise. Participants who have PAM will not be included in these trials.

There's also going to be a trial to test a program known as structured pacing which is designed to help participants with PAM identify, control, and minimize symptoms that developed after having COVID-19 by regulated or easing their daily activities. People are going to be a little bit careful with this one. Participants will be randomly assigned to receive either structured pacing with a trained coach or a basic PAM education for three months. All right.

Now, the next one is hitting in an area that people may know is a sensitive area for me, and this is the, “Psychometric Analysis of the Modified COVID-19 Yorkshire Rehabilitation Scale in a Prospective Multicenter Study,” published in *BML Open Respiratory Research*. This is an app Vincent. There's now an app for Long - there's actually a lot of apps for Long COVID, so certainly not only the first, and actually at the end I'll leave a link for people with Long COVID who want to start using an app, but the data here come from the Long COVID Multidisciplinary Consortium optimizing treatments and services across the NHS.

They cleverly call this the LOCOMOTION Study by pulling some letters out of those words. In this study, 1,314 patients attending 10 UK specialists Long COVID clinics completed both the COVID-19 Yorkshire Rehabilitation Scale and the EuroQol 5D-5L. Now, they're going to look at these scales. Let's talk a little bit about what these scales are, what's going on here. The COVID-19 Yorkshire Rehabilitation Scale is a 17-item instrument designed to capture the key symptoms of Long COVID and its impact on activities of daily living.

These include four subscales. We've got a symptom severity of functional disability and overall health and other symptoms. Then the responses are recorded on a Likert scale, which is a really fancy way of saying, on a numerical scale, like 0 to 10, 3 to 10. Then depending on what you're looking at, zero might be zero symptoms, and then three might be a lot of symptoms. The overall health, zero is in my worst possible health, and 10 is in my best health. The score is a little different for each subset.

Now, the EQ-5D-5L is a preference-based instrument with five domains. Mobility, usual activities, self-care, pain, discomfort, anxiety, depression. It's got five response categories ranging from one, no problems here, to five, severe problems. Here it's like golf, the lower the numbers, the better. Lots of analysis. This is open access, so our listeners can spend time going through. Ultimately, they interpret these results as showing that the Yorkshire was able to detect changes as patient's symptoms fluctuated, and was really more sensitive to change.

Suggesting this might be a scale for us to use, maybe an app for people to use in future controlled trials. In the supplements, you can actually see the scale, which they suggest only takes about 10 minutes to fill out. If you've got COVID, it might take you longer. Now, there's also an app, so let's talk about the other apps. Not an extensive list, so I'm going to leave in some fun links here. Not only can we now, Vincent, track our weight, our steps, our sleep, but we can now track our Long COVID. We have Makevisible, we have Bearable.app, I like that' flaredown.com, BrainHQ.

I'm also going to leave in a link to - Vanderbilt University has created a resource where you could actually, not only link to a whole bunch of these apps, but they even have books and podcasts. Not sure why ours is not there, but just saying. Let me wrap it up there before questions and emails. No one is safe until everyone is safe. I want everyone to pause the recording right here, go to parasiteswithoutborders.com, and click on that big "Donate" button. Even a small amount helps. We're doing our floating doctors fundraiser, where for May, June, and July, we double your donations up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Susan writes, "I'm a 75-year-old healthy woman currently undergoing complicated treatments for a large squamous cell carcinoma on the palm side of my thumb that was shown by immunohistochemistry to be caused by an oncogenic strain of human papillomavirus.

Fortunately, the cancer cells stayed in the epidermis, but so much tissue had to be removed that a normal skin graft failed and I had to have a subsequent second flap surgery that involved grafting of blood vessels as well as skin. Now, I may also need a nerve graft to restore full function to my thumb. I've been told that this kind of HPV-induced cancer is very rare, yet I now know of several people in my life with recent cases of HPV-associated tongue, throat, and anal cancers. Of course, most cervical cancers are caused by HPV variants.

My questions are these: Is there any reason that the existing HPV vaccine could help prevent these non-cervical related cancers? If so, why is that vaccine only being recommended for young teens? In fact, why is this the only population eligible to get the vaccine to prevent cervical cancer? Lastly, could there be any value for me to get the vaccine now, even if it would mean paying for it out of pocket? Thoughts greatly appreciated."

DG: Susan, I'm really sorry that you had to go through this. Best of luck getting through it. You asked some really excellent questions. Really, key here is, which oncogenic HPV variant triggered this, and whether or not that HPV variant is in the current vaccine? If it is, then there's two ways that it might be protective. One is, if we can actually really remove or reduce the HPV oncogenic variants in society, in our community, then that's going to help at a population level. At an individual level, yes, if you had immunity, it might have actually prevented this.

Now, your next question, probably the timing's really good on it. Why don't we just vaccines for everyone? Why do we even have to prove they work? Let's just give vaccines because they're inherently good. As we talked about, there can be risks. If something works, and I think Paul often has made this point, something is biologically active, there is unlikely to be a zero risk. That risk might be one in a million like we talked about. This is one of those things. We don't just give vaccines until we actually show, not only that they're safe, but we actually show that there's an efficacy that outweighs any risk.

That's the logic here. We don't want to just do this until we've shown that this vaccine prevents other cancers. Maybe those head and neck cancers would be the next thing. Lastly, is this question of, so you at this point, would you get any vaccine benefit? Let's say, you paid out of pocket, your infection in the hand, not clear to me that you would. I think what you're doing, it's localized. They're removing it. That's really the treatment that we would recommend.

VR: I think the recommendation is up to 27 years of age, and then you could get it up to 45, but beyond 45, you're already likely to be infected, so a vaccine is not going to help you, right?

DG: Yes, that's the interesting thought is, the earlier, the better. Our studies in the most compelling, if you get vaccinated before you get exposed to one of these oncogenic viruses. Once you've been exposed already, is it too late? I think that's the concern and that's why our guidance is the way it is.

VR: Of course, as you say, this is a population level conclusion, and so individuals could also benefit, but you just don't know, right?

DG: Yes, we don't know, and that's a tough thing. That's hard, at an individual level with such a rare cancer, to know. Is there some therapeutic benefit to jumping in when the disease is already there?

VR: Connie writes, "I can't thank you enough for your show. My question concerns pneumonia vaccines. I'm 74. In 2015, I had a series of shots, Prevnar 13, then PPSV23. Is that good enough, or should I receive the Prevnar 20? I have asthma, and last year, developed pneumonia, so I just want to make sure I'm not missing anything."

DG: This is a great question. There's little subtleties here of pneumococcal vaccination strategies. The Prevnar 13, when we had Prevnar 13, when that was the conjugate pneumococcal vaccine of choice, we would then supplement it with the PPPSV23, which is a polysaccharide-based vaccine. You get your Prevnar once, and then you get your PPSV maybe once, maybe every five years. Then we got Prevnar 20.

I look at you and I say, wow, it's been about nine years since you had the PPPSV23. You're 74. You have asthma. There's an argument here. I should say, you should have a discussion with your primary care doc about, is there really a downside to getting that Prevnar 20 at this point? It's a reasonable thing to consider.

VR: Christian writes, "In your last clinical update, you mentioned prices in Germany for Paxlovid. For your information, prices have been no longer funded by the government. There are rumors that the government paid €650 since the beginning of the year. It's no longer €59 euro, but now €1,100." Wow. "Though a little bit below U.S. prices, still far too high to be provided widely when needed."

DG: That's really tough that it's gone that way. Is this probably Christian **[unintelligible 00:38:34]** writing us? No, I'm joking. Thanks for the update.

VR: It's a lot of money. Don't they have health insurance in Germany, Daniel?

DG: I'm wondering what the story is, but often, what happens is, when something gets this expensive, then it really becomes a rationing issue. If it's going to be this much, they'll run these risk-benefit analysis and they'll say, "You only get it if it's this." Then by the way, you can't even buy it, so a tough situation.

VR: Martin writes, "During a recent episode, you touched on some very preliminary research that, if I recall correctly, involved the use of a particular nasal antibiotic to stimulate interferon, possibly with a view to prophylactic or early exposure use for COVID. I appreciate neither you nor Vincent were very excited by the idea at this stage. I happen to follow MedCram, which as you likely know, is a medical training organization that helps students gain formal course credits.

Their Dr. Roger Seheult, who's a clinical professor at the University of California Riverside School of Medicine, and also an assistant clinical professor at Loma Linda, previously mentioned on their YouTube channel that at the first signs of COVID infection, taking certain specific steps to deliberately raise and temporarily maintain one's temperature for successive intermittent short durations at a level below danger threshold during week one is a way of trying to initiate a sustained interferon response in the hope of overcoming COVID's strategy of blocking that pathway.

My understanding is that the downstream benefit of stimulating interferon throughout week one of infection is a reduction in viral load, thereby hopefully moderating cytokine storm week two. Trying to recall if you've ever advocated this as a tactic and if not, whether you think it's a reasonable approach to adopt. If you broadly support that idea, then might simultaneously co-opting the nasal antibiotic you mentioned, helping accomplish the interferon goal?

I appreciate that the antibiotic's use purely as a prophylactic currently has limited appeal, but if the intention is instead for someone infected to nudge interferon into action and keep it going for the first week of infection, then that's a somewhat different proposition." Let's do that first.

DG: OK, I'll do that first. Yes, so MedCram is great actually. I've met Roger, and I think I was on MedCram at one point.

VR: You were [laugh].

DG: OK. I was on [laugh], so, Roger, kudos. This is a little interesting and as listeners probably know, I'm a huge fan of evidence-based as opposed to I've got this great, brilliant idea and I'm going to tell people to start doing it. I'm well aware it's a humility, 90% of my great ideas are just wrong and sounds very interesting and exciting and a little strange to maintain my temperature at this really high level, but again, it's one of those things you really got to test this out and see if it makes any sense.

I mean, here someone has gotten COVID, now you got all this craziness where you got to stay really hot for a while to - I think that this is something you need to actually verify was true before really encouraging folks to do.

VR: Then here's an FYI, here in the UK, you currently can't get Paxlovid, even if paying cash to a private doctor for a script. It's only available through the NHS if you're over 70 and in a nursing home hospital or on a cancer, other extreme medication regime. This is mainly down to cost, but NHS doctors in their professional body have adopted the stance that “prescribing obstacles,” for example, patients other meds and comorbidities, are just too complicated for them to confidently work around so have kicked prescribing back to local health authorities. Messy and depressing.

DG: Yes. I will just nod.

VR: Daniel, is it really that complicated to figure out if someone should get Paxlovid?

DG: It really isn't, actually. We pride ourselves, we're so intelligent, we got to medical school, we should get paid a certain amount. If you can't handle this, I'm not really sure. There's a website you can say, "All right, what medicines you on? Let me plug them in one at a time." I'm not even sure you need to go to medical school to do that. You just need to know the website, Liverpool COVID-19 drug interaction checker, by the way.

You go through each and it even explains, you're like, "Oh, but this is a C3A." Then it explains why in this situation, it's a concern. In this situation, it isn't. It really takes all this, so it's not that complicated. Is their time so precious, are they so overworked that they can't take those several minutes to go through that? It's a little messy and depressing that this is the situation.

VR: John writes, "My question is regarding measles protection for our 8-month-old grandchild since she is not old enough to receive an MMR vaccine. We will be traveling to states with reported measles cases in the next few months and we are concerned we might be exposed and be a possible risk to her. As grandparents over 65, should we get an MMR vaccine prior to traveling to raise our antibody levels to reduce our risk of infection so we don't unintentionally expose her?"

DG: John, you bring up this little window issue, we normally don't do the MMR vaccine, we don't normally do the measles-mumps-rubella vaccine until a child is 12 months. We do have that little, like if it's 6 to 12 and they're traveling to a risk area, then you might get that first

dose early. If you've been vaccinated, over 65, we're not recommending that you get a vaccine to bump those antibody levels. Measles is a disease of the unvaccinated and the transmission is from the unvaccinated. We wouldn't recommend this for you in this context.

VR: It's also seasonal and now is not the season for measles anymore, right?

DG: Things should be getting better but I guess the challenge we keep seeing is people travel overseas. Most of our outbreaks that we had were a U.S. citizen travels to a measles endemic area, brings it back and that traveler is someone who's unvaccinated either because they're too young for other reasons, and different seasons depending where you want to travel. We're coming into winter in certain parts of our globe so depends where you travel.

VR: Mark writes, "After listening to the episode," (I don't know which one) "I was hoping you can expand on a couple of points. You frequently refer to standard versus increased risk for more severe COVID illness. While I am pretty sure I could list all of the increased risk comorbidities, what do you define as standard risk?"

DG: OK, we'll start with that because it looks like there's a couple questions here. This is from Mark Schechter who I know as a fellow Optum Doctor. When we talk about standard risk, we're basically talking, it's interesting, it's like having none of the risk factors. You're under the age of 50. You don't have comorbidities. You don't have an elevated BMI. It's really an absence of issues. You're a non-smoker and then you start to increase the risk and it really isn't a binary. It's not like now you're at risk, therefore you weren't before. You hit the age of 50, you're 51.

OK, so we're starting to add that, but being 51 is not the same as 85. You've been diagnosed with hypertension, but they haven't started you on medicine. A little bit different than I've had hypertension for 15 years and I'm on three medications. There really is a gradation and we start looking at those comorbidities and that's part of the discussion with the patient about whether or not we should be jumping in with Paxlovid. Then also, like let's say your spouse has it, you might be counseling them about like the importance of why they want to avoid getting infected as well. That sort of gives you that standard risk versus all the comorbidities.

VR: I am also seeing tremendous hesitancy for patients to get COVID vaccination. Seems like the majority of my patients' last vaccine was in 2022. There's a small cohort of the over 65 crowd that has been keeping up on vaccines. Also been getting questions about recent journal articles highlighting the association between COVID vaccination and cardiomyopathy. Any insight you can share would be greatly appreciated.

DG: Yes. This is becoming a big part of our practice and I think it should have been a bigger part for a while, having conversations about vaccinations and the risk-benefits. It used to be before you get your flu shot and we'd sort of move right on you get your COVID shot this fall, we'd move right on. I think we need to have a little bit of a discussion and hopefully our podcasts help with giving you the content for that.

We've talked a bit about how that boost in the fall had certain benefits and we talked about that reduction and then what we knew from last year and what we will find out about this year as far as whether or not that that boost will end up being necessary, important and

helpful. I think when you have that discussion. The other thing is to point out, you may not be hearing about COVID in the news but it was a long time before we got back down to under a thousand deaths a week, that was pretty bad this winter.

Reinforcing to your patients, I know we're all done, we're exhausted, we don't really want to think about COVID. Great way to not have to think about it is to get that booster shot and reduce your risk about having to really think about it, a lot of it's having those discussions. Then we did talk in this episode and hopefully this is helpful about yes, there is a risk of an adverse side effect with the vaccinations, but that always pales in every single situation with the risk significantly higher with being unprotected when you get that COVID infection.

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

DG: Oh, thank you. Everyone be safe.

[00:48:52] [END OF AUDIO]