This Week in Virology

TWiV 1108 Clinical Update

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pdf of this transcript available (link)

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 1108, recorded on April 24, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today, not from New York, Daniel Griffin.

Daniel Griffin: Yes, it says that in the show notes, from Yosemite Valley. Actually, I am in Yosemite, and using my phone as a hotspot, so there might be little glitches where I don't know what Vincent is saying, and hopefully, it'll all come together at the end, but let me jump in. Hello, everyone. I have a quotation. This is a John Muir. "When we try to pick out anything by itself, we find it hitched to everything else in the universe."

VR: That's pretty serious, right?

DG: It is, actually. It's really great to - I'm here with my wife, Jessica, and my son, Barnaby. You'll learn so much coming to a place like this, and just seeing how everything is connected. Today we were up at the Grove where they've got those massive trees. Early on, they're trying to manage them, but then they realized by stopping the fires, they're not letting the sequoia trees grow, because the fire is part of their whole cycle. Just amazing to see how interconnected everything is in all these cycles.

All right, I will jump in now.

Interconnected we all are when it comes to infectious disease, with an update on measles. As of April 18, 2024, a total of 125 measles cases reported from 18 jurisdictions. Vincent, I was getting all these questions. I was even asked to be on the *Dr. Phil Show* right now instead of hanging out with you, but I would never miss an opportunity to hang out with you and hang out with Dr. Phil instead. I figured if everyone's asking, I should jump in.

What is happening with H5N1 avian flu? I am certainly going to ask Vincent to jump in on this. April 21st, so just a few days before we're recording this, and a few days before it drops, the USDA published 239 genetic sequences from the US H5N1 clade 2.3.4.4b influenza virus recently found in samples associated with the ongoing, highly pathogenic avian influenza

outbreak in poultry, wild birds, and the recent H5N1 event in dairy cattle. Sequences posted are from cattle, cats, chickens, skunk, raccoon, grackle. I don't even know what a grackle is. Blackbird and goose. Where's Dickson when you need them? You could look it up for us, Vincent.

Now, APHIS routinely publishes influenza genetic sequence on GISAID, so the Global Initiative on Sharing Avian Influenza Data. However, we hear that in the interest of public transparency and ensuring the scientific community has access to the information as quickly as possible to encourage disease research and development to benefit the U.S. dairy industry, APHIS is also rapidly sharing raw sequence data to the National Institute of Health's National Library of Medicine and National Center for Biotechnology Information. I'm going to leave a link into that announcement.

What do we know? There are a number of folks who are making comments about this. We hear from Michael Worobey, Doctor of Philosophy, Head of Ecology and Evolutionary Biology at the University of Arizona, Tucson, tells us that the virus was confirmed in another dairy herd in Idaho, raising the number of H5N1 detections to 33. Michael tells us, "Analysis of the hemagglutinin-neuraminidase and internal genes hints that the virus hasn't changed much from its introduction into cattle in late 2023 or 2024. The virus could have jumped to cattle once, but the information from the sequences can't rule out multiple introductions." He goes on to state, "There is a strong possibility that the virus has been circulating undetected for months, even before a mysterious illness began affecting dairy cows in February."

We hear from Sam Scarpino, PhD, director of, I love this, Artificial Intelligence and Life Sciences at Northeastern University. He tells us, "The genome data strengthened the evidence for cow-to-cow transmission. The early analysis shows no obvious changes that would increase the human-to-human transmission risk," but he added that it will take time to fully analyze all the genomes.

I'm going to leave an article into a CIDRAP, but the thing that tends to be getting a lot of people's attention, Vincent, and hopefully we can weigh in on this, is that they are finding evidence of the genetic material in milk. We have lots of calls from our followers to do plaque assays on the milk samples.

VR: Well, they should look for infectious virus, because they're doing PCR. Let's assume it is infectious virus. Milk is pasteurized for most people. If you drink raw milk, you're taking risks, folks. Don't do it. If it's pasteurized, it's going to inactivate the avian influenza virus. I don't think that's a risk. The real question is whether this will become a human virus or not, because now many animals are infected, many cows. I just got back from Ohio where cows are infected and humans are getting infected from the cows. This is very interesting. They're getting conjunctivitis.

DG: Yes, I think that's interesting.

VR: The eye has alpha-2,3- sialic acid receptors for avian H5N1 virus, and the rest of the upper tract does not. It's only deeper down in the lungs, so this is good in a way. Those infections have been mild in humans so far. Not to say it won't change. There's no evidence for human-to-human transmission. That could change as well. The thing is, don't worry about the milk.

Even the beef is not a problem. You're going to cook it. That's not the issue. The issue is human-to-human community transmission of a respiratory virus, if that should ever happen. Nobody can predict it, whether it will happen or not. I think we should be ready. Let's see. We have a couple of antivirals. We have Tamiflu, Relenza, and baloxavir.

DG: Yes.

VR: Some experimental H5N1 vaccines. I think we're better prepared than we were for COVID, don't you?

DG: Yes, no, I really think we are. I think that it's great that people are interested. I think it's great if we continue to strengthen our surveillance systems. Yes, how do I keep myself safe? How do I keep my family safe? Don't drink unpasteurized milk. Drink pasteurized. The other, as our Twitter followers have commented, we don't even know if it's infectious virus in there, if there's picking up genetic material. That is another thing for those of you that have to drink your milk raw, but yes.

Moving into COVID, I have to say, we are continuing to move in a positive direction. The percentage of provisional deaths, something I've directed people to following, really is less than 2% in much of the country, really less than 1% in most of the country. We're really moving to, hopefully, a number of better months. The wastewater is really tracking down to the low of where it was, dare I say, this time last year. National trend's going in the right direction. All right.

Children and other vulnerable populations, just a little time on the *MMWR*, “Durability of Original Monovalent mRNA Vaccine Effectiveness Against COVID-19 Omicron–Associated Hospitalization in Children and Adolescents, United States 2021-2023.” "Despite the fact that COVID-19 vaccination was shown to be effective against pediatric COVID-19 hospitalization during the emergence of the Omicron variant, there has not been great uptake in the pediatric population." Here we get vaccine efficacy of greater than or equal to two original monovalent COVID-19 vaccine doses against COVID-19-related hospitalizations across 34 overcoming COVID-19 network sites gets evaluated using a case control design.

The case patients were children, adolescents, 5 to 18, who were hospitalized for acute COVID-19 received a positive SARS-CoV-2 test result. Control patients hospitalized for COVID-19-like illness were matched to case-patients by site, age group, admission date, but had a negative SARS-CoV-2 test. Critical COVID-19-related illness was defined as receipt of noninvasive or invasive mechanical ventilation, vasoactive infusions, extra corporeal membrane oxygenation, and illness resulting in death.

Now, vaccine efficacy of original monovalent mRNA COVID-19 vaccines against COVID-19-related hospitalization was 52% when the most recent vaccine dose was received seven to 119 days before hospitalization. Interesting enough, dropped to 19% when it was received more than 120 up to 364 days before hospitalization, and 31% if you just grouped everything together in the previous year.

Vaccine efficacy against critical COVID-19 related illness was 57% when the dose was seven to 119 days before hospitalization. Not significant when you got up to 120 to 364 days; 38%

when the most recent dose was received at any point within the previous year. Really seeing that there is efficacy here, but there seems to be this loss of efficacy as time goes out.

VR: Did they track death at all?

DG: They do mention that they were looking at that, but it's really in these combined endpoints.

VR: What do you think about this? I'm surprised for this age group that it's so low.

DG: I'm also surprised that it's waning, right? Yes. That was -

VR: Yes, because I would think that at that age, you make a good T-cell response, and that's going to be a conserved. I'm very surprised at these numbers.

DG: I also would think that we're getting to a point where there's just so much COVID that there's these repeated exposures. You would think there'd be some kind of statement from that, so yes, I was a bit surprised.

All right. Now this is the controversial part. A little excitement in the ventilation transmission area this week, Vincent. Get ready for lots of emotion. Let's walk through. In the news release, "Leading Health Agencies Outline Updated Terminology for Pathogens that Transmit Through the Air." The WHO said the terminology challenge stemmed from a lack of common terminology across several scientific disciplines, a problem that became more acute when experts across disciplines were tapped to weigh in with guidance and recommendations.

From the 692-word or three-minute read news release, let me pull this, the extensive consultation resulted in the introduction of the following common descriptors to characterize the transmission of pathogens through the air under typical circumstances. Individuals infected with a respiratory pathogen can generate or expel infectious particles containing the pathogen through their mouth or nose by breathing, talking, singing, spitting, coughing, or sneezing.

These particles should be described with the term, ready for this, infectious respiratory particles or IRPs. IRPs exist on a continuous spectrum of sizes and no single cutoff points should be applied to distinguish smaller from larger particles. This facilitates moving away from the dichotomy of previously used terms aerosols, previously smaller particles and droplets, generally larger particles.

The descriptor through the air can be used in a general way to characterize an infectious disease where the main mode of transmission involves the pathogen traveling through the air or being suspended in the air under the umbrella of through-the-air transmission. [laughs] I see you nodding your head. Shall we take a little break here? What are you thinking, Vincent? What's going on?

VR: Well, first of all, why infectious respiratory particles? It's a droplet, right? You could say infectious respiratory droplets. Why a particle? That's so confusing.

DG: [laughs] I think the problem is that people since 1910, 1920, since the early part of 1900s, thanks to Chapin and his efforts to fight against the concept of miasma, actually created the concept of a droplet as a physical particle that would hit you, would strike you in the eyeball, strike you in the mouth, and then you would get a direct germ theory contact. In the early description, contact meant touching something that was infectious or getting touched, sprayed by physical germs. [laughs]

VR: That's weird. Sorry. I don't think particles works. I think we should just call it droplets. I know that droplets are not the smallest ones, but I think we could homogenize it.

DG: Yes. I think the challenge they're trying to get away from was that 110-year-old idea that only certain things could make you sick when you got more than six feet away. I still remember when I was in medical school and I was doing research on tuberculosis and the history there was, we had moved from the idea of the mal air getting people sick. Even when they did these experiments where they had guinea pigs, back when we used guinea pigs on the other end of this air shaft. They had the person coughing with tuberculosis in the one room, and the infection was spreading and infecting guinea pigs much more than six feet away in a separate room. It could only have gotten there if somehow things floated through the air to where the guinea pigs were.

There was a lot of resistance, and the interesting issue, a lot of the resistance, I have to say, is financial. Because for a hospital, for a medical center to have to equip people with N95s, for them to have the air exchanges, that's actually quite costly. Anyway. So they do go on to basically give us this updated terminology where the IRPs fall under the number one, airborne transmission or inhalation, but not the old-fashioned airborne aerosol, but this transmitted through the air versus direct deposition. This is where these IRPs are expelled into the air from an infectious person and then directly deposited on the mouth, nose, or eye.

I feel like they started so strong with this concept of, let's just say, transmission of pathogens through the air as we do with transmission of pathogens through food or through water. Then this one and two almost seem like they're just reframing the airborne versus direct droplet deposition, yes.

VR: I see a quote here of someone who said the old categories were more straightforward. [laughs]

DG: Well, I love this. Carl Zimmer has an article in *The New York Times.* They should have certain *New York Times* articles that just get tagged as it should be open for everyone, so unfortunately. Here we have Dr. Walter Zingg, an infectious disease expert at the University of Zurich, and a member of the advisory group said, "The old categories offered more straightforward guidance, staying a few feet from someone coughing and sneezing was once thought to be an effective way to avoid droplet transmission. It was simplistic and probably not true, but it served a purpose." I love the way he brings it together. It was simple. It probably wasn't true. [laughs]

VR: Now, if it wasn't true, it's not useful, right?

DG: I think that was the problem, is this was simple, it was straightforward, it's what we all were taught. Now, in the words of the father in that famous *Mary Poppins*, now we are

confusing things with the truth. Let's go back to simpler times when it wasn't necessarily good guidance, didn't necessarily keep everyone safe, but it was simple. It was easy to understand.

All right, [laughs] with that aside, COVID active vaccination immunity, remember there is that recommendation from the end of February for that additional monovalent dose for folks 65 and older. We did hear on March 22nd about Pemgarda, which is going to be the pre-exposure prophylaxis. Still waiting for more on that. All right, let's move into COVID early viral phase. Now, I'm going to keep leaving links to the NIH treatment guidelines, the IDSA guidelines, but then I'm also going to talk about an article about guidelines, "Comparison of WHO versus National COVID-19 Therapeutic Guidelines Across the World: Not Exactly a Perfect Match," published in the *BMJ Global Health*.

The authors were able to obtain COVID-19 therapeutic national guidelines from 109 of the 194 WHO member states. They report that the therapeutic recommendations in many national guidelines differed substantially from the WHO guidelines. Overall, in late 2022, 93% of the national guidelines were recommending at least one treatment, which had proved to be ineffective in large randomized trials and were not recommended by the WHO.

Corticosteroids were not recommended in severe disease in nearly 10% of the national guidelines despite this being not only inexpensive but overwhelming evidence for their benefit. Now, the national guidelines from countries with low resource settings show the greatest divergence. Now, I feel confident that most of our listeners can guess many of the recommended therapies that just don't work that were in many of these guidelines such as vitamin C, zinc, Ivermectin.

I have a couple of comments. One is when you mix science and politics you get politics. Perhaps a less cynical view is that some of the effective therapeutics are expensive, so there's a motivation to avoid including them in areas where they might be cost-prohibitive. As we've seen with some therapies, if it's difficult, if it's challenging, if the doctor has to look through drug-drug interactions and make adjustments, they would prefer if that wasn't in the guideline as well.

All right. I had sort of a standing-on-a-soapbox thing here, Vincent, which I feel I've vented enough already. So we will move into what is recommended. One, Paxlovid, two, remdesivir, three, molnupiravir, four, convalescent plasma, and we have the updated isolation guidance. We'll see how they incorporate this new terminology of the particles. Then we have the early inflammatory week steroids at the right time in the right patient, anticoagulation guidelines, pulmonary support.

What about remdesivir? We have the article, "Remdesivir is Associated with Reduced Mortality in Patients Hospitalized for COVID-19 Not Requiring Supplemental Oxygen," published in *Open Forum Infectious Diseases*. Here the investigators used a large multi-center U.S. hospital database to look at in-hospital mortality among patients hospitalized for COVID-19 not requiring supplemental action, and admission between December 2020 and April 2022, receiving or not receiving remdesivir.

This is going to be matched one-to-one. They're going to use propensity score matching. They're going to look at 14- and 28-day in-hospital mortality or discharge to hospice. Among

the 121,336 eligible patients, 58,188 remdesivir-treated patients were matched with 17,574 unique non-remdesivir patients. Overall, 5% of remdesivir-treated and 7.3% of non-remdesivir patients died within 14 days while 8% of remdesivir-treated and 9.8% of non-remdesivir patients died within 28 days.

We're actually seeing this statistically significant reduction in in-hospital mortality with the introduction of remdesivir. The interesting thing is there's a really nice figure where you get to look at all the different variant of concern periods. This significant mortality benefit endured across all the different VOC periods. Dura mentioned, even and actually most striking in the figure, during the Omicron period.

Moving into COVID, the late phase, PASC/Long COVID. For this section we have the *MMWR Notes from the Field*, "Long COVID Prevalence among Adults - United States, 2022." Now, prevalence, Long COVID prevalence. This is a tough number to pin down, as we have discussed before, and here the CDC analyzed data from noninstitutionalized U.S. adults aged 18 or older participating in the 2022 Behavioral Risk Factor Surveillance System, a population-based cross-sectional survey. Respondents were sampled using random digit dialing of both landline and cellular telephones. Sounds like fun.

Self-reported age, sex, previous COVID-19 diagnosis and ever having experienced Long COVID were ascertained via telephone interview. Long COVID was defined as the self-report of any symptoms lasting greater than three months that were not present before having COVID-19. I already see some potential biases. A lot of folks with Long COVID, and this is joking aside, are at home, not able to work, probably answering that landline. They report that 6.4% of noninstitutionalized U.S. adults reported ever having experienced Long COVID.

The weighted age and sex standardized prevalence ranged from 1.9% for the U.S. Virgin Islands to 10.6% for West Virginia and exceeded 8.8%, the highest prevalence cut-off in seven states. Prevalence tended to be lower in New England and the Pacific, higher in the South Midwest and West. They actually have a nice map where you can see these dark areas where you have just the highest incidents. Kind of amazing, Montana, Wyoming, North Dakota, Oklahoma, Tennessee, West Virginia. That's Alabama, or is that Mississippi? Hard to tell those two apart. One of those down there.

VR: Why do you think there this state-by-state variation?

DG: One of the things that has come up over time was the protection that vaccines offered. I don't know and we don't really get the granularity to look at this, so we're speculating, but was it areas that were able to get vaccines and then the infections where after we're going to see a significant reduction? I don't know, it'd be great to do some kind of analysis to see why is this prevalence so different.

VR: There are a lot of reasons, I don't think incidence is one of them because that's pretty even state by state.

DG: At this point, it's been, yes, it's really been all these areas.

VR: It could be the health status of people in certain states could vary based on healthcare systems and other issues as well, right?

DG: That's an issue, too.

VR: None of the Northeast really have the highest rates. California does not. The states with really good healthcare systems.

DG: New England looked like it did really well; up in the Pacific Northwest also doing quite well.

VR: Northwest as well.

DG: All right. Well, we also have another rather contentious article we will talk about, and it's really, the topic seems to be fraught with lots of misinterpretation. The article, "The Persistence of SARS-CoV-2 in Tissues and Its Association With Long COVID Symptoms: A Cross-Sectional Cohort Study in China," published in *The Lancet Infectious Diseases*.

My first word of caution as we discuss this article is the important distinction between persistence of replication-competent virus versus the persistence of viral remnants. When people talk about viral persistence, they're usually not just talking about the skeletal remains of the virus in the form of RNA or protein. Let's be careful here as we review this article.

These are results of a single-center cross-sectional cohort study done at the China-Japan Friendship Hospital in Beijing, China, following the Omicron wave of COVID-19 in December of 2022. Individuals with mild COVID-19 confirmed by PCR or a lateral flow test, scheduled to undergo gastroscopy, surgery, or chemotherapy, or scheduled for treatment in hospital for other reasons at one month, two month, four months after infection were enrolled in the study. Residual surgical samples, gastroscopy samples, blood samples were collected at these time points at one month, two month, and four months.

After infection, telephone follow-up was done at four months post-infection to assess the association between the persistence of SARS-CoV-2 RNA and Long COVID symptoms. Between January 3rd and April 28, 2023, 317 tissue samples were collected from 225 patients including 201 residual surgical specimens, 59 gastroscopy samples, 57 blood component samples. Viral RNA was detected in 30% of the 53 solid tissue samples collected at one month, 27% at two months, 11% at four months. Viral RNA was distributed across 10 different types of solid tissues including liver, kidney, stomach, intestine, brain, blood vessels, lung, breast, skin, and thyroid.

Now, this can get a bit more interesting as we read that subgenomic RNA was detected in 43% of 61 solid tissue samples for genomic RNA that also tested positive for viral RNA. We're going to get back to that. What exactly does that mean in our discussion? Among 213 patients who completed the telephone questionnaire, 34% reported at least one Long COVID symptom with fatigue being the most frequent, detection of viral RNA in recovered patients was significantly associated with the development of Long COVID symptoms, patients with higher virus copy numbers had a higher likelihood of developing Long COVID symptoms.

Now, the next part I thought gets interesting. In an attempt to investigate the potential mechanisms underlying the association between this persistence of viral remnants and Long COVID symptoms, they did transcriptome sequencing of 11 blood vessels and 24 lung tissues.

In the lung tissues, they observed downregulation of several genes involved in the innate and adaptive immune defense against pathogens in the viral persistence group.

They also noted a significant downregulation of zinc finger protein-related genes in the persistence of viral remnant group, which they say may play a role in defense against SARS-CoV-2. They interpret these findings as suggesting that dysfunction and host immune defense might contribute to poor virus clearance.

In the blood vessel samples with persistence of viral remnants, they identified dysregulation of genes related to the complement and coagulation cascades. They also observed dysregulation of genes involved in cholesterol metabolism pathways. They go on to conclude that these findings suggest that persistence of viral remnants might affect host cell functions which could be another contributing factor to the occurrence of Long COVID symptoms.

VR: Daniel, I don't know the details but do they have people without Long COVID that they got comparable time points of tissues to look at?

DG: Exactly. Exactly. What they're doing is they've got these groups. Basically, they have the whole group and they get the samples and then they're going to ask the people and say, who's got Long COVID and who doesn't? They're going to divide up the people and then they'll say, OK, so we've got people that have Long COVID, we've got people that don't and then boy, the people with Long COVID, higher percent of the time are we going to end up with a positive PCR for picking up - [crosstalk]

VR: It's not black and white.

DG: It's not black and white.

VR: I don't know what any of this means because I think if you did this for any infectious disease you would find reactive material in multiple tissues, which is never looked to this extent and with such sensitive assays before.

DG: Actually, that's interesting. I'll leave a couple nice discussions about this. One was a nice discussion by Danilo Buonsenso and Kelan Tantisira, “Long COVID and SARS-CoV-2 Persistence: New Answers, More Questions.” A lot of what they bring up is, is this so unique or is this something that goes on in other infections? Because we talk about Long COVID but there's also “long flu,” there's other post-acute sequelae, not just COVID, and this growing literature that there might be persistence of certain genetic materials, certain proteins, and certain body tissues and cells that might be associated with those ongoing symptoms. Nice in that.

I think a couple, what I think is critical as this gets all heated up and emotional, is that we're not sure, and I'm not saying anything here tells us either way whether this is ongoing replication competent virus. I wish it was. Because then we could just throw antivirals at it, we could put people on long courses of remdesivir or Paxlovid. Those trials are ongoing and we're not even hearing any whispers of good news. Is it that these viral remnants are triggering ongoing issues or are they evidence that something was wrong with the host immune function up front that allows these to be in all these tissues?

VR: Yes, that's what it is exactly. I think the antiviral effect is going to be important because I agree, I don't think this is continuing replication and if there's no effect of extended remdesivir, then that will confirm it, there's something else going on, and maybe as you say, there's something wrong with the host and therefore they can't clear a virus. It doesn't mean it's the other way around, right?

DG: Yes and we don't know.

VR: It will be difficult to know because we don't have an animal model where you could do the right kinds of experiments so, very tough.

DG: All right. Low- and middle-income countries, I just always like to wrap up here as I have for the last four years, no one is safe until everyone is safe. I encourage everyone to pause recording right here. We're coming towards the end of April and we're still not there in our American Society of Tropical Medicine and Hygiene fundraiser. We're trying to get up to a potential maximum donation of $20,000, so even a small amount helps, we're going to be doubling your money to get up to that goal, and a portion of these funds will go to providing travel awards for two female qualified students early-career investigators.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Alan writes, "If you've never seen it, this *XKCD* should bring a smile. Thank you for your lucid, informative and engaging contributions to *TWiV*." If you don't know, *XKCD* is a comic strip. Here is one, the first panel we have someone at a lectern, “an apple a day keeps a doctor away or at least it used to.” In panel two, the guy's pointing to a chart, “over time some doctors have developed a resistance to apples. Keeping them away takes two or three apples instead of just one. There are worrying signs that a few doctors may have become completely immune.” Third panel, “so we must stockpile our finest apples in reserve using them to fend off only the very worst doctors. Honeycrisps still work on most of them but we don't know for how long.”

DG: [laughs] I love that, it's funny.

VR: A good parody of antimicrobial resistance, right?

DG: Yes, exactly.

VR: Thank you, Alan. Marianne writes, "I was just reading in *The New York Times* today about dead H5N1 viral particles found in milk. Would ingesting these dead particles enable our immune systems to recognize and help kill the live H5N1 virus if we were to become infected? I don't know enough about virology or immunology but I know enough to ask you and Vincent. Thank you for continuing clinical updates on *TWiV*."

DG: Thank you.

VR: Daniel, it's always important to know who to ask, right?

DG: I think that's one of the things. Since our knowledge is by definition finite, it's always important to be able to reach out and ask the right people and boy, are we the right people here? I hope so, Vincent. Well, I like the fact that you're referring to these as dead H5N1. We

have no evidence to date that this is replicating, replication incompetent or some people would say live virus in the milk samples. As mentioned by *The Times*, if it's pasteurized you're going to be in good shape.

Now, pasteurization, so that heating is going to do a few things. One thing is actually going to modify the proteins, so I'm not really sure that you want to be rushing out there thinking that if you drink enough of this contaminated milk you're going to develop some sort of immunology, some sort of immunity. Vincent, what are you thinking?

VR: I don't think there's enough antigen in the milk to immunize a mucosal surface. We don't have any - infectious viruses can do that. Like poliovirus and norovirus and rotavirus, they can get into your gut and infect the gut and get an immune response but these are not going to do that and so I don't think there's enough antigen to do that whatsoever.

DG: All right. Thanks for asking.

VR: Janet writes, "We are planning a 99th birthday party for the matriarch of the family the first week in July in Seattle. Family members from all over the country will be attending. One of those will be, the newest edition, our now 5-month-old grandson who will be 7 months at the time, he'll be flying with his parents, and healthy vaccinated 2-year-old and 13-year-old sisters. I'm concerned about the recent rise in measles cases in the U.S. you've been discussing on *TWiV* in recent months and the fact that standard vaccination protocol is that a child receive their first MMR between 12 and 15 months of age.

A quick Google search reveals that for people traveling with infants internationally to areas with known measles outbreaks, babies 6 to 11 months old should receive their first MMR vaccine dose at least two weeks before traveling. I understand they will still need the two-dose series if they receive a dose before age 12 months. Would you think it prudent that my grandson get vaccinated about two to four weeks prior to traveling to Seattle when he will be just 6 months old or am I being an overly worried grandmother? Are there any significant downsides to getting vaccinated early other than the fact that he would need to be revaccinated and thus would be getting an extra shot if he were to get vaccinated early? Is there a separate measles vaccine or only the combination MMR formulation?"

DG: OK. I'm going to sort of be doing this backward. The first question you had, is there any downside? Because we are making this recommendation in certain contexts. If a baby was going to be 6 to 11 months, they're going to be traveling internationally, particularly to international destinations where there is significant ongoing measles transmission, really a very safe thing to be recommending.

Then the other comment is, is this really high-risk? Is this an experience that warrants that? As we keep people updated we talk about where the outbreaks are, what's going on, they're occurring in different contexts. Traveling in the U.S. out to the great Northwest is really a pretty low-risk activity, so this really wouldn't be a part where we would be generally recommending vaccines for this kind of a context.

VR: Sue writes, "A letter to you in clinical update 1106 made me realize I've had a question for you all along. (What have you learned today, Dorothy?) My husband's three, count ‘em,

three types of arthritis have gradually made a near complete comeback, especially the worst of them, psoriatic." Psoriatic? How do you say that, Daniel?

DG: Psoriatic.

VR: "Psoriatic in the four years since the COVID-19 pandemic made him reluctant to suppress his immune systems to any degree with methotrexate plus the danger then of visiting his rheumatologist in a high-rise office deep in New Orleans when we were a hot spot. He now suffers frank pain in his hands, left knee, and right hip. Risky, discomfitting flare of skin psoriasis on his lower legs, resolved by his old drug regimen, keep him in long pants all summer, in this climate now hotter than ever.

“He used to take methotrexate. Humira biweekly injections, supplement folate and D3 and colchicine as needed for, thankfully, infrequent bouts of acute gout. Maybe something else I don't recall. Osteo tics along in the background, it too vastly improved by that regimen. If that makes sense, what do I know? I'm just a biochemist who became a radiographer for better job security and a lot less sexual harassment back in the day, lucked into meeting this wonderful partner.

“Oh, my question. Does being on any immunosuppressant always decrease the efficacy of any vaccines or boosters? Can you go off the meds for a time, get your booster, wait for a while to build up your arsenal of programmed immune cells, and then go back on, say, methotrexate, and maintain your level of immunity with a normal rate of diminution of immunity, if that's why we get boosters, apart from new variants?"

“Oh God, she has another question.” (laughter) “ Will going back on these meds erase any of the immunity he's gotten in three years of vaxing and boosting as recommended? If this strategy is a thing, can y'all point me to timing guidance out there or suggest a program yourself? His overworked GP doesn't even want to talk about it."

DG: Oh, OK. Well, I'm happy to talk about it. The nice thing is we started thinking about this early on, because there are millions of others in the same situation as your husband here. What to do? Well, one of the things we've realized, we'll take certain medications, certain of the immunosuppressive medications, like methotrexate. This has been studied, if you stop them for two weeks and then get vaccinated, you're going to get a better response than getting vaccinated while staying on those.

The other issue that you bring up is once you get back on those, you're going to have that immunosuppressant issue associated with that. So, what do we recommend? If you can get off these for two or three weeks, do that. That's the timing. You get your vaccine, and then when you need to get back on them then you just realize you continue to have that immunosuppressed issue, and that's why we're hoping something like Pemgarda can actually get out there to give us another option for these drugs.

VR: Will writes, "In yesterday's clinical update you talked about active and passive vaccination. I understand that a baby can have passive immunity from the mother for a few months after birth, but what is passive vaccination? I've not come across the term before.:

DG: This is great, this is actually a distinction we've talked about for a while. I think during the days of COVID, this has gotten on to the main screen. The active vaccination is, we're expecting your immune system to be active in the process. You got to do some work. You're exposed to the antigen in some way and then you mount a T- and a B-cell response. The passive vaccination is we give you the immunity in the form of preformed, preestablished, pregenerated antibodies in most cases. This is something that we've done when someone gets exposed to certain things, like with rabies, with the immunoglobulins we're actually using this passive strategy, and now we're actually starting to use it for COVID-19.

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

DG: Thank you, and everyone, be safe.

[music]

[00:43:36] [END OF AUDIO]