This Week in Virology

TWiV 1022 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 1022, recorded on July 6, 2023. 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: Daniel, we're in the heart of the summer here, and there's not much influenza, there's not much rhinovirus, is there not much COVID also?

DG: There's a little background COVID, and I have a few patients in the hospital that I'm taking care of with COVID. Had a couple of folks when I was just recently at Columbia. It's that low, background level at the moment.

VR: Is it the same? Would you also see a few flu patients as well? Respiratory syncytial?

DG: That's interesting. We're not seeing any flu patients. We haven't seen RSV. It hasn't locked into the same seasonality. That's the prediction. We have yet to see that happen. That's the whole idea, but we'll see. I mean this is new, right? This is novel, dare I say that?

VR: Yes. It's new. We will keep covering it, won't we, Daniel?

DG: Yes. I'm glad you bring this up because right now we feel like we're at a bit of a lull, but there's still lots of questions. People are still getting diagnosed. People are still, hopefully, taking the right steps to treat it. There is the predicted increase that we'll see in a few months. We'll be here ready to talk about it, but let's get right into it. I don't know if folks throughout the world are familiar with the Fourth of July. That's a big celebration here in the United States. This is when people do all kinds of crazy things to demonstrate their freedom, including eating food that is soaked in mayonnaise and sitting out in the sun for way too many hours. I thought I would pick a quotation from one of my favorites, Eleanor Roosevelt.

I was left to bring that up because my dad actually met her and was quite impressed by her. Her quotation, "With freedom comes responsibility." I feel like Marvel and Spider-Man stole and spun that a little bit. I'm going to jump right into, are you ready for this, leprosy. What are we doing talking about leprosy here in the United States? Well, the article, "Autochthonous Leprosy in the United States," was published in *The New England Journal of Medicine*. Autochthonous meaning people just staying here, not traveling, living in the U.S., getting leprosy. Not sure how many of our listeners have ever seen or physicians out there, clinicians out there, treated cases of leprosy, so a little bit of background is perhaps warranted.

Historically, leprosy was thought to be transmitted exclusively through extended close human-to-human contact, with infection acquired during brief travel considered to be extraordinarily rare, if even possible. In the 1970s, the nine-banded armadillo was identified as a zoonotic reservoir of Mycobacterium leprae which had been implicated in autochthonous leprosy among persons born or living in the U.S.. However, autochthonous leprosy without armadillo exposure has also been reported. Now, a challenge here is there's a really long incubation period for leprosy.

Here this is the report of six cases of leprosy in U.S.-born men, mean age 68.3 years, that were diagnosed between 2017 and 2022 in California. Now, none of these patients had exposure to an infected person. One person reported armadillo exposure more than 50 years earlier. All six patients reported international travel, and most reported domestic travel to the U.S. Gulf Coast. The interval between the initial clinical manifestations to diagnosis range from months to years. As mentioned, five of the six patients were older than 65, and all of them had multi-bacillary infections, so lots of teeming with these mycobacteria.

VR: What would be the symptom that makes them go to seek medical care?

DG: A couple different ways they can present. Great to tell, one of the times I was being harassed by the medical students when I was working in Katmandu, where a woman came in and her symptoms were tingling in the fingers, so that might be one of the things, and they, "Dr. Griffin, what should we be thinking about?" Then I did my exam, and I felt on the nerves the actual scarred areas that was leprosy. Also can present as skin patches that are anesthetic. You see skin patches, but then you touch it with a needle, you poke it with a needle, and the person cannot feel it. Couple different manifestations, but those, hopefully, you're going to pick it up early when it's just tingling before you've seen any significant changes, maybe just the skin manifestations.

VR: How do you treat them?

DG: The big distinction is pauci versus multibacillary. You're going to actually treat them for months with oral agents. This is something you can treat, something you can cure.

VR: All right. You don't have to go to Moloka'i.

DG: [laughs] Our listeners maybe will Google and figure out why Vincent said that. All right. Mpox. The article - I've an issue with the title here. I'm not sure where the reviewers were, but "A Systematic Review to Identify Novel Clinical Characteristics of Monkeypox Virus Infection." Shouldn't that be Mpox? Come on. "Therapeutic and Preventive Strategies to

Combat the Virus," was published in *Archives of Virology*. Unfortunately, this is behind a paywall, but these are the results of a systematic search in several databases, including PubMed, Google Scholar, Cochrane Library, and the grey literature.

VR: What is that? What is the grey literature?

DG: [laughs] Well, apparently, the grey literature, spelled either G-R-E-Y or G-R-A-Y, are materials and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels. I'll leave a link for everyone here to the Wikipedia about grey literature. We are delving into the grey literature. Maybe we are - Are we grey literature?

VR: We are not grey, no.

DG: [laughs]

VR: We're not gray. I don't think we should be delving into the grey literature. It sounds sketchy to me.

DG: [laughs] Doesn't it sound kind of sketchy?

VR: Yes.

DG: I have to say, I was very curious, but I think the reason I bring this up is they looked at 21 eligible studies that included 18,275 Mpox cases. Couple things that they described was a mean incubation period, about seven days, but an interquartile range of three to 21. The big thing is that when people started first talking about Mpox back last spring into the summer, they always started off with, "How did Mpox present 40 years ago in Sub-Saharan Africa?" Now, hopefully, people are saying, "Let's teach how Mpox presents now." They do actually describe the clinical manifestations we're seeing. The severe skin lesions, I think you should also look for ones that aren't so severe, on the palms, in the mouth, in the genital regions, proctitis, penile edema, tonsillitis, ocular disease, myalgia, lethargy, sore throat.

Then sometimes they have a prodrome, but a lot of times they don't. They just develop these skin lesions right away. Then as we've talked about and they mention here, there are some they say fully asymptomatic cases. Are they really cases, or they're just PCR-positive? They also mention encephalomyelitis and angina. Just want that back on the radar because in a few parts of our country, we're starting to see cases. If you don't think about it, if you don't test for it, you're going to miss it. If you miss it, that might then lead up to onward transmission.

All right, polio. I was excited to read this article and then rather concerned. The article, "Two-Year Duration of Immunity of Inactivated Poliovirus Vaccine: A Follow-up Study in Pakistan in 2020," was recently published in *JID*. I was thinking this would be a great look into the durability. We might even start to get some kinetics of the immune responses. Now, as the authors write, unexpectedly, the findings revealed an increase in serial prevalence of type-II antibodies from 73.1 to 81.61 and two years after IPV respectively. The increase in type-II immunity, they say, could result from the intensive transmission of circulating vaccine-derived poliovirus type II in Karachi during the second year of IPV administration.

They go on to say, this study suggests that the cVDPV2 outbreak detected in Pakistan infected large proportions of children in Karachi.

VR: That's surprising because they don't really - All they do is look for paralysis. Many more kids are infected than get paralyzed. This is not surprising me at all that there's extensive circulation of this virus there.

DG: Here you're basically saying people get - It's a nice figure, actually, if people take a look at this. You see the IPV gets administered. Nine months later, there's another IPV administration. Things then go up, they start to come down and, boop, then things go up, and you're like, OK, so. All right. Now I'm going to balance this with the article, “Evaluation of Novel Oral Polio Vaccine Type 2 SIA Impact in a Large Outbreak of Circulating Vaccine-derived Poliovirus in Nigeria,” where we look at the impact of nOPV2 on a large outbreak of circulating vaccine-derived poliovirus type 2 in Nigeria. The authors let us know that since 2021, over 350 million doses of the nOPV2 were used for control of a large outbreak of circulating vaccine-derived poliovirus type 2 in Nigeria.

Three-hundred-fifty-million doses. That is really impressive. They report that the novel oral poliovirus type 2 and the monovalent oral polio vaccine type 2 campaigns were highly effective in reducing transmission, on average reducing the susceptibility population by 42% and 38% per campaign respectively. Impact was found to vary across areas in between immunization campaigns.

Moving into COVID. I've got one right up front, which I think we're going to have to have a little discussion about it. I discussed this with our urgent care docs this week, the Wednesday meeting. A lot of really entertaining comments, which I think it's one of the great things. It's one thing to read these studies, but then it's really nice to talk to clinicians out there in the trenches, so to speak.

Does this really make sense? The article, “Performance of Rapid Antigen Tests to Detect Symptomatic and Asymptomatic SARS-CoV-2 Infection,” was published in *Annals of Internal Medicine*. These are the results of a prospective cohort study where they enrolled participants between October 2021 and January 2022. Participants completed the rapid tests and RT-PCR testing for SARS-CoV-2, are you ready for this, every 48 hours for 15 days.

Among 154 participants who tested positive for SARS-CoV-2, 97 were asymptomatic. 57 had symptoms at infection onset. Serial testing with the rapid test twice, 48 hours apart, resulted in an aggregate sensitivity of 93.4% among symptomatic participants on different days past the index PCR positivity. The aggregated sensitivity among the asymptomatic folks was lower at 62.7 but improved to 79% with testing three times at 48-hour intervals.

I really like Figure 3. Just to remind folks that have been listening for a while, remember those CT values, those cycle threshold values? This is, "How many times do I have to run that PCR machine before I finally get a positive test?" The people that are acutely ill, we're running that maybe 15, 20 times picking those folks up. Now, once someone either starts to get better or very early or in some cases, we're actually seeing folks that have had a recent infection or recent vaccination, we might never get really high levels of viral RNA. We might have to run that out to 30, 35, 40.

Nice thing here about Figure 4 is they give us the sensitivity for symptomatic and asymptomatic CT value relative to the predicted probability of having a positive rapid test. Basically, if that CT value is 20 or less, if they are "teeming with viral RNA," you're picking them up all the time. Once you start to get to about 25, the sensitivity starts to go down. Once you get to particularly 30, asymptomatic, it really drops off. Even 30 with a symptomatic person, you're still doing an over 80% sensitivity.

Couple of comments I got from the clinicians on the call yesterday. One was, "Dr. Griffin, what about those expired tests from two years ago?" [chuckles] "What about those tests that were sitting out on the doorstep for hours until the person finally got home, baking in the sun? What about those tests that actually have two lines and they show it to us and say it's a negative test?"

This is more of an ideal world, and I think the takeaway from here is that folks that are teeming with viral RNA, symptomatic, great sensitivity if the test is not expired and actually working properly and performed properly, so a positive test is very reliable. A negative test, as we've been saying, you want to repeat that to see, and if the person is symptomatic and qualifies for treatment, you may want to actually jump on with a molecular test as the CDC recommends. All right, love that figure, though.

All right. COVID, active vaccination. Now this is a good one, and we'll hopefully spend a little time drilling in this, but the article, “Effectiveness of the Coronavirus Disease 2019 Bivalent Vaccine,” was published in the June volume 10, Issue 6, issue of *OFID, Open Forum Infectious Diseases*. I think they should have right in the title, when you say effectiveness, what are you talking about? Effectiveness to do what? This is a study that one really needs to read carefully. Otherwise, you can just use this to feed any confirmation bias that you choose.

In this study, they included employees of the Cleveland Clinic where the bivalent COVID-19 vaccine first became available. The cumulative incidence of COVID-19 over the following 26 weeks was examined. This is COVID-19. This is incidence of infection. We're not talking here about hospitalization, death. Protection provided by vaccination, analyzed as a time-dependent correlate, was evaluated with change in dominant circulating lineages over time accounted for by time-dependent coefficients. The analysis was adjusted for the pandemic phase when the last prior COVID-19 episode occurred, and the number of prior vaccine doses.

Here they're going to look at over 51,000 employees. COVID is going to occur in 4,427 during this study, so about 8.7%. Now, what was the estimated vaccine effectiveness protection against infection? During the BA.4/5-dominant period, 29%, during the BQ-dominant period, 20%. Now in the time we currently are, during the XBB-dominant phase, decreased risk was not found, so no reduction in infection added by getting a booster during the XBB-dominant phase.

VR: Then the booster is bivalent, correct?

DG: This is the bivalent. This is the ancestral P48/45.

VR: Four-five. Not surprising, right?

DG: I think this is important for people to keep on their radar. Someone comes in now and they say, "Oh, hey, I haven't gotten that bivalent vaccine. Should I get it? Should I wait till the fall?" I think this gives you the answer. This says, "Listen, I don't think we have compelling science that we're going to get any neutralizing antibodies that we're going to be able to offer any reduction in your chance of getting infected."

The other side, which I think is really reassuring, is that we tend to have durability with protection against severe disease. We'll hopefully have a discussion come October when we start to get some data on the updated boosters and talk a little bit about, for whom it makes sense, what does the science tell us?

VR: In the meantime, Daniel, you would say, if you are at risk, then you should take Paxlovid.

DG: That's the biggest thing, and let's move right into that because that's the whole issue. Hopefully, the majority of people that are listening to us have been vaccinated if they were able to do that. What if you get infected? Does it matter? Unvaccinated, vaccinated? Does Paxlovid still make a difference? We'll move right into the COVID early viral, upper respiratory, non-hypoxic phase. That first week, you test positive. Maybe it was a rapid test, maybe it was molecular. The article, “Oral Nirmatrelvir and Retrovir for COVID-19 in Vaccinated Non-hospitalized Adults, Ages 18 to 50,” was recently published in *CID.*

The science is rather clear that Paxlovid is highly effective in the unvaccinated when they have risk factors such as age over 50, other medical comorbidities. Also, compelling science that we could reduce the risk of progression in the vaccinated when they have risk factors such as age over 50, medical comorbidities, but what about Paxlovid for COVID-19 in vaccinated adults 18 to 50? Here the investigators generated two propensity-matched cohorts of 2,547 patients from an 86,119-person cohort assembled from the TriNetX database.

Then they did a comparative retrospective cohort study. Patients in one cohort received Paxlovid and patients in the matched control cohort did not. They looked at a composite of all-cause emergency department visits, hospitalization, and mortality. Basically interaction with this level of the healthcare system. The composite outcome was detected in 4.9% of the Paxlovid, 7% of the non-treated, indicating about a 30% relative risk reduction.

Now, interesting the different numbers needed to treat. I actually pasted into the show notes today, Table 3, which I think is worth looking at. Let's say what qualified this individual was cardiovascular disease. By cardiovascular disease, what do we mean? Hypertension, hyperlipidemia, ischemic heart disease, atrial fibrillation. The number needed to treat to prevent someone from ending up in the ER or the hospital was only 30. If the person had cancer, the number needed to treat was 45. If they had both cancer and a cardiovascular risk, it was 16. If this is someone who has been in the ER in the last three years, only 19 needed to treat.

A couple questions. What about Long COVID? What about other outcomes? I think it would be nice to know, because a lot of people say, "You know what? My risk of ending up in the ER, ending up to the hospital, is really pretty low. Should I bother? Should I go through all this effort?"

VR: These numbers are not bad, in other words, except for the no ER visit hospitalization in the prior three. Basically, healthy people, right?

DG: Yes, and I think that's really where we get - You don't need to give this to everyone. If someone's healthy in this 18-to-50-year-old, they don't have comorbidities. You don't need to give this to everyone. All right, number two. As we've talked about, remdesivir, but continues to be an issue. There's no website you can jump on and say, "Hey, where's the closest outpatient three-day IV remdesivir to me? Maybe that's a call to action. Molnupiravir, Thor's hammer, convalescent plasma for that particular immunocompromised patient. The biggest thing, let's not do harmful and useless things.

VR: Daniel, at the ASV, at lunch one day, I sat across from a guy who had a coffee mug, it said, "Team Molnupiravir" on it.

DG: [laughs]

VR: He worked at EIDD, the Emory, what is it called? Emory Infectious Diseases Drug - Oh, come on, I got to figure this out. What is EIDD?

DG: That's where they started with the flu work down there at Emory.

VR: Emory Institute for Drug Development, yes. He works there, and he said they have more things coming out. Good stuff. [laughs]

DG: [chuckles] This is one that - I don't know if our listeners know, but for a while, I was doing a lot of remote consultation for the refugee camps over in sort of the Bangladeshi refugees, the Myanmar refugees. It really is a great drug in a situation like that because you don't have to worry about drug-drug interactions. You're taking it twice a day. You don't have to worry about renal adjustments. It's a nice option in certain settings.

VR He did admit that it didn't work so great. [laughs]

DG: That's the only downside, dare I say, [laughs] it doesn't work so great. All right, well, what about folks that progress? This does happen. I got a couple of folks in the hospital right now who got admitted. Second week, oxygen saturation is less than 94%. Number one, we've talked about this and let's keep our order sets up-to-date, dexamethasone, 6 milligrams a day times six days, not seven, not 10. We've learned more: 6 milligrams times about 6 days, so time to update those order sets and recommendations.

Number two, anticoagulation. Number of organizations giving guidelines out. A little sad today for me, it was our last meeting of the American Society of Hematology guideline panel. Met some wonderful people over the last few years, but they've got some guidelines. I love the way the guidelines point out. This is the population that's studied, keep that in mind when you're looking at your patient and how those risks compare.

Pulmonary support, we've talked about all the issues there. Proning, trying to avoid intubation when possible. Remdesivir, if we're still in the first 10 days before they've ended up on a ventilator. Immune modulation in some situations. Tocilizumab.

Let's move into late phase, PASC Long COVID. Couple of nice studies here to wrap us out. The first is actually posted as a preprint on *medRxiv*, "Genome-wide Association Study of Long COVID.

Here the authors start by commenting that infections can lead to persistent or long-term symptoms and diseases such as shingles after varicella-zoster, cancers after human papillomavirus, or rheumatic fever after streptococcal infections. Similarly, you're getting a parallel here, infection by SARS-CoV-2 can result in Long COVID, a condition characterized by symptoms of fatigue, pulmonary, cognitive dysfunction.

Here the investigators let us know that they leveraged the COVID-19 Host Genetics Initiative to perform a genome-wide association study for Long COVID, including up to 6,450 Long COVID cases and 1,093,995 population controls from 24 studies across 16 countries. They identified the first genome-wide significant association for Long COVID at the FOXP4 locus. FOXP4 has been previously associated with COVID-19 severity, lung function cancers. A really nice Manhattan plot in Figure 2A and Figure 2B breaks it down by the different studies.

I don't know how many folks have looked at a Manhattan plot, but I spent a little time in the genetics universe doing GWAS stuff.

The idea here is that they're picking up a change that is associated with FOXP4 expression in the lungs. Expression analysis of the lung and cell-type specific single-cell sequencing analysis showed FOXP4 expression in both alveolar cell types and immune cells of the lung. Little background, FOXP4 belongs to the subfamily P of the forkhead box transcription factor family genes expressed in various tissues, including the lungs and the gut. Moreover, it's highly expressed in mucus-secreting cells of the stomach and intestines, as well as naïve B, natural killer, memory Treg cells and required for normal T-cell memory function following infection.

VR: Basically, if you have a certain change in the FOXP4 gene, you may be predisposed to Long COVID?

DG: We think it may be right in the regulation part of FOXP4, at least where I was looking through. It may not be so much a modification of FOXP4 itself, but it may be a modification of the expression sequence preceding it. All right, and I really like this one. I thought this was really an interesting way to look at this. We've been talking for a while about folks have Long COVID, and then they get a vaccine dose and then a certain percent of them get better.

The article, "Vaccination Ameliorates Cellular Inflammatory Responses in SARS-CoV-2 Breakthrough Infections," was published in *JID*. The reason I like this is people had this idea, well, a vaccine is just going to boost your immune response. I like to think a vaccination is going to correct your immune response. Here the authors conducted a prospective study of peripheral blood cellular immune responses to SARS-CoV-2 infection in 21 vaccinated patients and 97 unvaccinated patients stratified based on disease severity.

They enrolled 118 persons with SARS-CoV-2 infection compared to unvaccinated patients. Vaccinated patients with breakthrough infections had a higher percentage of antigen-presenting monocytes, mature monocytes, functionally competent T-cells, and mature neutrophils, and lower percentages of activated T-cells, activated neutrophils, and immature B cells. This whole idea, why could vaccination protect you against Long COVID?

Now, these differences widen with increased disease severity in unvaccinated patients, and longitudinal analysis showed that cellular activation decreased over time, but it persisted in unvaccinated patients with mild disease at eight month follow-up. They have a really nice graphical abstract. We can see all the different cell types and the surface markers.

VR: That's an interesting result. Very interesting.

DG: All right. I think I'm going to wrap us up here with our last study, the article, “High Incidence of Autonomic Dysfunction and Postural Orthostatic Tachycardia Syndrome in Patients with Long COVID: Implications for Management and Healthcare Planning,” published in the *American Journal of Medicine*. Basically, the big thing I want people to take away from this is they did a number of tests and basically saw a significant amount of autonomic dysfunction and postural orthostatic tachycardia syndrome in these folks.

Big thing is if you don't test for this, if you don't look for this, you're not going to find it. Something as simple as the NASA Lean Test might be a way to approach this, and in this study, they mention a number of different ways of looking at this and detecting this. I'm going to wrap it up there with no one is safe until everyone is safe. We're in the last month, we're in July, the last month of our Foundation International Medical Relief of Children fundraiser. We're hoping to get to our goal. We're not quite there yet. Thanks for everyone who's helped so far, but everyone else, stop what you're doing, pull over to the side of the road, go to parasiteswithoutborders.com, click the Donate button, and help us get to our goal.

VR: I have a question about that last paper, POTS. It's also something you see in ME/CFS patients, correct?

DG: It is.

VR: That's interesting that there are two common symptoms in these two different diseases or syndromes, right?

DG: Now you're going to get yourself into trouble. I don't know if you know about this, Vincent, but there's actually a lot of -

[laughter]

DG: Like you never did it before. There's a lot of controversy about sometimes people with Long COVID feel like, "Oh, the ME/CFS folks are stealing our narrative." Are there commonalities? It's really an interesting challenge. David Teller and I, we've been emailing a little bit here and there, we talked a while back. Some of the stuff, I think, if you are familiar with the ME/CFS literature, that can actually help you interpret some of these things.

Like we talked about pacing, David and I, where subjectively people felt better, but if you looked at - where they actually monitor how much activity they're doing, I'm not sure you were seeing the increase in activity you hoped for. The Cargill Behavioral Therapy. Again, people felt less fatigued. They felt like they were all doing more, but if you actually monitored, they weren't really doing much more. I think that you can learn from a lot of the mistakes in the ME/CFS literature. Hopefully, that'll help us. I am hoping there is some commonality of

mechanism here so that when we help one population, that we can get some help for the other as well.

VR: I think if you'd say they're both the same, then people get mad at you. [laughs] I understand that.

DG: We're not saying that.

VR: They're commonalities which can help you understand both. That's the whole point. POTS clearly is in a fraction of both patients. You have to use that to drive your understanding. That's all I'm saying.

DG: OK. [laughs]

VR: Don't get me in trouble.

DG: [laughs] OK.

VR: I did get an email about pacing, because remember last time I said Teller has been writing about pacing, and someone wrote and said, "Pacing is actually good," but I wrote Teller, and he said, "Well, it's not really a therapy. It's just a way of-"

DG: That's the tough thing. If you look at this actigraphy that they do, where you actually able to monitor, this is what David comments about, they had that data. They said, "Oh, look, people who did pacing, they felt better. People who stuck with pacing had less fatigue." They had the data on the actigraphy, and they should have published that, I think, for full disclosure. Say people are feeling better, there's a subjective improvement, but by the way, we're not seeing the improvement in performance that you would expect to go along with that. Just full disclosure makes sense.

VR: All right. It's time for your questions for Daniel. You can send to Daniel at microbe.tv. James writes. All right. Many people came across this article, which is saying there is a rare link between COVID vaccines and Long COVID, which they're calling Long Vax. Many listeners wrote in about it, and they want to know what you think about it.

DG: I saw the article. I actually thought it was a good article. I have a couple patients who develop problems after the vaccine. Some of those patients have what seems very similar to what my patients who develop problems after COVID developed. Akiko and Harlan Krumholz at Yale have actually a study called “Listen.” I like the name of the study because what they've said is, "Listen, if you had a vaccination and you started to develop problems afterwards, we're interested in hearing from you. We're interested in trying to understand this."

I think that's really positive. As scientists, you don't just say, "Ooh, we don't want to hear - Oh my gosh, you're going to pull me into the wrong realm with this." Actually, a couple of my patients who have developed problems, they say, "Ooh, you have to be careful online because if you mention this, out of the woodworks comes this anti-science movement." These folks are not necessarily anti-science, they're just someone who got a vaccination, developed problems afterwards. They're trying to figure out what's going on. I think it's OK to have this discussion.

VR: It's just the problem is then somebody like RFK Jr. will say, "See, I told you vaccines are no good."

DG: It's unfortunate.

VR: Do we know that these people didn't have previously an undetected asymptomatic infection that could have influenced the response?

DG: These are the challenges. Bad things happen. People - What was it? One of the vaccine studies where there were higher incidents of children swallowing marbles in the vaccine group. I think the vaccine was triggering marble swallowing. It's hard to know. That's why I think it's good to study these folks, to look and say, "Did you just get the onset of an issue and the vaccine happened to precede it, or was it really triggered?"

I think there's a Paul Offit story where the mother is not sure about vaccines, and they're having this discussion, and then the child has a seizure. Child hasn't had a vaccine yet. His story is, "Oh my gosh, if they had just received a vaccine like five minutes earlier, instead of us having this discussion, then it would've been related." These are challenging things that we need to understand.

VR: This is a very rare condition, so people should not -

DG: I think that's what makes it a challenge, is that this is not like we're seeing it. You hear some of these people, that said, "Millions of people will all be dead by 2022." We're here. These are incredibly safe, effective vaccines. I think as an email I wrote in one time, there's no side effect from the vaccine that even compares to the outcomes that we see post-COVID infection.

VR: Joanne writes, "Would you give me your medical opinion on getting the XBB booster for a 65-year-old woman with H/O breast cancer remission, asthma, second-degree heart block, Mobitz 1 who is normotensive, non-diabetic, and not obese?"

DG: OK. This is good. We've talked a little bit over time for that durable protection against disease, ending up in the ER or hospital or worse. Three doses seems to be durable. For a period of time, we just discussed some of the literature, you could get a little bit of a reduction, 20%, 29% reduction in risk of even getting infected for a short period of time prior to the XBB circulation.

Right now I'm not sure that we can offer much with the current vaccine, so it's going to be really interesting. It's, like, stay tuned for the data we get September, October because we'll come back with the answer. Do those updated vaccines produce a significant level of mucosal-neutralizing antibodies? Can we offer that extra boost for a few months? An individual like this, ideally you'd like to avoid infection at all. Probably the most important is if they do get infected, you want to jump in because we know that the medications can significantly reduce the risk.

VR: Joyce writes, "I really appreciate the responses from both Russ and Dr. Griffin about the issues with Paxlovid and anti-arrhythmic medications. I've tried to find locations offering remdesivir in the Phoenix, Arizona, area but that information does not appear to be readily

available. I'm wondering how a layperson can find a location offering these infusions, or must one consult a physician to even find that out?"

DG: This is a challenge. I'm glad you bring it up. I remember when we were in the days of the monoclonal antibodies and a lot of organizations jumped in. Survivor Corps actually set up a website. Got COVID? You go there, you put in your zip code, and helped you get to the place. Remdesivir, really nothing has been set up like that. I think, as we discussed, there's certain people where it's really a problem with drug-drug interactions, and something like remdesivir would be a great option. A little bit of a vacuum here. Maybe some of our listeners are thinking, hey, they want to fill that vacuum and provide a resource.

VR: Jen writes, "I'm a family practice physician in Ohio. On prior *TWiV* episodes you commented that three COVID vaccines are sufficient for the general population. For patients over 65 or immune compromised, what are the recommendations? I don't want to recommend unnecessary vaccines and would like data that additional boosters beyond the three are preventing morbidity and mortality, if possible, not just increasing titers. Is there a new vaccine coming out in the fall? Should I wait to give additional boosters if there is a new one coming?"

DG: This is great. Repetition is good here. Come October, November, we are hoping to have an updated XBB-type vaccine. It'd be really interesting to see what variants are circulating at that point in time and to see if we're actually going to be able to have the science to support going forward with the vaccines. Fingers crossed, we've got a game plan in place, but we'll have to see.

VR: She also asks for measles. "Can you clarify if checking immunity titers should be done for certain patients traveling, or all people, as we are seeing measles in the U.S.?"

[laughter]

DG: We talked about this last time. There's measles out there. You really basically want to make sure people are up to date with their measles. We haven't really gotten to the point yet where we're checking serology on all our travelers. Actually, if anything, it was a recent CDC, I think it was *MMWR*, where they just bemoaned how few people even get pre-travel guidance. That may be something where we have to start including that as a benefit, but at this point, make sure everyone's vaccinated.

VR: Finally, Christina writes, "I'm a chemist, not a virologist." Isn't that something from *Star Trek*, Daniel?

DG: [laughs] I think it's like, "I'm a doctor."

VR: "I'm an engineer, not a--" "I'm a doctor, not -" I don't remember, it's something like that.

DG: Something .

VR: Anyway, "I was wondering if you could talk a bit about shingles vaccine. I just received my first dose, wanted to know your thoughts on it. I've known people who got shingles, it seemed to incapacitate them, so I'm hoping to avoid it. I had chickenpox as a teen."

DG: Across the board, anyone out there who's 50 and above, just to let you know, you got a 50/50 chance you're going to end up with shingles if you don't do something about that. The Shingrix vaccine, it's a protein-based, it's like the Novavax of shingles vaccine, has over 90% efficacy in reducing your risk of shingles, of the clinical disease, size 97% in a healthy population. Even people who are immunocompromised, you're still seeing over 80% efficacy. Incredibly effective vaccine. There is a little bit of reactogenicity. You get your one shot, you may not feel so great. Do it on a Friday or Saturday, so you got the next day to get over that.

The recommendation to get the next shot one to six months later. We're already getting high 90% efficacy just four weeks later. Most of us with a background in immunology might say you might want to wait three to six months, get that second shot, get the best germinal center boost you can there, but no, recommended across the board. As you say, yes, shingles is a horrible disease, can be incredibly painful and debilitating.

VR: Daniel, I had shingles when I was recording *TWiV* number eight.

DG: Wow. [laughs]

VR: I know this because *TWiV* number eight was on herpesviruses, and we talked about it.

DG: Wow.

VR: Just last year, I got my Shingrix because I could get it again, right?

DG: Yes. That's even after an episode of shingles, this has been studied. Go ahead, get your vaccinations.

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

DG: Thank you. Everyone, be safe.

[music]