This Week in Virology

TWiV 1060 Clinical Update

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Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick. [music] From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1060, recorded on November 9, 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: All right, Daniel, I want to know what's on your bow tie today.

DG: I don't know if you can zoom in and see. Nurse cells. This is my official Parasites Without Borders bow tie, and I even have special Parasites Without Borders socks.

VR: You have underwear too?

DG: [laughs] I'm definitely wearing underwear today. All right, well, let's get right into it. "I have no idea what's awaiting me and what will happen when this all ends. For the moment, I know this. There are sick people and they need curing." That's Albert Camus, *The Plague*. The last couple of weeks, I've quoted MLK and then FDR, and then this week, Camus.

I'm going to start by mentioning that recently the results of a survey from the American Psychological Association came out highlighting the collective trauma of the pandemic that most of us have suffered. This report is based on responses from 3,185 U.S. adults. Lots of people report that they're struggling with anxiety, depression, financial concerns, and ongoing stress. Younger individuals, parents, and women seem to be impacted even more so, with many women reporting they feel stressed, misunderstood, and alone.

I always like to sort of set this tone. I feel like we're living in pretty contentious times. I just want to point out a lot of people look around. A lot of people, they're struggling. Let's all try to keep that in mind and let the humanity shine if we can. Speaking of trauma, right into flu, while influenza activity is still low, we did have our first child die of the flu this season. I don't know, can you hear all those dogs freaking out, Vincent?

VR: No. Why are they freaking out?

DG: My dogs have decided every time the phone rings that they have to throw a fit. For those of you that like dogs, there are dogs in the background, but for those of you that don't like

dogs, well, OK. Not sure if people caught the announcement from the CDC newsroom, but here it is.

CDC expands testing of international air traveler samples to include flu, RSV, and other respiratory viruses. People might be familiar with this, but this program will involve nasal sampling of arriving international travelers, aircraft testing, and wastewater sampling at seven airports nationwide. This will be a means of not only early detection of SARS-CoV-2 variants, but early detection of flu, RSV, and several other respiratory viruses in addition to SARS-CoV-2.

Samples that test positive for these viruses will be sequenced and uploaded to public databases to provide valuable information to public health officials and policymakers. I don't know if people caught in there, but this isn't just like coming over and attaching these devices to planes and sucking out and sampling the wastewater from the planes or sampling wastewater at the airports, but there are going to be these testing stations where you can actually go over, and there's little iPads and you stick a thing up your nose.

VR: This is going to be when you get off the plane? Is that the idea?

DG: Yes, the idea is people coming into the country. Let's say you fly into Dulles, which I once did coming back from Africa, and you'll go over to this little kiosk type thing with the CDC banners and you'll do some stuff on the iPads, wash your hands probably afterwards and before, put a swab up your nose, and yes, that'll help with surveillance.

VR: I'm just wondering what they're going to do with this. Is this going to be like, "All right, these viruses are coming in, there's nothing unusual here," or what? Do you have any idea?

DG: It's one of those things, you sort of wonder, remember when people used to use phones to make phone calls, and now they use phones for everything else? Once we get this data and this information, maybe it'll be like the wastewater that you and I talk about each week. Will it help us? Will it let us know, "Oh, we're starting to see flu activity at Dulles, we're starting to see flu activity in Dallas or Miami."? I don't know if this will sort of help us, and maybe you've got all this stuff there. I would love them to do - what do they call that? Non-biased metagenomics where you actually can keep track of other things. Now I'm thinking science fiction, Vincent.

VR: Yes. I don't think we'll ever hear any of these data. That's the problem.

DG: No, it's going to be public databases. I share your cynicism. All right. Sharing your cynicism, we're going to move right into - this is a public awareness messaging here. Big and troubling this week, I'm actually glad this is out there in a lot of the media sources, but we are hearing about syphilis. What did we hear?

The *MMWR*, "Vital Signs: Missed Opportunities for Preventing Congenital Syphilis - United States, 2022,: was released. Here we read that congenital syphilis cases in the United States increased 755% during the last decade, 2012 to 2021. We read that most of this is preventable. In 2022, we had a total of 3,761 cases of congenital syphilis in United States. This included 231 stillbirths, over 200 stillbirths, over 50 infant deaths. What's going on? Lack of

timely testing and adequate treatment during pregnancy contributed to 88% of the cases of congenital syphilis.

What's going on here? First, we have folks not testing, but then in more than half of the congenital syphilis cases, the mom tests positive during pregnancy but does not get proper treatment. There's a couple of things going on. One is, I think there's sort of this denial. "I don't know. I see the test is positive. That doesn't make sense." It does. There also has been a short supply of benzathine penicillin injections, the main medical weapon against congenital syphilis. What does the CDC want clinicians to do? To start syphilis treatment when a pregnant woman first tests positive, rather than waiting around. Really, this is something we really should be able to turn around.

All right, moving into COVID. New cases, we're still seeing them. Still have over 13,000 in hospital. We're still averaging over 200 deaths a day. It's interesting. I listened to different sources. I was listening to an IDWeek update, and they pick that moment in time and say how many deaths does this translate into a year. Current trajectory, if we just stay where we are, we're talking about 75,000 deaths a year from COVID. That's status quo.

Unfortunately, we're not looking at status quo. Our weekly hospitalization admissions have stopped going down, started to tick up a little bit. If you look at wastewater across the country, the Midwest, it's rising, the entire West, it's rising.

VR: Not the Northeast.

DG: No, you Italians are doing well. [laughter] I know not everyone in the Northeast is Italian, by the way. Now, I am going to star this next article as the most important article this week. I just wish people would pay attention to this article, and then just stop saying stuff that's not true. Take a deep breath. Vincent, I hope you enjoy it. We have two articles you're going to really like this week. This is the first one.

The article, “Intrinsic and Effective Severity of Coronavirus Disease 2019 Cases Infected with the Ancestral Strain and Omicron BA.2 Variant in Hong Kong,” recently published in *The Journal of Infectious Diseases*. This is going to be a chance hopefully for us to look at what is the intrinsic severity in an unvaccinated, uninfected population with the different variants.

For a while, I've been suggesting that whenever we hear things improving with regard to COVID, this is a chance to say, "Wow, those vaccines really were a game changer," instead of thinking that in the course of a few years, this virus somehow got intrinsically milder. Here, time-varying and age-specific effective severity measured by case hospitalization risk and hospitalization fatality risk was estimated for all individual COVID-19 case data collected in Hong Kong from 23rd of January 2020 through 26th of October 2022 over six epidemic waves.

The intrinsic severity of Omicron BA.2 was compared with the estimate for the ancestral strain with the data from unvaccinated patients without previous infections. Why are we doing this in Hong Kong? Maybe I need to give the context for people. In Hong Kong, in China, there was what people remember the COVID zero goal. It was this goal to have no cases of COVID, to keep the cases at zero. Really a lot of lockdowns. We really ended up with two things going on. One is we did not have a lot of pre-existing immunity, previous infections prior to the unleashing of things. Also, there were a bunch of misunderstandings about vaccines. A lot of

vaccine hesitance, "Ooh, if you're too old, I don't want to vaccinate you. You might be too frail to tolerate a vaccine."

Apparently, rather good to let you get COVID. We actually had this population over all the epidemic waves where we had a significant number of individuals without pre-infection, pre-existing survivor immunity, and without vaccination. Here we're asking this simple but important question, did something intrinsic to the virus change or are things better, thanks to science, vaccines, pre-existing immunity, and the death of the most vulnerable and improved therapeutics?

We read that with 32,222 COVID-19 hospitalizations and 9,669 deaths confirmed over six epidemic waves, the age-specific fatality risk in unvaccinated, hospitalized Omicron cases was comparable to the estimates for unvaccinated cases with the ancestral. Omicron has comparable intrinsic severity to the ancestral Wuhan, although the effective severity is substantially lower in Omicron cases due to vaccination.

VR: Vaccination.

DG: Yes. Actually, I put up Figure 3 for you and I to look at as we chat. If anything, the relative risk, though it doesn't reach statistical significance, it's going in the wrong way. It's actually trending towards an increased relative risk with Omicron versus ancestral. Not a decrease, but an increase.

VR: Right. This is what we've been saying for a while. It could've been that it went the other way, but we just needed the data to make the conclusion. Now we have it.

DG: Yes. Hopefully, in the future, Vincent, and every one of our listeners will correct their fellow human being and say, "Actually, the virus hasn't gotten milder. Vaccines work."

VR: That's right.

DG: All right. Now, this is another one that you're going to enjoy, Vincent. “T-Cell Immunity Against Severe Acute Respiratory Syndrome Coronavirus 2 Measured by an Interferon-γ Release Assay Is Strongly Associated with Patient Outcomes in Vaccinated Persons Hospitalized with Delta or Omicron Variants,” published in *JID*. We should discuss this with Paul and Theodora tomorrow night over drinks. Who wins? Is it all about the antibodies or the T cells going to save us all?

These are the results of a prospective longitudinal study, including vaccinated patients hospitalized with Delta and Omicron SARS-CoV-2. TrimericS-IgG antibodies and SARS-CoV-2 T-cell responses were measured using a specific quantitative interferon-gamma release assay. This is going to give us a quantitative T-cell response. The primary outcome was all-cause 28-day mortality or need for ICU admission.

We read that 87% had detectable SARS-CoV-2 antibodies, but only about half, only 50.8% showed SARS-CoV-2 specific T-cell responses. Just about everyone has antibodies, but only about half have a detectable T-cell response. It turns out patients who died within 28 days or were admitted to the ICU were less likely to have both unspecific and specific T-cell responses.

Both having T-cell and antibody responses at admission, 0.16 and 0.38 reduced hazard for 28-day mortality and ICU admission.

VR: T-cells save your life, right?

DG: Yes. That's really what we're seeing here. We're seeing everybody gets those antibodies, but it was the people that got that T-cell response that had this 84% reduction in death and a 62% reduction in ending up in the ICU.

VR: It's good. Very nice.

DG: Good job, T-cells. All right, masks. We're going to have a theme today of masks. I wanted to discuss the article, "Masks During Pandemics Caused by Respiratory Pathogens - Evidence and Implications for Actions," published as a special communication in *JAMA Network Open*. Mask-wearing and their effectiveness became a very emotional and political topic during the pandemic. Did you notice that, Vincent?

VR: I did happen to notice. Yes.

DG: Mask-wearing is also a very visible intervention. If a person chooses to wear a mask, it's a public decision. Let me start with this article, and then perhaps, Vincent, you and I can talk about the history of masks in medicine and public health, and it is fascinating. I know people are maybe not listening to all our episodes, but this is one to listen to. This is a great one on masks. Let's start off with the article.

First, the authors in this article discuss two random controlled trials, RCTs, conducted during the pandemic, and we've talked about these. The first is the study in Denmark with over 3,000 people who, despite the fact that the majority of the people in the masking group didn't actually even wear masks as recommended, they still saw the incidence of SARS-CoV-2 as 20% lower in the group, and this is only with 46% of the people in the masking group actually masking as recommended.

We get a 95% confidence interval compatible with a 46% to 23% decrease in infection, but the p-value is only 0.33. It depends on how you look at statistic here. Then we get, I think, the more impressive study we've spent more time on, the larger Bangladesh study, and we've discussed this here before, where they looked at 600 villages, 340,000 residents, and here, yes, they showed that mask-wearing was associated with a reduction in getting COVID-19.

They were doing seroprevalence testing, and yes, here the intervention reached statistical significance. They then, in this article, discuss the flaws with the Cochrane meta-analysis, where they pile all the cow pies and are shocked that this does not magically turn them all into gold as promised by the alchemists. They move on to a number of observational studies that showed masking was associated with a reduction in infection, such as that 30% risk in infection associated with masking on the USS Theodore Roosevelt. Then they do a nice discussion, different sources of information that helps educate us, strengths, weaknesses, and they even comment on mandates.

Now I wanted to do a little bit of context, and I'm going to leave in a few links here, but as people probably can imagine, masks as personal protection are found very far back in history,

and also lots of times have met with skepticism and derision. Pliny the Elder is reported to have used a mask to protect himself from the inhalation of toxins. Marco Polo describes the servants attending the Chinese emperor to have been required to wear silk masks to prevent their breath from contaminating the emperor's food. Apparently, after Louis Pasteur described the presence of bacteria in the air in the 1800s, cotton masks were discussed as a way to limit the spread of these germs in air.

Then we get to the 1900s, and this is where it gets to the fun part for me. They actually start studying masks and transmission, and there's this particular publication where they have people gargle with a solution of Serratia marcescens, and this is like, "Wait, I feel like I just read this study a few years ago." Then they speak in ordinary tones, they speak in a loud voice, and then they cough, and they measure the distance away that they can grow colonies of this bacteria, and then they're actually testing different masks for effectiveness at blocking this transmission. Do why they use Serratia, Vincent?

VR: Yes, it's red.

DG: Exactly. This is like that Operation Sea-Spray that I want everyone to Google after this. When the Serratia lands on the Petri dishes, it grows these red colonies. You can actually see that it's from the Serratia. Great there. Many great stories in history of masking. Then I want to move on to a study that – a story, actually, that I was discussing with my family. It's what we do in the Griffin household, and this is the story of Dr. Wu Lien-teh.

Dr. Lien-teh was the first medical student of Chinese descent, they say, to study at the University of Cambridge. He's actually from Malaysia. He was born in Penang, Malaysia, reportedly spoke terrible Mandarin, worse than mine, but is brought in by the Chinese Imperial Court to help with the pneumonic plague epidemic that broke out in China in 1910. He introduces mask-wearing as a way to protect those attending the sick, and apparently, it was based – he did an autopsy, he saw all this lung involvement.

He thought, "Well, maybe there's a pulmonary thing here. Let's start wearing masks," so he institutes this, but then there's this famous story where this French doctor shows up, and he's encouraged by our hero of the story to wear a mask. The French doctor basically tells him that the idea of germs in the air is foolish and says, "What can we expect from a Chinaman?" The French doctor then goes in, attends the patients without a mask, and a few days later dies of pneumonic plague. Some degree of justice there. Now we're at Columbia Presbyterian Hospital in New York, it's 1932, it's before our time, maybe Dickson was alive, but the surgeon - actually, he was not alive then, but the surgeon doctor, the famous doctor, surgeon Meleny, is there doing surgery and he's really just beside himself because the high rate of surgical infections at Columbia Presbyterian Hospital. Don't worry, we're going to fix this.

He actually introduces masks and sees a dramatic reduction in wound infections. I think we all know what surgeons do these days when they get in there and start doing surgery, and then just to bring us up to the modern era with the N95s being created and introduced in the 1970s by 3M.

VR: Columbia was the first to introduce masking during surgery, then?

DG: Maybe.

VR: [laughter] Maybe.

DG: Maybe. It seems like there was some other stuff going on actually in Asia and some other areas. All right. I'll leave in some links because this is just a great story, and it's just amazing. When you read these studies from 100 years ago, you're like, "My gosh, we just did the same studies, [laughs] the same things." Reinventing the wheel over and over.

Right here in the transmission section, I'm going to talk about the article, “Behavioral Factors and SARS-CoV-2 Transmission Heterogeneity within a Household Cohort in Costa Rica,” published in *Communications Medicine*, another *Nature* journal. This is always that issue. You're in the household. Somebody's got the COVID and these are the results of a household transmission study of SARS-CoV-2 in Costa Rica with SARS-CoV-2 index cases selected from a large prospective cohort study, and they enroll their household contacts.

A total of 719 household contacts of 304 household index cases were enrolled from November 21, 2022, through July 31, 2021. Blood specimens were collected from contacts within 30 to 60 days of index case diagnosis, and serum was tested for presence of spike and nucleocapsid IgG antibodies. What they're going to do is evidence of SARS-CoV-2 is going to be having both spike and nucleocapsid antibodies. We know there's some issues there.

They found that mask-wearing by the index case was associated with household transmission risk reduction of 67% and not sharing the bedroom with the index case was associated with the risk reduction 78%. All right. Nothing particularly new in the early viral phase. You test positive, Paxlovid, remdesivir, molnupiravir, convalescent plasma, some cases, isolation for the infected.

Actually, there was a recent NBC news piece with lots of opinions and comments about how the science has not changed and that this is really a public health decision, the recommended five days. I will quote Anthony Fauci, if you look at the safety of the public and the need to have society not disrupted, this was a good choice.

All right. I will move on to the article, “Convalescent Plasma.” We're in the hospital now. Second week, as we've talked about, steroids at the right time, anticoagulation, pulmonary support, remdesivir if it's early enough, immune modulation with tocilizumab. Much like last week, when is it too late to jump in with convalescent plasma? I think this is interesting because actually if you talk to folks who are bullish about convalescent plasma, Arturo Casadevall comes to mind, they will tell you that it is a very effective antiviral, but they will also sort of suggest that maybe it has some magical powers beyond that.

Does it? Do we really need to get this in right away or can we wait a little bit of time and hopefully those magical powers will come to bear? The article, “Convalescent Plasma for COVID-19-induced ARDS in Mechanically Ventilated Patients,” published in *The New England Journal of Medicine*. These are the results of an open-label trial where they randomly assigned adult patients with COVID-19-induced ARDS who were receiving invasive mechanical ventilation for less than five days in a one-to-one ratio to receive either convalescent plasma with a neutralizing antibody titer of at least one to 320 or standard of care alone.

Randomization was stratified according to the time from intubation to inclusion, and the primary outcome was death by day 28. We read that 475 patients underwent randomization,

September 2020 through March 2022. Overall 237 patients were assigned to receive convalescent plasma, 238 to receive standard care. Then we run into a problem. They end up with a shortage of convalescent plasma, that has a neutralizing antibody of 1 to 160. They end up only giving that to 17.7% of the patients in the convalescent plasma group. Actually just about everyone, 98% get glucocorticoids.

What happens? At day 28, mortality was 35.4% in the convalescent plasma group and 45.0% in the standard care group, p-value 0.03. In the pre-specified analysis, this is really critical, this effect was really observed in patients who underwent randomization 48 hours or less after initiation of invasive mechanical ventilation. Then we actually see that they have different convalescent plasma antibody titers.

A few limitations, not blinded, so no placebo. Effectively, those getting plasma were also getting this 500 ml bolus, there was no sort of 500 ml bolus of folks that were not. Also, if we look at a lot of the people that died, many people actually, clinicians had decided to limit therapy. The clinicians actually knew whether or not the patient had gotten plasma or not, but about 15% of the time in the people without, they just decided to withdraw care versus less than 10% in the folks that did get plasma. No real good explanation for why there might have been some difference there. I mentioned the plasma shortage.

There also was a lot of use of remdesivir, HCQ, azithromycin, and about twice as many people in the plasma group ended up getting the anti-IL-6 treatment. Really nice figure where you can look through, and it's sort of panel C of the figure. You can see that it really was the folks that were randomized 48 hours or less after intubation where you see a separation of the curve, a little bit, barely overlap of the confidence intervals. Once you randomize more than 48, you're not really seeing much of a difference. Unfortunately, when you follow people out, that difference starts to decrease once you get out 100, 200, 300 days.

VR: Basically, if you catch them early, you can have some effect.

DG: I think it reinforces this message that with all of our antiviral agents, whether it's a small molecule, whether it's oral or IV, whether it's convalescent plasma, whether it's a monoclonal antibody, earlier is better. I'm not sure there's this magical immunomodulatory effect that once a person's been on a ventilator for a couple of days, we're not seeing any magical effect.

Let me close out today's update with good things that come to those that wait. You may have to wait three years. Anyway, the article, “Olfactory and Gustatory Function Three Years After Mild COVID-19 - A Cohort Psychophysical Study,” published in *JAMA Otolaryngology-Head & Neck Surgery.* Of the 100 patients enrolled in the study, 88 completed all the follow-up assessments. These folks are about 49 years of age, 58% women.

What do we see? We see a decline in the prevalence of olfactory dysfunction, OD, observed during the follow-up with the frequencies going down over time. Actually, by three years, they did not see a significant excess of olfactory dysfunction. It actually drops down to 13.6% versus a background of 10.2%. Only an absolute difference of 3.4%, overlapping confidence intervals there. It does look like most people are getting that olfactory and gustatory function back. Three years.

All right. No one is safe until everyone is safe. I want everyone to pause the recording right here. Go to parasiteswithoutborders.com. Click on the 'Donate' button. We are doing our MicrobeTV fundraiser where for November, December, and January, we double your donations up to a maximum donation of $20,000 for MicrobeTV.

VR: Go for it folks, go to parasiteswithoutborders.com, support these programs that we do here. Time for your questions for Daniel. You can send yours to Daniel@Microbe.TV. Ellen writes, "Thank you for keeping me informed about COVID. Even though to my knowledge I haven't gotten COVID yet, I got my doctor to prescribe me a course of Paxlovid before I go to a large indoor conference in a state where I don't know that doctors believe in the effectiveness of Paxlovid. Just in case, I'm startled to see on the package that it expires in only a month. Really? Now I feel like what a waste if I don't get COVID."

DG: This is great, Vincent. It's so funny. I just had some patients recently, they got a box and they put a sticker over the box extending the expiration date to February. It's the same box, had the original one, just someone put a sticker on there. There's a legal thing in the U.S. where everything has to have an expiration date whether it expires or not, all the pharmaceuticals. I am in no way convinced that this Paxlovid is going to expire by that printed-on expiration date.

VR: Often the date is just as far out as they have tested in the laboratory, and it could actually go longer, but they haven't tested.

DG: Yes. I know some of the tests that the government is giving out have expired and don't work anymore. Great. No, the Paxlovid has not expired. I think you're going to be OK there.

VR: Louie writes, "Hello from Baltimore. Hope you do more events in Baltimore." Yes, we were there in August, I think, for a flu meeting. "Question, I am 61 years old, history of asthma all my life, no other comorbidities. I want to take the RSV vaccine, but I got scared off by the reports of Guillain-Barré. I had no problems with any other vaccines including Shingrix, planned to get it at CVS and use the Glaxo. Any more updates on this after over 2 million vaccines? Do you advise people in similar positions to go for the shot? I know I have to consult my physician, but just wanted to know your general take."

DG: Yes, I'm sort of glad you bring this up because I feel like this will give us a chance to refresh because I think things have moved forward. We've discussed repeatedly, RSV, it's not just for children. If you look at adults, we're talking probably about 100,000 or more hospitalizations every winter, maybe 10,000 deaths every winter. This is just adult. We're just talking about adults. Forget about the 100 to 300 kids that die every winter, the tens of thousands of hospitalizations there. Back in the spring, we had FDA approval of the first two vaccines for adults, lower respiratory tract disease due to RSV in adults. The GSK and the Pfizer vaccine, and at that point, there was this recommendation for shared decision-making. Let's go through, what did we see? First, we'll start off with GSK, which is what you're going to get. I think that's what Vincent got. That's what CVS has gone with.

When initially we had these recommendations, the GSK safety data came from two RCTs. Randomized, double-blind, placebo-controlled trials over 17,000 almost 18,000 participants. What happened is there were - we'll start with GSK and then we'll get to Pfizer. With GSK,

there were three events reported. There was one case of Guillain-Barre syndrome. That was the Japanese man in his late 70s. About nine days afterwards, he has GBS. Then we get these two cases from South Africa, also individuals in their 70s. Those individuals were initially reported to possibly have acute disseminated encephalomyelitis, this thing called ADEM.

One of those individuals died, and I say initially reported because those two cases in South Africa, basically just symptoms, clinical findings, no diagnostic testing, no brain imaging, no CSF, no nerve conduction, nothing. Then actually when they went back and looked, one of the guys actually died from hypoglycemia and dementia. It really wasn't. That's our GSK before we get into post-marketing. What about Pfizer? Pfizer, we've got similar to RCTs, we've got over 20,000 participants.

Here we also get the report of three neurological issues. What do we have? We have the GBS issue in a gentleman in their 60s in the U.S., I think it was a gentleman, but an individual in their 60s, about 14 days after vaccine. There's another GBS variant also, individual in their 60s, something called the Miller-Fisher syndrome. This is Japan. This was symptom onset about 10 days afterwards. Then there's an individual in their 60s down in Argentina with a sort of polyneuropathy that gets reported.

When this first comes out, they say, "We're not sure whether or not these events occurred due to chance or whether there's increased risk of inflammatory neurological events. Let's follow the post-marketing surveillance." Now we're talking about millions of doses out there. We are not seeing any issues. Most of us have actually moved from this shared decision-making to just a broad recommendation for all those 60 years of age and older.

VR: All right. We have more questions about shingles vaccines. This is Larry. "I'm 70 years old. I received Zostavax and one dose of Shingrix. I had an uncomfortable reaction from Shingrix and chickened out from getting the second dose."

DG: Chickened out. I like that. He chicken poxed out. [laughs]

VR: Very good. "It's been over a year since my first Shingrix. Few questions. One, did I get any positive benefit from the single Shingrix shot? Two, does receiving both Zostavax and one Shingrix provide me with decent prevention? Three, can I safely get a second Shingrix, and will it be effective or do I need to restart the series?"

DG: Yes. Let's go through all these questions. We'll start off with one. The original vaccine for adults to prevent shingles was not as effective and we're only about a 50% reduction. Now we're talking about a 90% reduction. The Shingrix is a better vaccine. We don't have a lot of great studies. We sort of do, we'll take one and the other, but we'll probably suggest that you probably have some benefit, some boost from the second. Now why did he not finish? Why did he chicken pox out?

VR: Because he got a bad reaction.

DG: OK. Talk to your doctor about what that bad reaction was, if it was just reactogenicity because, getting shingles, 50% of individuals will get shingles if they don't get vaccinated, if they had chicken pox as a child. If possible, you want to finish that off. You do not want to have shingles. We have a poor woman in the hospital right now and she's got shingles on her

back and shingles on her chest and shingles up on her neck and face. Yes, you just do not want to get shingles. Talk to your doctor, find out what that reactogenicity is. What were the other questions there, Vincent?

VR: Having gotten a Zostavax and a Shingrix, does he have any protection?

DG: Yes, there's probably some, not quite as good as the double shot.

VR: Can he complete the Shingrix now or does he have to start at dose one?

DG: No, I don't think he has to start at dose one. Just go ahead and finish it off.

VR: All right, Cecily writes, "In 1988, at the age of 3 ½ , my son contracted chicken pox from his school-age siblings and then went on to develop viral encephalitis with cerebellar ataxia. Took him two years to fully recover his muscular coordination and speech. Then when he was 19, he contracted shingles. He's now 39. Is he a candidate for the two-dose shingles vaccine? Would you recommend it in this case?"

DG: This is tough. This is why we vaccinate, and the coverage is over 90% of children vaccinated for chicken pox. We used to have over 100 deaths a year. In the U.S., we used to have all - this isn't death, this is survival, but with a really bad outcome. The Shingrix vaccine is recommended for everyone over the age of 50, but also for those under the age 50 who have some concerns. I would put that an individual like this would qualify as that sort of under the age of 50, over the age of 18, but with these concerns.

It's an interesting thing I want to get into here. Not only does the chicken pox vaccine protect children against death and bad outcomes from chicken pox itself, but it's an attenuated vaccine. You can get shingles later in life, but it's about a quarter of the risk. Instead of that 50%, it's maybe down at a 10% lifelong risk.

VR: Finally, Jim writes, "I'm a community pediatrician practicing in Nashville, Tennessee. We found it very difficult to obtain nirsevimab for our patients this season. Best estimates from the company indicate we'll only be getting enough doses to give to 40 of our patients. We are an 11-person group, tends to get about 40 to 60 newborns a month. This means we'll have about 280 kids who should be getting nirsevimab, but are only going to be able to protect 40 of them. That estimate doesn't count children in their second season who would also benefit from the monoclonal, but it gets even better.

We're only getting the 50 milligram dosage which means we can only offer help to those kids we have who are weighing less than 11 pounds. I know you only care for adults in your ID practice, but this essentially means that we can only offer protection to the very youngest of our kids. This situation has been frustrating for us and our families as most parents have kids who weigh at least 11 pounds and are quite concerned about them being hospitalized for RSV. We also have families whose kids have already been hospitalized for RSV twice this season. Speaking to other practices in our community, the situation is the same. I only bring this situation to your attention to ask you that you not say we have Beyfortus to protect young children against RSV disease because we essentially do not have it. I'm hopeful that enough nirsevimab will be available 2024-25 RSV season to really make a difference.

DG: Thank you, actually, for bringing this. There's a lot of reasons why it's important to bring this to people's attention. First, what do we do? The CDC is aware of this. Public health people are aware of this. The recommendation is to reach out to your obstetric colleagues and really let them know like, "Hey, the way we can protect these kids is mom gets the vaccine during that last trimester." We've got that. We've got the vaccines for the ladies to take during the last trimester. That's really what we're pushing right now.

The other is this awareness. We live in the United States of America and here we are again with another shortage. Everyone - "Oh, my gosh, they're charging too much." What wouldn't we be willing to pay to protect these children, to prevent the 100 kids that will probably die this winter when that didn't need to happen because we could have protected all these children? We could have really reduced that. Yes, this is a huge - I think of this as a national security issue. Why do we not have enough of this medication to protect our children? The demand is there.

VR: Yes, this is something that Paul Offit addressed this week on *Beyond the Noise*. He said you could try breastfeeding, that would help also.

DG: Yes, breastfeeding is actually huge. I think underutilized. We're still suffering from all the commercial activities of the formula companies.

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

DG: Thank you, and everyone, be safe.

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