This Week in Virology

TWiV 1150 Clinical Update

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Aired 21 September 2024

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 1150, recorded on September 19, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Looking very scholarly with the books and the bow tie, Daniel. What's on it?

DG: I have Ebola again.

VR: It's not Friday. Yes, it's not going to be a clap.

DG: It's not Friday. Actually, I've got some things going on tomorrow. I'm actually going to wear a betacoronavirus bow tie tomorrow on a Friday. Imagine that.

VR: Imagine that. It is spreading, you know.

DG: Yes. All right, let's jump in. We got a lot to cover. We're recording late here on a Thursday night. I will jump in with my quotation. “They conceive a certain theory, and everything has to fit into that theory. If one little fact will not fit in, they throw it aside. It is always the facts that will not fit in that are significant.”

VR: Daniel, you think that's how scientists sometimes work?

DG: The way this is written, it's a little ambiguous. What is the “it” that they're throwing aside? Are they throwing away that little fact that doesn't really fit? Are they throwing away the theory? Well, as long as it's the theory, I'm good with it. There certainly are scientists and clinicians where it's the facts that get thrown away, the actual facts.

VR: It's interesting. What is she talking about? The thing that doesn't fit or the theory?

DG: I have to say that the reading I like, it's the fact that gets thrown away.

VR: Well, how do you know when to throw it away, though?

DG: You never throw the fact away as we learned from Agatha Christie. It's the facts that don't fit that are often the most -

VR: You keep them on the side and ponder them.

DG: Yes. Why does that not fit? What is wrong with our theory?

VR: That's right.

DG: Why did we not anticipate that?

VR: You just said it. What's wrong with our theory? That's the key. Questioning.

DG: Yes. Make sure - Question your hypothesis, your idea, your premise. All right. We've got West Nile virus. I wanted to mention this because we just had a couple of deaths from West Nile virus in New Jersey. Just to keep some awareness on this, as we see deadly mosquito-borne infections. Now, what we read in this, it's actually a *CBS News* piece is we have so far had eight total cases in New Jersey, seven were hospitalized, experienced swelling of the brain or swelling of the lining surrounding the brain and spinal cord.

I have to say, I suspect this number of cases and severity distribution is probably due to a lack of diagnosis of milder cases. Just a lack of diagnosis of cases in general, because just at the one hospital where I spend a lot of time, we've seen, three cases just in the last few weeks. It's really a question of people don't often look for things and then you only see the worst.

Polio. It sounds as though things are progressing well in Gaza with respect to the polio vaccine. We had a report this past Monday that the polio vaccinations had already reached 90% of goal. On a not-so-good note, at the same time, we heard that the Taliban has suspended polio vaccination campaigns in Afghanistan.

Now trying to get a little more understanding and maybe, Vincent, you have some ideas. My understanding, there's been discussions about moving away from this house-to-house vaccination approach and instead having immunizations in places like mosques. I'm hoping maybe this is just a shift in the approach rather than an end to the vaccinations.

VR: Yes, I don't think the Taliban likes the house-to-house approach and wants to shift to mosques. That's my interpretation. They're still stopping for the moment. They're suspending and I read a quote somewhere that they think it's an American plot to sterilize their children. They're not very happy about it. This is all misunderstanding again.

DG: It's really important to keep politics and everything out of vaccination campaigns. That's been an issue. That was an issue in the smallpox campaign in - it was actually Vietnam and the French were involved. There's a lot of mistrust. There was a lot of issues there. Yes, there's a lot of parts of the world where you want to really be sensitive to what the local people are concerned about and really the importance of partnerships, letting them be involved and actually modify the campaigns to what they're most comfortable doing. I will try to be optimistic.

Dengue. [chuckles] L.A. County Public Health just announced two more locally acquired dengue cases. This is L.A. Now California, Florida. In this, we have a cluster. This raises the number in that cluster to three. The two latest patients are from Baldwin Park, the same area where a first case was reported last week.

We read that the *Aedes* mosquitoes are common in L.A., but local dengue cases or diagnosed local dengue cases are rare. Back in 2023, two similar cases were reported, one in Long Beach, the other in Pasadena.

VR: This is interesting because locally acquired means there's no travel involved. There's some reservoir of the virus there.

DG: Yes. That's a concern. We had, years ago, a teenage boy, I think it was in Huntington, just a few miles from where I live, no travel, nothing, gets dengue. Quite the astute clinician to actually even think to order the proper testing and pick that up.

VR: When it's so rare, it's difficult, right?

DG: Yes. How did that get into your differential? He'd say he's never traveled. That's always our challenge.

VR: You would say, Daniel, that now that we have local dengue, say in L.A. and other places, it should be on the differential, right?

DG: Yes. Hopefully, a lot of times, I think people say, "Oh, medical school, we're learning all this stuff and I'll never see it." Well, you might not diagnose this if you didn't realize. There is a rather characteristic rash that we often see in dengue. That might be a little bit of a trigger, the timing of the fever and the fever abates, and then a characteristic rash. You may clinically raise your suspicion even though, yes, it isn't necessarily endemic otherwise.

Flu, a reminder, sort of a morbid reminder, but a reminder schedule that influenza shot for you and your loved ones, including your children. It's about this time every year, we hear what were the total deaths from last year. We're hearing from the CDC that last year, 199 children died from flu. We're back. That was the level that we were at in 2019, 2020.

Among the fatal cases, 73 were younger than 5 years old, 126 were aged 5 to 17. Some 18-year-olds died. Interesting that about half were influenza A. Half were influenza B. They do mention that three children had co-infections, influenza A and influenza B. Now, two, I think, really important points of the 189 children with health status information, the majority, just over the majority, 51%, did not have a single underlying medical condition. These were, up until this point in time, otherwise healthy children.

Now, of the 158 children that were eligible for flu vaccine, for whom the vaccination status was known, 83% were not fully vaccinated. Really suggesting these are mostly preventable deaths. I know a lot of people, concerns, why am I vaccinating my children? Well, 200 children died last year from flu.

All right, mpox. We heard on September 13 that the WHO pre-qualifies the first vaccine against mpox. WHO announced the MVA-BN. This is the Modified Vaccinia Ankara vaccine

made by Bavarian Nordic, and it's added to the pre-qualification list. A little bit of terminology, what is a pre-qualification, emergency use? These are mechanisms used to evaluate quality, safety, and efficacy of medical products, such as vaccines, diagnostics, medicines, and product suitability for use in low- and middle-income country contexts.

These PQ, pre-qualification, and EUL, emergency use listing, these assist decision for international, regional, and country procurement by UN and partner procurement agencies. A little context here, the available data. We've covered this. It shows about this 80%. What we're seeing here is available data shows that the single dose given before exposure has an estimated 76% effectiveness in protecting people against symptomatic mpox, with the two-dose achieving an estimated 82% effectiveness. We've talked about the studies sort of really in the same ballpark, but also the fact that even if you end up getting symptomatic mpox, severity, so great impact on severity, like folks that get vaccinated don't usually end up requiring hospitalization.

Good safety profile, vaccine performance consistently demonstrated, also seeing real-world evidence here. The WHO, even a little flexibility, there might be situations where a single-dose use is applied in supply-constrained outbreak situations.

Still exciting news in this area. We did hear on September 18th, that's yesterday, the day before we record this, a few days before you hear it, that Gavi, the Vaccine Alliance and Bavarian Nordic announced an advanced purchase agreement to secure half a million doses of the Jynneos mpox vaccine for African countries. They're going to be delivered this year.

All right, still in the mpox area, we got the publication, "Tecovirimat Use under Expanded Access to Treat Mpox in the United States, 2022 to 2023," published in *NEJM Evidence, New England Journal of Medicine Evidence*. This is really a descriptive publication. Tecovirimat, this is this antiviral for mpox, was prescribed to over 7,100 patients in the U.S., really most often for lesions in sensitive anatomical areas, such as anal-genital lesions.

Now, the demographic clinical characteristics mirrored those of patients worldwide. You sort of get a nice ability to look across, even though we're only looking at this particular population. Now, among the 7,181 patients with returned intake forms, 1,626 also had these outcome forms. We're sort of getting to smaller numbers, but many patients with severe immunocompromised, so HIV, CD4 counts less than 200, received multiple courses of tecovirimat.

Now, overall, 223 serious adverse events and 40 deaths were reported. Now, most of the serious adverse events were among patients who were severely immunocompromised. One had experienced hallucinations after tecovirimat being given at twice the standard dose. I think just the takeaway here I want to say is we're learning about tecovirimat, which we're still waiting for some really good, solid human efficacy data.

VR: Daniel, we should know how late after the rash appears that you could give it and have it be effective, right?

DG: I think that's important. What's a challenge with mpox is that it seems that as soon as you get into the prodrome, you start to have some symptoms, don't necessarily have obvious lesions. There's already case transmission, documented transmission. You also, even when

the vesicles are gone, you've got scabs, you do not yet have full intact skin, we're seeing spread to others. Evidence at both extremes here that there's still replication-competent virus here.

It is interesting, like when do you jump in? We really need the data on when does it make the most difference because we would really anticipate that the sooner you start, the better outcomes we're going to see.

VR: Many of these patients are immunocompromised so that also plays a big role. It's probably going to be less effective in that cohort, right?

DG: I would agree. It may actually be that you - different durations.

VR: Sure.

DG: All right. Bird flu. Oh my gosh, we're still talking about bird flu. We read from the CDC, one new human infection with a novel influenza A virus was reported by the Missouri Department of Health and Senior Services. The patient was infected with an influenza A(H5) virus. We read that the patient is older than 18 years, has multiple underlying medical conditions. The patient developed symptoms during the week ending August 24, 2024, hospitalized, since recovered.

A respiratory specimen collected from the patient tested positive for influenza A at the hospital. They forwarded the specimen to the Missouri State Public Health Laboratory. The CDC confirmed the infection was caused by influenza A(H5) virus. Now, a subsequent investigation by state, local public health officials did not find any direct or indirect contact with wild birds, domestic poultry, cattle, including no consumption of raw dairy products or other wildlife prior to the patient's illness. That has everyone, “what's going on here?”

Now, the other got people sort of hackled up was one close contact with the patient was also ill at the same time. Initially, we read, "was not tested and has since recovered." We read a little bit more. We read in *The New York Times* article that someone who lives with a Missouri resident infected with bird flu also became ill on the same day. Coincident or causation.

We go on to read. It's getting all exciting. Maybe the Agatha Christie was a good quote up front, "The disclosure raises the possibility that the virus H5N1 spread from one person to another, experts said, in what would be the first known instance in the United States." Now, on Friday night, this is last week, CDC officials said that there was no epidemiological evidence at this time to support person-to-person transmission of H5N1. The coincidental timing of the illness, especially outside flu season, concerned independent experts.

Then we read this article by Brenda Goodman at CNN that a second close contact to health care workers developed mild symptoms but tested negative for flu. [laughs]

VR: This is the problem with he said, she said, the CDC that says there's no evidence. What does Barbara Goodman know?

DG: Brenda Goodman is actually the one who points out that the test was negative. It's actually our buddies at *The New York Times* that are speculating about human-to-human transmission.

VR: The thing is, outside of the U.S., there has been limited human-to-human transmission, especially when people live together, right?

DG: Yes.

VR: If one person had it and the other was living with them, it wouldn't be surprising. We have so little information that it shouldn't even make the news.

DG: Yes, but we can speculate. It's exciting.

Vincent: Of course. According to Agatha Christie, what do we do with this piece of information?

DG: Exactly. We need more. We need more. All right. Let's jump into COVID here. We always bring up our map, what's going on. This is the percentage of provisional deaths due to COVID-19 in the past week, looking at the different states in the U.S. and now not only Kentucky, but we also have West Virginia at that 4% to 6% of all deaths due to COVID, lots of 2% to 4% in our country as well.

Now, a couple of interesting things, Vincent, you and I have been following this, is the wastewater. We're going to look at this a couple of ways. One is our traditional way and it looks like in most areas, we might be on the way down. Out West, it was down and then looked like it was rising. In the South, it looks like it's on the way down, nationwide, maybe a little down and then rising. In the Midwest, just plateauing.

I went back and I looked at it really data all the way back to January '22 to get this pattern of what we're seeing. For instance, last year, we saw a little bit of a summer bump and then we saw a winter peak. Now we're seeing actually this peak here, end of summer into fall, wastewater that was as high as last year. We'll see what happens. The bets are in.

VR: It's funny, in '22, we had a summer peak, and then we had another one in the winter. Then in '23, a small one at the end of the summer, one in the winter and now we have a big one in the summer.

DG: (Cross-talk)

VR: There's always been a little summer activity. Yes.

DG: - 2022 where we see -

VR: There's a little summer activity every year but it varies in intensity, it looks like.

DG: I'm going to put in a new link for wastewater this week so people can take a look at this. It's really nice, actually. This is data where you can actually click on the left and, you can look at SARS-CoV-2, you can look at RSV, influenza, human metapneumovirus, norovirus, mpox, rotavirus, EV-D68, maybe we'll talk about that, *Candida auris* and hep A. They actually have,

with the SARS-CoV-2, you've got this map, we've got medium out West and high really basically most of the country. Then you go to EV-D68 and actually medium across the country. I don't know if you had any comments on that, Vincent.

VR: Yes. EV-D68 is one of these late summer-fall infections and we haven't seen a lot of cases in the past few years, although now they've been picking up. The key here is that enterovirus D68, the member of the same genus as poliovirus, has been associated with acute flaccid myelitis. In this current activity scenario, there have been no reported cases of AFM which associated with EV-D68, which is good.

DG: All right. We'll keep our eye on that. All right. Moving to vaccines and remind me, Vincent, if I forget because people always ask, "When should I get my vaccination?" We have the article, "Effectiveness of Updated 2023-2024, (Monovalent XBB.1.5) COVID-19 Vaccination Against SARS-CoV-2 Omicron XBB and BA.2.86/JN.1 Lineage Hospitalization and a Comparison of Clinical Severity-IVY Network, 26 Hospitals, 18 October 2023 - 9 March 2024," published in *CID*.

We spent a time trying to sort of sort out what information we actually have here. Here are these investigators analyze patients hospitalized with COVID-19-like illness at 26 hospitals in 20 U.S. states, admitted 18 October 2023 through 9 March 2024. We're thinking like last winter season roughly. They're going to use a test-negative case-control design, and they're going to estimate the effectiveness of an updated 2023-2024 monovalent XBB COVID-19 vaccine dose against sequence-confirmed XBB and JN1 lineage hospitalization.

We're going to get to look at an XBB vaccine and how did it do with the two different lineages. Because we talk over time, is it about time that goes by? Is it the lineage? Is it the virus that really makes the difference? Now, we only have 585 case-patients with XBB lineages. We only have 397 case-patients with JN lineages. I would love to have more, but OK, we've got 4,580 control patients.

Now, Vincent and I will go through this figure here in a minute, but the vaccine efficacy in the first, let's say 90 days, seven to 89 days after receipt of an updated dose, they're going to say 54% against XBB lineage hospitalization and 32.7% against JN lineage hospitalization. Odds of ICU admission or invasive mechanical ventilation and death were not significantly different among the JN compared with the XBB lineage.

In the discussion, the authors point out that these findings indicate that despite substantial genomic divergence of JN lineages from XBB, updated COVID-19 vaccines continue to provide protection against COVID-19-associated hospitalization. Wide confidence intervals for some estimates precluded competent assessment of the extent to which vaccine efficacy differs by lineage.

VR: Daniel, what is the age and comorbidities of these patients do we know?

DG: It actually is in the -

VR: Are they matched in other words?

DG: Yes. Yes. They are matched. That's at least good.

VR: OK. Yes. I suspect that it doesn't matter which booster you've got. I think you're going to have those T-cells protecting you unless you're really, really ill and are quite old because then you won't have memory T-cells.

DG: If anything, it's encouraging. It really looked like, even when it was, the JN lineage, the J1 lineage versus the XBB lineage, it looks like we're getting some overlapping sort of efficacy here.

VR: I want to find all the people that got just the original vaccine, three doses, and see how they've fared over the years if they have stayed out of the hospital.

DG: Yes.

VR: I bet they've done fine as long as they're healthy.

DG: Well, it is interesting. I think, this was actually something I talked about when I was in Taiwan. If you look at individuals under the age of 65, was actually a study I was looking at in Taiwan, there's this phenomenon where you get your first three vaccines, if you get reinfected, you tend to do fine, your chance of ending up in the hospital goes down, sort of this concept of boosting. Now the whole interesting issue was if you then looked at people over 65 with medical issues, it was the opposite. You actually saw that, things were sort of chipping away with each infection.

Yes, it is important as you bring up, you got to know who are we talking about, what age, comorbidities. Really the importance, I think, of that, personalized discussion, with your medical provider about what you need to do and what your risks are.

VR: In fact, in this paper, it would behoove them to stratify the results by age groups and see if you get a higher protection or VE under 65 versus over 65. That would be quite compelling that the T-cells are involved in other mechanisms maybe also.

DG: I bemoan, I say, 585,397, I'd love to have more. You need larger numbers to really narrow those confidence intervals.

VR: Now this is where in countries that have, what is it? Electronic health records, yes, then you could just access them and look at it.

DG: Yes. Somewhere like Norway where whether you like it or not. All right. We also have the article, “Early, Robust Mucosal Secretory IgA, but Not IgG, Response to SARS-CoV-2 Spike in Oral Fluid as Associated with a Faster Viral Clearance and COVID-19 Symptom Resolution,” published in *JID*. Here they're going to investigate the role of oral mucosal antibody responses in viral clearance and COVID-19 symptom duration.

Just a quick reminder for our listeners, what are we talking about? IgA is the main mucosal antibody type as opposed to IgG, that's the main serum type. Think particularly of the secretory IgA as being this antibody that we're hoping to have at our mucosal surfaces, such as the whole upper and lower respiratory or GI tract. Now, the way they did the study was to give participants with PCR-confirmed SARS-CoV-2 infection this oral fluid testing, so they're going to get the nasal swabs, they're going to get all these follow-ups for the symptoms.

They found that high and moderate oral fluid anti-spike secretory IgA post-infection was associated with a significantly faster viral clearance, so dropping an RNA copy number to be, and symptom resolution across age groups with effect sizes equivalent to having COVID-19 vaccine immunity at the time of infection. Sort of break it down, but those with high and moderate anti-S secretory IgA cleared the virus 14 days, I think it was this confidence interval, and recovered nine to 10 days earlier than the folks that had those low IgA levels. Delayed and higher anti-S IgG was actually associated with significant longer-term clearance of recovery. They're sort of interesting.

VR: Yes, that's surprising that an IgA would be doing this, and we know that everybody is slightly different when they respond, so you're going to have high responders and low responders, so it makes sense.

DG: I think maybe in the future we're going to maybe be asking for more information from our vaccines. We know about serum-neutralizing antibodies, we know about Th1 versus Th2, are we going to start requesting, "Hey, can you give us mucosal immunoglobulin?"

VR: Daniel, fundamentally, why would secretory IgA be better than secretory IgG? Because IgG does make it into the mucosa. Is there something better about IgA?

DG: It's interesting. There are people out there, it's like one in 700, one in 1,000, depending upon your sort of genetic background, that actually do not make IgA, so they actually compensate with the other antibodies. In most people, that's going to be 99.99% of the time, it's IgA that we're measuring when we're looking at mucosal surfaces. No, if you're one of those folks that are using a different immunoglobulin at your mucosal surfaces, I don't think the actual antibody would matter.

VR: It's the timing.

DG: Yes, it's probably timing. All right. For passive vaccination, right, PEMGARDA, for that 70% risk reduction of developing symptomatic COVID-19 compared to placebo, based upon those early trials.

COVID early viral phase, the treatment guidelines have not changed, NIH, IDSA, number one, Paxlovid. There's been some nice commentaries out there about like, be careful when you look at these meta-analysis and they start including preprints and stuff. We now have 100-plus articles, randomized control trials. We have real-world efficacy data. Paxlovid, particularly if you can get it the first day, within the first three days, really up to the first five days, reduced risk of progression, hospitalization, and death. Really compelling data in the high-risk population. Growing amount of data in Long COVID as well, which we'll continue to share.

Number two, remdesivir, three, molnupiravir, four, convalescent plasma. Remember, when you're sick, you are contagious. Three, so they're moving on to the early inflammatory week. Remember, this is that bad week. My daughter's off at college, Eloise, with the, they now call it pledge week or recruitment week. I don't know. Whatever the sororities and Greek organizations do, they've renamed it from, we used to call it, I think, pledge week or some other -

VR: Rush.

DG: Rush. [laughs] That's what it was. Yes. For those who don't know, I was in a fraternity at University of Miami. It was really more of a scholarly gathering.

VR: Which one, Daniel?

DG: I was in Alpha Tau Omega.

VR: OK, good.

DG: It's so interesting I'm getting descriptions of folks that are, can you believe this? They're having Paxlovid rebound, but they never got Paxlovid.

VR: They just had COVID, right?

DG: Imagine that. They got COVID. They started to feel better and oh my gosh, that second week, they felt horrible. Anyway, so yes, just to remind people, it's that second week when people can really feel rotten. That's when we often see the hypoxemia, hospitalization, and death. In general, you weather the storm, but for folks, right patients, right time, there are rules for steroids, anticoagulation, pulmonary support, remdesivir still in the first 10 days, immune modulation. Interesting, a little bit more tocilizumab being used in Taiwan than we probably use here in the States.

All right, this is an interesting one. We'll spend just a little bit of time. I suspect we'll get some letters about this, emails. The article, “Prevalent Metformin Use in Adults With Diabetes and the Incidence of Long COVID: An EHR-Based Cohort Study From the RECOVER Program,” published in *Diabetes Care*. These are results of a retrospective cohort analysis using the National COVID Cohort Collaborative (N3C). This is important. We're going to talk about N3C. That's the first cohort.

We also have the Patient-Centered Clinical Research Network. That's the PCORnet Electronic Health Record databases. They're looking at individuals with type 2 diabetes who were or who were not taking metformin when they were diagnosed with COVID-19. None of that complicated ramp-up and one and this and that. It's just, "Hey, you got COVID-19, were you on metformin or not?" We have the two databases. Kind of mixed depending on which database they look at.

Just looking at the N3C data, we get a suggested 15% to 20% decrease in PASC, being on metformin. Looking at the PCORnet database, it might be decreased by 13%, it might be increased by 4%, but we see sort of these overlapping confidence intervals. Looking at raw percentages, we might be talking about a 1% overall reduction. The raw differences are not quite as impressive as what we're seeing here.

VR: Based on this, Daniel, would you recommend metformin for PASC?

DG: What they're really looking at here is if you've got diabetes, does metformin reduce your risk of getting PASC? Not really a treat. I think that's important. It's not recommending this as a treatment for PASC. It still also is unclear that if you get acute COVID, should we jump in

with that complicated metformin or do you just do Paxlovid, probably has pretty similar data. Is metformin something we should be using with Paxlovid, something we should be using instead of Paxlovid? I would say no.

I think, one of the authors on our COVID-OUT trial was thinking of metformin as like the poor man's Paxlovid. Maybe there's some antiviral, maybe there's some effect here, but the data we're getting with Paxlovid are much more impressive.

VR: Here, if you are diabetic and you're on metformin, the protection against PASC is minimal.

DG: It's minimal, but there may be some. All right. No one is safe until everyone is safe. I've been saying that now for a while. It's been true. It continues to be true. I want everyone to pause the recording right here, go to parasiteswithoutborders.com, and click on that Donate button. We're in the middle of our Floating Doctors fundraiser, really right in the middle, actually. August, September and October, we're going to double your donations. Hopefully, we're going to get up to a potential maximum donation of $20,000 to support the great work that the Floating Doctors are doing.

VR: It's time for your questions for Daniel. You can send them to Daniel at microbe.tv. Eli writes, "Are masks recommended for commercial flights or does the turnover of cabin air once in flight mean they are not needed?"

DG: Ellie or Eli, I'm not sure how you pronounce that, but we've actually over the last few years, we've shared a number of studies where actually the duration of that flight, so and it's sort of a binary. Once you get above five or six hours, you really start to see an increase in the number of folks that end up getting COVID-19, getting infected with SARS-CoV-2 on those planes.

It isn't just the getting off and on the plane. It's, unfortunately, the folks around you, we are seeing transmission. You got to ask the question if you're on one of these flights and people around you and particularly there's a lot of folks with COVID, there's a lot of SARS-CoV-2 on the planes, as Noah Kahan tells us, then yes, you might consider wearing a mask.

VR: They could be sitting next to you shedding and they have no symptoms, who knows?

DG: They don't even know.

VR: Then the guy in front starts hacking away and the HEPA filtering, you're going to stop that. Then they walk down the aisle and cough as they reach you, right?

DG: Oh, yes.

VR: Nothing is safe. No one is safe until everyone is safe. [chuckles]

DG: Yes.

VR: Anita writes, "While listening to the most recent *TWiV,* responded to an email about hepatitis B vaccination. I thought it may be worthwhile to mention Heplisav-B as an option for your listeners." What's that? Is that a Hep B vaccine, Daniel?

DG: It's a, I'm going to say, relatively new two-dose option. Historically, all our Hep B vaccines have been one, two, three. Hepslav is a two-dose. I'm really curious to see, how this gets introduced. It's great that you can go ahead and get that full vaccination. It's an adjuvanted vaccine.

VR: Linda writes, "I'm a 50-something who will be a poll worker on Election Day. I would like to get a COVID booster prior to this. What would be the best timing?" Let's take that first.

DG: OK. That's great. Thank you for reminding me that we should be talking about timing of vaccinations. As we've talked several times, two weeks prior is when you're going to hit that peak. If you really want to have peak on Election Day, you want to get that booster about two weeks before. A lot of people are looking at, "When am I going to get my booster here this fall?" You want to be thinking, and it's going to be a little bit individual. "OK. I had COVID recently, I got to wait three months and then you do it."

"Hey, I'm really going to be laying low, but I'm going to be really spending a lot of time with, family and friends and in November, December." OK. You might want to think about early November and try not to get it in the meantime. Maybe the high holidays are coming up for you. Boy, you probably want to jump in there and get it now or be careful with the high holidays and then be thinking about these other times.

We really think these are, they call them new vaccines, but they seem to be boosters. They seem to be giving us a period of, let's say, four to six months of increased protection. Even the study that we talked about earlier, when you look at past that 90 days, you start to actually see protection drop even with regard to outcomes like hospitalization.

Flu, right, we'll talk about that at the same breath. Flu, we have data now for, well, a number of years where you get that peak about two weeks afterwards and you're losing about 10% of that protection against medically attended flu per month. Think about the timing. The interesting thing about flu is sort of a word of caution, an update. It used to be pretty reliable, right, that flu would come December or maybe come a little bit later, but we're seeing earlier flu.

It used to be, "Oh, maybe September's a little too soon", and that was true six years ago. Now you want to start thinking about keeping track about what's going on with flu.

VR: All right. Linda's second question is, "I've never had chickenpox. I've had two chickenpox vaccines. The second was about 20 years ago. I had a negative varicella-Zoster IgG test in 2021. Do I still need to get a shingles vaccine?

DG: It's a great question. The reason I say it's a great question is that what we do now is the chickenpox vaccines that we're using, these are actually replication-competent attenuated vaccines, what some people would say were live vaccines. There are described, it tends to be pretty rare, that people will get shingles from those.

In general, we're starting to get to where we really have to address this question. In general, very, very low risk. Boy, even if you reduce that risk by 90%, you've already started with a very low risk. There's no harm to getting the shingles vaccine, but you're really, as far as efficacy, a 90% reduction in what's already a very low number.

Now, at some point, I would love if we moved away from using a replication-competent virus. Let's stop putting this virus out there, and let's just actually go ahead and use our protein-based shingles vaccine.

VR: Shingrix, right?

DG: Shingrix, yes.

VR: For everybody, for kids and adults, right?

DG: Yes, just use it across the board. Again, we've got to do the science, we've got to say yes.

VR: Jay writes, "I'm disappointed by Emily Schmall's piece in the September 3 *New York Times*, "The Best Time to Get a Flu Shot," in which she writes, "Experts said that for most people, getting a flu shot at the start of September may be too early to provide protection that will last throughout the flu season," What's disappointing is she did not provide any evidence to support this. There was expert opinion without naming the experts. I have not found any evidence that getting the flu vaccine later in the season, say October or November, leads to better meaningful outcomes. If I'm missing something, I do want to know. Do you know any evidence that getting the vaccine later leads to less disease or death?"

DG: Yes. Dr. Gladstein, we just actually mentioned this a little bit earlier. There's a number of studies where we're getting this 10% to 15% per month decay in the protection against medically attended flu. Now that is interesting. What about what we really care about is people ending up in the hospital, people dying. I think we've shared in the past that 90% of people that succumb to the flu were not vaccinated.

We even share the data on children, 85% of the children that died last year, 83% I think was the actual number, did not get that vaccine. The flu deaths that we see are largely the unvaccinated, not necessarily that, oh, they got it too early in the season. Yes, I agree with you. When experts are speaking about something, it's really nice when there can be a link to the actual studies or even at least knowing who those experts are.

VR: Scott writes, "Hello Dr. Daniel, Scott here." Maybe it's Scotty.

DG: Is this from *Trek*?

VR: "I'm going through my second infection in two years. I've taken all the boosters whenever available." You'll see this is COVID because he says, "The symptoms this time were incredibly mild. I still got Paxlovid, which was discouraged by the urgent care medical staff I spoke with bringing up concerns of rebound. Being a regular consumer of *TWiV,* I pushed back and got the prescription." This has got to be the scrappy Scotty.

DG: Yes.

VR: "The last time I took Paxlovid, I did experience the situation where I tested negative and then several days later, I got some sniffles and retested and was positive. In preparation for this possibility, my question, am I contagious if this happens again? I will be at day eight tomorrow and I'm symptom-free and testing negative."

DG: Scott, if you listen, what are you doing retesting?

[laughter]

DG: We've covered this. Look at your calendar. Stop sticking things up your nose. People can get positive antigen tests. They can get positive nucleic acid amplification tests after those most contagious first five days. You're asking for trouble by sticking stuff up your nose. Most of the contagion, 85% happens in those first five days. We really don't see documented transmission after day eight.

Vincent: All right. Now, we received a lot of emails because apparently, the Florida Department of Health sent out their latest COVID vaccine guidance in which they do not recommend mRNA vaccines. One of them here is from Laura. "No doubt, I am not the first person to send you this link to the Florida Surgeon General's updated guidance for COVID-19 boosters for fall and winter 2024-'25. As someone who taught and researched scientific and technical communication my entire career, not to mention courses in research methods, I find the rhetorical approach of this new, "guidance" to be, shall we say, interesting.

Links to external studies from credible sources, such as the Cleveland Clinic, provide readers with a sense of credibility. The logical flow then creates an overall narrative that invites trust. Yet, logical fallacies, incorrect interpretations, and much cherry-picking abound. I recognize there are too many issues to be addressed on *TWiV,* but I wondered if you could perhaps speak to two of the most egregious.

One, DNA integration, and what the memo suggests is the risk that DNA integrated into sperm or egg gametes could be passed on to offspring of mRNA COVID-19 vaccine recipients. Two, the claim made about the Cleveland Clinic study that, as efficacy waned, studies showed that COVID-19-vaccinated individuals developed an increased risk for infection.

I find memos such as this, which do not on their face appear to be misinformation, to be more worrisome than communication that is overtly not creditable. In order to avoid legal issues, many physicians in Florida don't know what they can safely say to their patients, except that when it comes to COVID boosters, you are on your own. To quote you, what does one get when you mix science with politics? Politics."

DG: All right. Thanks, Laura, for bringing this to our attention. Yes, there's a bit of a history with this. It's a challenge. We'll deal with the science. This whole, concern or raised concern of DNA integration, that was actually, when you go back a little more than a decade, when people were considering different vaccine technologies, different nucleic acid vaccine technologies, the DNA-based vaccine technologies, this was raised as a concern.

If you've got DNA and you got to get that DNA into the nucleus, could that DNA then integrate? Now, mRNA, right? This is basic science, but important basic science. It's about where that mRNA needs to traffic, where it needs to go. The mRNA just needs to get into the cell, into the cytoplasm, you're done. You're all good. That's where the mRNA serves as a template for the protein production, in this case, the spike protein production.

This was actually a big driver towards mRNA COVID-19 vaccine. Really, actually the exact opposite. Now, the other claim they make about, COVID-19 vaccinated individuals, and I

remember this study, and again, it's interesting because I spent a little time looking through. There's sort of like, have your cake and eat it too where they point out that the point of the COVID-19 vaccinations was to prevent disease. When they first introduced, Omicron was circulating. They tried to say, "Oh, well, they prevented disease, but only they were talking about Omicron back then."

Here we're talking about risk of infection. As we've talked several times, that's not what vaccines are about. Vaccines prevent you from getting disease, from getting severely ill, from ending up in the hospital, ending up in an ICU, ending up not surviving, and the data is very clear. I guess, Vincent, they could just get a Novavax.

VR: Well, there is an option, but there's just no evidence that these issues are real for mRNA vaccines. The integration is just a theory. There's no data, and we've given millions and millions of people mRNA vaccines with none of these untoward effects.

DG: Yes, billions. We have great safety data here.

VR: I think that Laura's point is very good, is that they don't come off as being misinformation because they reference enough places, but the way they create their narrative, you end up being suspicious. I'm sure there are people doing this who know what they're doing.

DG: Unfortunately, it's a billion-dollar industry, misinforming people and making it seem innocent and reasonable. No, this is not accidental. I'm sure that document took lots of time and they spent a lot of money making sure that the misinformation was effectively conveyed.

VR: Daniel, the bottom line here is the state says you don't have to get these vaccines, and the voters in that state love it, so they're going to vote for the governor, that's the bottom line. Politics. When you mix -

DG: When you mix science with politics, Vincent.

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

DG: Oh, thank you. Everyone, be safe.

[music]

[00:47:49] [END OF AUDIO]