This Week in Virology

TWiV 1094 Clinical Update

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

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VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1094, recorded on March 7, 2024. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me tonight from New York, Daniel Griffin.

DG: Hello, everyone.

VR: I can't see the - wait, wait. If I look closely, no. Are there antibodies in your tie?

DG: Oh, you're trying to see what's on the bow tie.

VR: I can't see.

DG: These are prions. This is Creutzfeldt-Jakob disease.

VR: How many different bow ties do you have?

DG: A lot. A lot.

VR: Like 20, 25?

DG: I wonder what is a longer list, the number of bow ties or the number of countries?

VR: That you visited?

DG: Yes, I got lots of feedback. I left a lot of countries out, and people are like, "You didn't even mention Uganda. What about Switzerland?" I'm like, "Oh my gosh, sorry."

VR: I thought that was an interesting exercise to do, and I thought people would be interested in that. In the end, how many countries did you visit? Did you count them up?

DG: No, I did have plans, right? I was going to sit down and make a list, and of course, that will - some other time.

VR: All right, well, maybe we can meet in Africa this year.

DG: Yes, we'll have to try that. All right, let's get right into it. We have a lot to talk about today, and I will start off with the quotation. "Sometimes people don't want to hear the truth because they don't want their illusions destroyed." That's by Friedrich Nietzsche, very similar to something my grandmother used to say. "Now, Daniel, don't let the truth stand in the way of a good story."

I think our mission here is to let the truth stand in the way of a good story. Yes, we are here to continue with our commitment to the truth. Onto the data, shall we? Let us start with RSV and good news here. We really are coming off. We're really heading down. RSV detections are really dropping. We're getting to the end of the RSV season, and I will have some interesting data next week to talk about how well did those new tools help us this season.

VR: Daniel, this decline in cases, do you think this is due mainly to seasonality or also population immunity?

DG: I think it's both. I think it is interesting. When we say seasonality, what exactly does that mean? It's early March. We're still all indoors. We're still all doing the things that - what changed? Why is flu still up, and we'll get to a pretty solid percent, and RSV dropped off? I think that actually some sort of that temporary RSV immunity is contributing to this. That's one of the big differences between getting RSV and getting the shots. The shots, as we've talked about before, may actually last more than one season. Getting a case of RSV may only give you enough temporary protection, enough serum, I guess, mucosal antibodies to drive things down. There's a lot like, what do we mean when we say seasonality and what drives that pattern?

All right. Flu, leading us right into that, we're doing OK. We seem to be slowly moving in the right direction, but we're still at a solid level. We're still seeing a fair number of flu cases. As we keep mentioning, I love looking at the map of the country because it's regional. They're starting to do a little bit better down there in Texas. We're doing much better here in New York. Montana has been doing great for a while. It's really different areas are doing better.

We will get right into COVID. At some point, I will talk about measles, but I'm refraining at the moment. COVID, in hospital, we're still over 15,000. In ICU, up about 2,000. New deaths, we are still over 200 deaths a day. It's still pretty significant. We'll be talking a little bit about that. Where are the trends going? We've been sharing the Biobot data, which shows across the country, in general, we are dropping down in most parts of the country, but also add a new link to the CDC, National Wastewater Surveillance data, where you can see, and actually, it's nice, you can 45 days, six months, a year, you can toggle different scales there. Really looks like both sources of wastewater data, we are moving in the right direction. Definitely down quite a bit from that end of December, early January peak.

Big news and put on my glasses for this, Vincent, this is going to be the big news this week. They wait till we record, and then they throw this out there. It's good, it gives me a little time to think about it. On March 1, at 3.40 PM, Eastern Daylight Time, we got the CDC's updated respiratory, and I pronounce it that way on purpose, virus guidance, what to do

when you are sick. It was the thing when I was at NYU, they used to refer to your belly button as the umbilicus. I think it was a way to signal who else had trained at NYU. Maybe at some point, I'll convince people to say respiratory. Anyway, the -

VR: Centimeters or sonometers.

DG: Yes, sonometers, umbilicus, respiratory. Don't worry, it's on purpose. They start with the two sentences. CDC released updated respiratory virus guidance in response to the decreased risk that COVID-19 poses to the population. I think that's important that they're not talking about every single individual. They're talking about a public health population focus. This updated guidance includes strategies to protect people at highest risk of getting seriously ill and provides actionable recommendations for people with common viral respiratory illnesses, including COVID-19, flu, and RSV.

Not just isolation guidance, which everyone's going to focus on that, but let's go through some of the things that are in this updated guidance. They start off, as they've been doing really for quite some while, doubling down on vaccinations. The most important thing you can do to protect yourself from COVID-19, flu, and RSV is to stay up to date on your recommended vaccines. Even when vaccines don't prevent infection, I want to say another time, I think we had some people not understanding that, but even when vaccines don't prevent infection, they often tame these viruses, reducing severity and preventing their worst outcomes like hospitalization and death.

Along with staying up to date on your vaccines, practicing good hygiene by covering your coughs and sneezes, washing or sanitizing your hands often, and cleaning frequently touched surfaces can help. Also, taking steps for cleaner air can help reduce the spread of respiratory viruses, and this can mean bringing in fresh outside air by opening a window, purifying indoor air, or having outdoor social activities.

Now let's get into what's controversial. If you get sick. They go on to say that even if you practice those core prevention strategies, you may still catch a virus and develop respiratory symptoms. If that happens, the updated guidance recommends two actions. Now, one of the things I thought was sort of missing from here, is we are now focused in this guidance on symptomatic infection. We're focused on disease. We're not talking about screening populations and now you have a positive test. This focuses not on healthcare providers, not on results of a positive screening test, but on results of a diagnostic test or clinical syndrome.

Number one, stay at home as much as possible. You should stay home and away from others until at least 24 hours after both of the following. Your symptoms are getting better overall, and you have not had a fever and are not using fever-reducing medication. I'm going to talk a little bit about that. If you're like, "Oh, I'm feeling better. I'm just taking a little bit of Tylenol and Advil. Maybe I'm taking that NyQuil or DayQuil." Yes, that doesn't count. You're not really supposed to go back to work yet. You're supposed to be symptoms better, no fever, and you're not requiring any medication. If you're taking medications, why are you taking medications? You're taking medications because you don't feel better yet.

VR: Yes, but what are you supposed to do? Stop and see if you feel worse and then start again? You're stuck.

DG: I think that's a good comment. Yes. At some point, you're going to be like, "I think I'm better. I don't think I need to take this stuff." Then you stop it for 24 hours, and if you're actually better, OK, then maybe you get to move forward. If you're still taking - I think every preschool and elementary and probably just about every teacher is familiar with the kids coming into school and the parents are loading them up with ibuprofen and Tylenol so that they get to go to school even though they're sick. That's not what the CDC is recommending. They're not saying, "Hide your symptoms and fever with medications." They're saying, "Yes."

Now, this is a part of the interesting part of this, and I will clarify this, public health recommendation. This advice is similar to what has been recommended for flu for decades, and they suggest will help reduce the spread of COVID-19 and other respiratory viruses during the most contagious period after infection.

Not all respiratory virus infections result in a fever, so paying attention to other symptoms, cough, muscle aches, et cetera, is important as you determine when you are well enough to leave home. If your symptoms are getting better and stay better for 24 hours, you are less likely to pass your infection to others, and you can start getting back to your daily routine and move on to step two. Now, I just want to point out, I say less likely. This isn't a free pass. It isn't that you are now not infectious, and let's move to step 2 with that in mind.

Step two, resume normal activities and use added prevention strategies over the next five days such as taking more steps for cleaner air, enhancing your hygiene practices, wearing a well-fitting mask, keeping a distance from others, and/or getting tested for respiratory viruses. People can choose to use these prevention strategies at any time. Since some people remain contagious beyond the stay-at-home period, taking added precautions can lower the chance of spreading respiratory viruses to others.

I see you're enjoying this, Vincent, but, the interesting thing here is, I don't think people actually read this guidance. I think people just read something where they say, "Oh, yes, I guess the CDC is dropping guidance. There's no more isolation," but I think what I laid out is actually quite something. If you're sick, you've got to wait till you're feeling better. You've got to wait another day on no medicines, and then you can think about going back to work. Here you are washing your hands, wearing a well-fitting mask, keeping distance from others. People aren't even doing that now.

Vincent: Now, it's conceivable that you could feel better in two days and go back to work, right?

DG: That's a little bit of the challenge here. You could feel better after two days. I think I described my sort of experience was I was about to go for a run. I felt a little bit of a scratchiness in my throat. I was like, "I've been at a big conference here. I should just check." That was it. By the next day, I was completely fine and fever free. Would it be appropriate for me as a health care worker to just go right back to work and infect others? Because you're still contagious during this period of time, even when you are feeling better.

This is well established. This is not for health care guidance. People like me, we should not be going back to work and infecting our high-risk patients. That's important.

Why did they do this? What is the elephant in the room? Why did they update the guidance? Did the science suddenly change? Some of it did. Let's talk about what that science is. The science on transmission did not necessarily change. As the CDC explains itself, we are in a different place with COVID-19 than we were. Weekly hospital admissions for COVID-19 have decreased by more than 75% and deaths by more than 90% compared to January 2022. It's a pretty low bar. Things were pretty bad then. That's my little side note.

Importantly, these decreases have continued through a full respiratory virus season, despite levels of viral activity similar to prior years. Almost 98% of people in the United States have antibodies against COVID-19 because of prior vaccination, infection, or both. We also have effective and widely available vaccines and treatment that work. More than 95% of people hospitalized with COVID-19 this last season were not up to date on COVID-19 vaccinations, and most had not received antiviral treatment. Now, they go on -

VR: That last statement, Daniel, are not up to date on COVID vaccines. I don't quite believe that. I can believe not getting antivirals because you have said that many times.

DG: Yes.

VR: You've said that many of these people are vaccinated, right?

DG: That's interesting. Let's be critical here because I think we should. Because one of my buddies out in Seattle, Juan Potu, sort of put this in, I guess, our Optum guidance when people get COVID. He made sort of this, 95% of people hospitalized were not up to date on their vaccine. Basically, they're not talking about people who are unvaccinated. They're saying, what was it? About 10% or 12% of our society got that latest booster? You're starting with an 88% of our population didn't, and then you're saying 95% of people, ended up hospitalized, didn't get that latest booster.

I have to say, I think that's a little misleading. Because they're talking about just 88% versus 95. We'll talk a little bit in a moment about how effective are those boosters, and what are you going to get for how long? This is not saying, these are unvaccinated people that we're talking about. The other, and I think this is something we repeatedly say, most of the people that end up in the hospital, these are the people who, "Oh, you're probably going to do well," and then they don't, because they're not offered or encouraged to receive antiviral therapy. Good point.

Now they also make another comment. The updated guidance change, they suggest, will not significantly increase COVID-19 community spread and severe disease. They talk about, when similar guidance in the past has been put out there that they're not seeing much of a difference. Here's the other thing they want, is they're looking for clear, simple, and actionable guidance regardless of the respiratory virus will help protect Americans. Maybe. They do it as trying to just say, "Here's what we want you to do across the board for everything." Then they do a couple scenarios, a couple examples, and there's four of them. I'm just going to run through Example 1, Example 4, just to sort of go through.

Example 1, person with fever and symptoms. Talking about COVID, but they're sort of saying you can talk about anything here. There's a first period of time when you're feeling sick. This duration really varies. Some people are sick for a day. Some people are sick for three or four days. Some people are sick for seven days. They're basically saying for that entire period of time, you're staying home and away from others. Then you feel better, fever ends, symptoms are getting better. It's another 24 hours before you're guided to go back to normal activities, but you're still going to take those extra precautions, including, as we read, wearing a well-fitting mask and keeping a distance from others for the next five days.

VR: It says, Daniel, this symptom and fever duration varies. What is the range there?

DG: That's a bit of a problem. Because people before had this five days, and maybe this is a bit of a problem. What if it's eight days? What if it's nine days and you're still feeling crummy? Still, as per this guidance, you're staying home and away from others.

VR: You may not be shedding, right?

DG: I'm going to suggest that if anything, this is a little bit too conservative. If it is day 10, day 11, you're not contagious. You don't need to be wearing a well-fitting mask. You can come and visit me and hang out in my poorly ventilated suburban home, and I'm not worried that you're going to make me ill. Now, the other is, person gets better, and then you get a fever, and you're like, "Ah."

Here this person, they're sick for some period of time, they're starting to feel better. Maybe they feel so well, they actually go back to work, and then they get a fever. Now, you're going to go back into that stay away from home and others, wait for the fever to end, another 24 hours, and then five days of wearing that tight-fitting mask and staying away from everyone else.

VR: Daniel, this late fever, is that an inflammatory phase?

DG: I guess that's what I worry about. That would make sense, and we certainly see that. We've sort of talked about the biphasic pattern with COVID. You get over the viral replication phase, you're feeling better, then you get hit with that cytokine storm, it's day 11, let's say, you're not contagious on day 11.

VR: Although realistically, maybe you feel bad enough that you don't want to go to work, right?

DG: That's why I've discussed this guidance with some individuals, and what they're worried about is that their employers are going to be like, "48 hours, you should be feeling better by now, get back to work." I think our employers will like the fact that unless you're a healthcare worker and you're trying to keep your coworkers and patients from getting sick, you got to get back to work, you got to toughen up.

VR: Also, there are essential workers that don't have the luxury of spending extra time recovering. We saw that during the pandemic very much.

DG: Yes.

VR: I think that the outcome, Daniel, is that it's very difficult to make public health measures that are going to satisfy everyone. This has always been a problem, and with other virus infections pre-COVID, people do what they want. They feel sick, they go to work.

DG: Yes. I think we hear that all the time. I think, people want to beat up the CDC. I'm not sure this is where you should do it because this is a no-win scenario.

VR: Of course, these are recommendations, Daniel. They can't make you do anything.

DG: They can't make you do anything. As we've learned that if you do make someone do something, they will resent it.

VR: That's right.

DG: In the future, they will find out what you want them to do and make a point of not doing it. This is where we stand, and I think the big caveats here is they are basically not saying that suddenly people on Day 3 are non-infectious.

VR: Daniel, a student in my class wears a mask every day. The other day we were talking, and I said, "You don't have to answer, but do you have some immunocompromised conditions?" She said, "No, I just want to protect other people."

DG: It's really nice.

VR: I said, "Well, you're pretty rare because most people are not altruistic."

DG: Yes, it's true. All right, well, kudos to that person who's putting others out there. All right, COVID active vaccination is timing everything. Last week we discussed the recommendation that those 65 and older should get another COVID shot if it has been more than four months, and we wanted to see the data and the interim effectiveness of that updated monovalent vaccine in our slides. Here we get them. It's a day late and a dollar short for that meeting. They could have postponed. They could have said-- come on, this is *MMWR*. They knew they had this data. They could have put it out there.

Here it is. *MMWR*, "Interim Effectiveness of Updated 2023-2024 (Monovalent XBB.1.5) COVID-19 Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalization Among Immunocompetent Adults Aged Greater or Equal to 18 Years - Vision and IVY Networks, September 2023 through January 2024." All right, so this is what we wanted to know. Are we going to see this cliff? Should people be getting another shot? What's the vaccine efficacy?

Here, the analysis evaluated vaccine efficacy of an updated COVID-19 vaccine dose against COVID-19 associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults aged greater than equal to 18 years during this period, September 2023 through January 2024, using a test-negative case-control design with data from the two CDC vaccine efficacy networks. First off, where's the mortality? I would have liked this mortality. I would have liked to break this down a little bit more, but OK.

Vaccine estimates against COVID-19 associated ED/UC, so that's emergency department, not erectile dysfunction, and urgent care encounters were 51% during the first seven to 59 days after an updated dose, 39% during the 60 to 119 days after an updated dose. Now, the vaccine efficacy estimates against COVID-19 associated hospitalization were 52% and then 43%, with a median interval from updated dose of 42 and 47 days, respectively. The updated COVID-19 vaccine provided increased protection against COVID-19 associated ED and UC encounters and hospitalization among immunocompetent adults.

Let's just go through a couple of the tables because I think it's worth looking at the efficacy and looking at it in different ages. First we've got Table 2, and this is going to be the effectiveness against COVID-19-associated emergency or urgent care encounters. If we look at those, I'm going to look at the 18 to 64 range and compare that to the greater than 65 and over. If you look right at the 18 to 64, in the first 60 days, we're seeing vaccine efficacy of about 52%, and then 60 to 119, 45%, not really dropping off a cliff. When we look at the greater than 65, it's 49% during the first 60 days, and then 37% 60 to 119.

VR: Daniel, they have the no-updated dose, but how do we compare that to the updated dose data?

DG: That's going to be our reference. They took basically the 85%, 90% of the population that said, "I'm not getting that booster." Then they compared them to the folks in the same age group who said, "I'm going to get that booster."

VR: For example, when they say 44, 47% vaccine efficacy, that is compared to the un-updated group.

DG: Yes. They're not comparing these to unvaccinated, not immune. This is people who just said, 'You know what, I'm not going to get that last dose." This is on top of the durable protection of the three-shot original series. Then we move to Table 3, where here we're looking at vaccine effectiveness for preventing hospitalization. We'll do the same thing, looking at the folks 18 to 64. This is, in a lot of ways, the data I'm particularly curious about. The first 60 days, 18 to 64, 42%; 60 to 119 days, 45%. Lots of overlap there. Really pretty similar, not seeing anything falling off a cliff. If those folks 65 and over, first 60 days, 54%; 60 to 119, 50%.

A couple issues. We're still waiting for the next, the 120 to 180. We want to see, did it really fall off a cliff at four months? Because that's what our recommendations have basically suggested, that, "Hey, if you don't get a shot at four months, you've lost this protection." We're not really seeing a huge cliff here with loss of protection against some of these, hospitalization, urgent care, ER. What we are seeing, and this is the other side, is we're seeing about a 50% reduction in your risk of ending up in the ER, ending up in an urgent care center, ending up in the hospital with those updated boosters on top of that durable protection from the first three shots.

VR: What's your opinion? Do these data justify a booster now as recommended last week?

DG: This doesn't necessarily support it. It's one of those things is, we need the data. We'll know in 60 days if they keep collecting this data. We don't know yet.

VR: Maybe that's why they didn't delay the meeting for this.

DG: Yes, because we get this, then you're like, "Oh, now it's confusing." Because the other data was a little bit more persuasive. That prior bivalent looks like it was losing efficacy, but was it losing efficacy because it was a new variant or was it losing efficacy because of the contraction of the antibodies or the waning of the T cell and other parts of the immune system? I don't know. I do hope that we get it updated in 60 days on this data. What happens after that 119 days? What's that 120 to 179-day data?

Moving into the early viral phase, I have a bone to pick in this section just to warn people ahead of time. You may think I was all focused on the guideline trains, but which guidance am I particularly interested in people being aware of? It is the NIH COVID-19 treatment guidelines that were just updated on leap day, February 29, 2024. This should be an easy day to remember. I want to have this link here so that you can share these with those that are following the media and not the science. I'm going to talk a little bit about number one, Paxlovid.

We have another article, “Combined Protection of Vaccination and Nirmatrelvir-Ritonavir,” that's Paxlovid, “Against Hospitalization in Adults with COVID-19,” published in *CID*. This is the article looking at the question of, "What if I do everything right? What if I get my vaccinations and I get early treatment? How can I expect to do?" Really, it's all in this one figure. We have this adjusted hazard ratio. Your reference is going to be - interesting enough, they've got these people out there. Unvaccinated, no treatment. That's going to be your starting point.

What about no treatment, but you only went for two mRNA doses? You're going to get about a 25% reduction. "What if I get that third dose?" You're going to get another 25%, so about a 50% reduction in ending up in the hospital. What if I take each one of those situations and I actually go ahead and give you Paxlovid? I'm going to reduce your risk of hospitalization in half each time. If you do everything right, you get your three mRNA doses and you get your Paxlovid, a 75% reduction in your risk of ending up in the hospital.

VR: Taking antiviral, Daniel.

DG: Yes. I just wanted to share a letter here because this is what - I think my wife was torturing me today because first she was like, "Nirmatrelvir, what is that?" I'm like, "Jessica, that's Paxlovid." She's like, "Oh, that would be such a good drug if it wasn't for the rebound." I'm like, "Ah. Oh, my gosh." She knows how to torture me, right? Her and the kids.

Here's the letter. I get this letter. It's an e-mail. It's an e-letter, I guess we call those. "Clearly, COVID has changed a lot since our past discussions." This is a provider. "I would like to know how you would handle this situation. A 60-year-old obese female with asthma, CAD, hypertension. She did not receive her fall COVID-19 vaccination. She now develops COVID and is presently taking Brilinta." This is ticagrelor. It's a platelet aggregation inhibitor.

"She's doing this to reduce the risk of cardiac stent occlusion. She's also on Lipitor or atorvastatin. Now I advise patient, who I follow for asthma to increase her inhalers, monitor her pulse ox, and I also recommended that she be treated with Paxlovid. I had her contact

her cardiologist because her Brilinta dosage, in addition to atorvastatin, would have to be lowered or temporarily discontinued. She had been on Brilinta for cardiac stent since 2022." Big long pause. "Her cardiologist advised me that Paxlovid was not indicated in this high-risk patient during the first week and did not want her to start the medication, stated that the patient is three days into the illness and only has upper respiratory symptoms. The chances are that she will do fine."

VR: Famous last words, the chances are.

DG: Exactly. Chances are. Really a challenge here. I recommended that this physician first pat himself on the back for actually keeping up to date and making the correct recommendation. I suggested that he share the latest NIH COVID-19 treatment guidelines that clearly state that this would be an indication for treating this high-risk patient with Paxlovid. Just a little painful. Yes.

All right. Number two, remdesivir, approved down to 28 days of age, and this is a three-day. I was actually talking to one of our providers out in Jersey about trying to set this up to provide better access because we really don't see a lot of people getting access here. Molnupiravir is a third and not as great option, convalescent plasma only in certain contexts. We have those updated isolation guidelines from the CDC.

Another exciting study here. We finally have the peer-reviewed published results of the PRINCIPLE trial on ivermectin, looking at both short- and long-term outcomes in the article, “Ivermectin for COVID-19 in Adults in the Community, (PRINCIPLE): An Open, Randomized, Controlled, Adaptive Platform Trial of Short- and Longer-term Outcomes,” published in *Journal of Infection.*

I was reviewing this paper last night while I was attending something called Schreiber Slam, and this is where the teachers all perform in this sort of mock wrestling that they do. I thought it was really appropriate to read this paper in that venue. Some of our listeners may pick up on why I say that. This article published in *Journal of Infection* shares with us the results of a multi-center, open-label, multi-arm, adaptive platform, randomized, controlled trial that included participants aged 18 years of age or older in the community with a positive SARS-CoV-2 test and symptoms lasting less than or equal to 14 days.

Patients were randomized to usual care, usual care plus ivermectin for three days daily, or usual care plus other interventions. They have co-primary endpoints, time to first self-reported recovery, and COVID-19-related hospitalization, death within 28 days. The other was recovery at six months, and this was the primary long-term outcome. Primary analysis included 8,811 SARS-CoV-2 positive participants, median symptom duration five days. In general, we're targeting that first week. We get 2,157 randomized to ivermectin, 3,256 usual care, 3,398 other treatments. This is from June 23, 2021 to July 1, 2022.

Now time to self-reported recovery in the ivermectin group compared with usual care was a hazard ratio of 1.15 and a median decrease of 2.06 days at a range of one to three, COVID-19-related hospitalization deaths, odds ratio 1.02, estimated percent difference zero, serious adverse events, three and five respectively, and the proportion of feeling fully recovered were similar in both groups at six months, also at three and 12 months.

They break it down, so you get a nice Kaplan-Meier curve, cumulative percent recovery. They do a breakdown looking at vaccinated or not, different severity scores, et cetera. At the end, the authors concluded, ivermectin for COVID-19 is unlikely to provide clinically meaningful improvement in recovery, hospital admissions, or longer-term outcomes. Further trials of ivermectin for SARS-CoV-2 infection in vaccinated community populations appear unwarranted. Maybe we're done with ivermectin.

VR: OK. Maybe. I've heard this statement before.

DG: Yes. To be honest, I know there's a lot of conspiracy theories out there, but we have done a lot of trials. We've done the science. We've looked at whether or not ivermectin could make a difference. I feel like we've looked pretty darn hard and as long as you only include studies that were actually done as opposed to those ones which were faked or fraudulent or not done and just contrived, yes, it just does not look like this has a role here.

All right. Number two, or second week, the cytokine storm week, remember, steroids, right time with the right patient. We have anticoagulation guidelines, pulmonary support, remdesivir still in the first 10 days, immune modulation, perhaps with tocilizumab. Remember, just don't throw the kitchen sink at these people, only stuff that can make a difference. Let's not do harmful things.

All right. Now, a couple of articles that we're going to discuss this week, it's actually going to be three, but two are going to be dealing with cognition, memory. The article, "Cognition and Memory after COVID-19 in a Large Community Sample," was published in *The New England Journal of Medicine*. Now here, the investigators invited 800,000 adults in a study in England to complete an online assessment of cognitive function and estimated a global cognitive score across eight tasks. Not everyone does it. Of the 141,583 participants who started the online cognition assessment, 112,964 completed it.

They reported that participants who had recovered from COVID-19 in whom symptoms had resolved in less than four weeks or at least 12 weeks had similar small deficits in global cognition as compared with those in the no COVID-19 group. Just want to sort of repeat that. They're actually finding that people who had COVID-19, mild or not so mild, actually had cognitive deficits. I want to give a little bit of a context of what are we talking about here.

Compared to the uninfected participants, apparently they're still out there, that's a control group, the cognitive deficit was commensurate with a three-point loss in IQ and was evident even in participants who had mild COVID-19 with resolved symptoms. However, larger deficits were seen in participants with unresolved persistent symptoms, and here the participants with unresolved persistent symptoms had the equivalent of a six-point loss in IQ, and those who had been admitted to the ICU had the equivalent of a nine-point loss in IQ. Larger deficits were seen in participants who had SARS-CoV-2 infection during periods in which the original virus or B.1.1.7 was predominant than in those infected with later variants and in participants who had been hospitalized than in those who had not been hospitalized.

VR: Daniel.

DG: Yes.

VR: How do they come out with this? If they don't have a baseline assessment and they just do a post-COVID, how do they know there's a decline in IQ?

DG: Yes, actually, that's a good. Yes, where they're going with this is, I think people are saying you get SARS-CoV-2 and then your IQ declines. What they're really saying is we're looking at people that have had COVID, we're looking at people that did not have COVID, and we're comparing their IQ. Maybe the people that didn't get COVID were smarter to begin with.

VR: Yes, I don't know if that's - I think the real comparison is the same patient pre-and post-COVID.

DG: That's ideally like if we could get IQ tests once a year or twice a year, and then something happens and look after the fact. Yes.

VR: I'm not sure this is terribly meaningful.

DG: I'm glad you bring this up because we've got some data coming up that might address this. Just to finish up this one, we'll get into the next one. In a comparison of the group that had unresolved persistent symptoms with no COVID-19 memory, reasoning, and executive function tests were associated with the largest deficits. People who say, "I'm just not doing well, I've got memory, all kinds of other issues."

Interesting was the finding that COVID-19 vaccination provided a cognitive benefit, while reinfection was tied to an IQ loss of nearly two points compared with no reinfection. As pointed out, this is a spot in time. It's not like they looked at the people and then they got reinfected and then tested them after the fact. This is just looking at people that were vaccinated, not vaccinated, people who got one infection, people that got two infections, and looking at this one spot in time.

Now, in the same *New England Journal of Medicine*, we have a letter to the editor, “Prospective Memory Assessment Before and After COVID-19.” You asked for it, Vincent, and they're right hot on the heels. Here they start with 188,137 participants in the nationwide Norwegian COVID-19 cohort study from March 27, 2020 to April 26, 2023, a total of 137,373 participants, so 71%, completed at least one everyday memory questionnaire, and 60% had documented tests showing positive or negative status for SARS-CoV-2 infection as determined from the Norwegian Surveillance System for Communicable Diseases.

They use something called the Everyday Memory Questionnaire. I'm going to leave a link. This is a simple questionnaire where people report how often they might be having memory problems with a higher score reported being worse. The more problems, the more severe, the higher number you're going to get. Is prospective. All these individuals start with the same scores, but then the mean everyday memory questionnaire scores were numerically higher, indicating worse memory problems after a positive test than after a negative test at all time points. Zero to one month after a test, one to three months, three to six months, six

to nine, nine to 12, 12 to 18, 18 to 36. While they were, as mentioned, they were the same before that SARS-CoV-2 positive test.

A couple of things here. One is they did this the right way. They didn't just look at one spot in time and see. They followed these people over time. What I was quite concerned about is I was hoping these curves would come back together, but what we're actually seeing is they separate and actually we're getting out, 18 months to three years, we're starting to see pretty significant separation. Actually quite a lot more separation than we saw in the first few months.

VR: The error bars are also getting bigger. You're having variation in the population, right?

DG: Yes.

VR: I don't know if you went longer, they might come together. I don't know.

DG: I hope so.

VR: I don't know what these numbers mean in terms of, how significant an impairment this is.

DG: Yes, there's a lot of limitations. I went through and I was looking at this, the EMQ. It's very subjective. You ask people, "So have you had a memory problem? Was it really bad? Was it mild?" Then they get these numbers. Yes. It's very subjective. They didn't actually, formally, and I think I would love that too. They did the right thing with prospective, but I'd love formal challenges. Have them do some memory testing, have them do some formal validated testing. Because really, you're just saying like, "What do you think?"

Now this is a troubling, but confirmatory article that's going to close this out today, which is, “What is the Impact of Long-term COVID-19 on Workers in Healthcare Settings? A Rapid Systematic Review of Current Evidence,” published in *PLOS One*. Here the investigators sought to assess the effects of Long COVID among healthcare workers and its impact on health status, working lives, personal circumstances, and use of health service resources

Here they conducted a systematic rapid review by searching for relevant electronic databases. They start off by identifying 3,770 articles, narrow this down ultimately to 30, where we've got two studies providing qualitative evidence, 28 survey studies providing quantitative evidence. Thematic analysis of the two qualitative studies identified five themes: uncertainty about symptoms, difficulty accessing services, importance of being listened to and supported, patient versus professional identity, and suggestions to improve communication and services for people with Long COVID.

Common long-term symptoms in the studies included fatigue, headache, loss of taste and or smell, breathlessness, dyspnea, difficulty concentrating, depression, anxiety. They report that the healthcare workers struggled with their dual identity, the patient versus doctor. They felt dismissed or not taken seriously by their doctors. The findings were in line with those in the literature showing that there are barriers to healthcare professionals accessing healthcare and highlighting the challenges of receiving care due to their professional role.

They found that, unfortunately, a lot of the participants, a lot of these physicians were turning to social media groups for support, validation, and information.

VR: This indicates that we need to be addressing these issues on a big scale.

DG: I think it's huge. I think it's not great for our profession to hear that when a healthcare worker gets sick and goes to a provider that they often feel dismissed, that they don't feel listened to, they don't feel supported. Yes, I think this is a call to action. We need to do a better job here. All right, and I will close us out with no one is safe until everyone is safe. We are still in our American Society of Tropical Medicine and Hygiene fundraiser where February, March, and April, if we can get donations up to $10,000, we will double it up to a potential maximum donation of $20,000.

VR: It's time for your questions for Daniel. You can send yours to daniel@microbe.tv. Lori writes, "Could you clarify for me so I'm not spreading incorrect information? Is it fair to say the avian flu, H5N1, that is presently in birds in North America is not the flu that is spread in people at this time? The risk of humans getting avian flu from infected birds is very low due to receptor binding site preferences. Although we want to be cautious, we don't need to be too worried about getting flu from bird poop on our porch."

DG: OK. Yes, this might be an easy way for people to remember it. Maybe. You could tell me. Think about those numbers, the H1N1, H5N1. We start numbering at one. H1, H2, H3, N1, N2, N3. If you're down in the low numbers, we'll say one to three, you're probably talking about a human. When you get up to five, you get up to nine, you're starting to talk about non-human influenza viruses.

Yes, the H5N1, that's not the common circulating virus that we're talking about. The H5N1's been in the press a little bit because there have been a few cases where human beings have actually gotten H5N1. Usually, there's been pretty significant exposure, there's been poultry workers. I think there was actually one of these down described in Antarctica in the penguins recently. Any other comments, Vincent?

VR: That's right. H1, H2 are the ones that are human viruses, yes.

Anna writes, "I have one suggestion. If you reference any wastewater data, you may consider using the new and improved CDC National Wastewater Surveillance System dashboard at cdc.gov/nwss instead of the Biobot data. CDC now has a nice national summary, but their data set reflects over 1,200 sites as compared with a few hundred in Biobot's. You can get to the number of sites if you dig down in the COVID data tracker.

Also, NWSS will be adding new targets to their dashboard beyond Mpox and SARS-CoV-2 in the coming year, including influenza A and B and RSV, but also adenovirus 40/41, Campylobacter jejuni, Candida auris, norovirus G1 and 2, Shiga toxin-producing E. coli, and some specific antibiotic resistance genes, carbapenemases, ESBLs, and colistin and vancomycin resistant genes. Thanks again from Anna."

DG: Oh, this is great. Yes, we actually included it for the first time, but I cheated. I saw your email and that's why I put it in. Thank you.

VR: All right. These are some questions from office hours last night, and they said, "Can you get Daniel back and answer our questions?" Maybe in a couple of weeks, we'll get you back, Daniel. First, "I had MMR vaccine, measles, mumps, rubella in the 1960s, 1970s, 1980s. Do I need another dose now that there's measles again in the U.S.?"

DG: Yes, that's interesting, right? A lot of us, when we went to medical school, they would draw titers and, oh, if it's below a certain level, they would revaccinate us. We think that the vaccine for measles is, I think, the number that we throw out is 98% effective at preventing a symptomatic case of measles. We have not made any recommendations across the board for people to get revaccinated, but I didn't talk about measles and maybe I should talk about it in the next. We're up to over 40 cases. We're really seeing a huge resurgence in measles. We'll have to see if we still trust that 98% number.

VR: Another question, how early can children get MMR vaccine?

DG: Oh, I have to look up the schedule. Yes, I'd have to look that up. Ask your pediatrician. I'll defer.

VR: Can you check your measles antibody levels? Will that help?

DG: You can. Yes, you can, actually. Now, does that actually really correlate with immunity? That I'm not sure about. Vincent, do you know?

VR: I think it does, but I don't know what the number is.

DG: OK. Yes. As I mentioned, that was one of the sort of entering into medicine that needs to be - there is a threshold they give us. Yes.

VR: All right. Lori writes, "I always look forward to clinical updates. A friend just asked if I'd heard anything about changing arms with COVID booster. I told her the last thing I heard is that it really doesn't matter, but I heard at one time that using the same arm might be better to target the same lymph node. As far as I know, that advice hasn't changed, but I told her I would ask you."

DG: Yes. We've talked about the different studies about trying to get in the same arm and trying to do opposite arms. If you look in the first 30 to 45 days, if you do the same arm, maybe you get a little bit of a head start and the antibodies come up earlier. If you did on the other arm and you follow it out to 90 days, maybe the opposite arm is doing better at that point. I would say at this point, I do not think we have any compelling science to tell you that you need to choose one versus the other arm.

VR: All right. Then finally, Tom writes, "I assume this is somehow common in both of your professional milieus, but it comes up so incredibly often on a show discussing COVID that I'm finally breaking down and asking you both, you know you are mispronouncing it, right? Love absolutely everything else about what you do." The word is what Daniel has been pronouncing throughout this episode. I don't know, do we both say respiratory? Is that the problem?

DG: No, I don't know. I don't know.

VR: What do you say?

DG: How are you supposed to pronounce that word?

VR: The American pronunciation is RESpiratory, with the accent on the first syllable.

DG: Back accent.

VR: The British is res-PIE-ratory.

DG: We're not doing anything right.

VR: What do you say? Say the word.

DG: I say res-SPEAR-atory.

VR: Respiratory. You're putting the accent.

DG: I'm not doing - I'm pulling the S into that first. Respiratory.

VR: In the Brits, they drop the O. It's like respir-a-tree.

DG: Oh, OK. Respiratory.

VR: We're supposed to say respiratory. I think we both say res-PIE-ratory. Because that's the way I heard it when I was trained. All the people around me said respiratory. I'll try to say respiratory.

DG: It's a living language. You and I are trying to kill it. (chuckles)

VR: Indeed. Then Tom writes, "Love absolutely everything else about what you do." Thank you, Tom.

DG: Except the way you pronounce that one word. Yes.

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

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

[music]

VR: Be safe from res-SPEAR-atory. Oops. Be safe from RESpiratory viruses.

DG: Exactly.

[00:53:09] [END OF AUDIO]