This Week in Virology

TWiV 1074 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

Aired 30 December 2023

pdf of this transcript available (link)

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

[music]

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1074, recorded on December 28, 2023. I'm Vincent Racaniello, and you're listening to the podcast All About Viruses. Joining me today from New York, Daniel Griffin.

DG: Hello, everyone.

VR: Daniel, it's our last clinical update for 2023. We've done 52 of them, I guess, 52 weeks, right?

DG: Yes, that is crazy. We haven't missed since sometime in February of 2020.

VR: That's right.

DG: Wow, OK.

VR: What have you got for a bow tie there, Daniel?

DG: This is my anthrax bow tie. One of my - I have more than one. Can you believe that? One of my anthrax bow ties. [laughs]

VR: You can't have too many anthrax bow ties, in my opinion.

DG: [laughs] OK, that'll be a quotation for the future. I got a list of them that go on the gravestone. The guac is extra. You cannot have enough, too many. All right, let's jump into an actual quotation. "For every complex problem, there's an answer that is clear, simple, and wrong." That's by Henry Louis Mencken. Hopefully our listeners appreciate that, because there's so many clear, simple, and wrong answers out there. We have a lot to talk about this week.

I'll share with you, Vincent, I guess I'm also sharing with everyone, that I was on this last weekend, and we saw lots of RSV admissions, lots of flu admissions, lots of COVID admissions, and lots of flu and RSV, lots of COVID and flu, COVID and RSV, parainfluenza 3 and COVID. Lots

of folks double-dipping. This week we have the article, “Outcomes of Pediatric SARS-CoV-2 Omicron Infection versus Influenza and RSV (Respiratory Syncytial Virus) Infections,” published in *JAMA Pediatrics*. First off, I was reminded of the piece in *Wired* by Roxanne Khamsi, published back on, yes, February 8, 2020. That was, "Coronavirus is bad. Comparing it to the flu is worse." Well, OK.

VR: [laughs]

DG: We're comparing it to flu and RSV. All right. These are the results of a multicenter, retrospective cohort study that used five population-based data sources and included three pediatric emergency departments in Stockholm, Sweden, covering approximately 500,000 individuals younger than 18. They identified individuals younger than 18 years old attending the ED from August 1, 2021 to September 15, 2022, with a PCR test positive for SARS-CoV-2, influenza A or B, or RSV from one day before to one day after the ED visit.

Multiplex PCR testing of all three viruses was introduced February 2021, and more than 99% of the study population was tested for all three viruses. For the cohort with Omicron, only visits from December 27, 2021 onward were included, a period when Omicron was the dominating variant (greater than 99% of sequences from Stockholm). Now, they excluded patients testing positive for more than one virus. [crosstalk] I guess you can't compare severity, like what's worse? I guess you could say, "What's worse, having more than one?"

They ultimately included 2,596 pediatric patients. We had 34.5% with Omicron. We had 16.4% with the flu. We had 48% with RSV. Of the RSV folks, 77.7% were younger than 2 years, so little kids. 72% with Omicron and 19% with influenza. It sort of gives you a distribution there. Hospitalization rates were 31.5% for Omicron. I want to sort of point that out, pause there for a second, right? Because all the folks about how Omicron is so mild. If you look at these kids, 31.5% for Omicron, 27.7% for the flu, 81.7% for RSV. For infants aged zero to1, the odds ratio for hospitalization was 11.29 comparing RSV to Omicron and 1.67 for flu versus Omicron.

For children aged 2 to 4 years, the odds ratio were 3.96 and 0.31 respectively. For youths aged 5 to 7, the odds ratios were 5.22 and 1.10 respectively. ICU admission rates were 0.7% for Omicron, 0.9% for influenza, and 2.9% for RSV. Three patients died within 30 days with Omicron and one with RSV. Seeing not only the comparison here, just really how serious an issue RSV is by comparison, but just seeing we have children dying of Omicron. We had a child die from RSV. We have all these children ending up in the hospital. All right. What to do? Well, we have the article, “Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants,” just published in *The New England Journal of Medicine*.

These are the results of a pragmatic trial where infants who were 12 months of age or younger, had been born at a gestational age of at least 29 weeks, were entering their first RSV season in France, Germany, or UK, randomly assigned in a 1:1 ratio to receive either a single intramuscular injection of nirsevimab or nothing before or during the RSV season. The primary endpoint was hospitalization for RSV-associated lower respiratory tract infection, defined as hospital admission and an RSV positive test result.

A key secondary endpoint was very severe RSV-associated lower respiratory tract infection, defined as hospitalization for RSV- associated lower respiratory infection with an oxygen

saturation of less than 90% and the need for supplemental oxygen. We end up with a total of 8,058 infants randomly assigned to receive nirsevimab or standard of care. We have 4,037 infants get nirsevimab. 4,021 get standard of care. 0.3% in the nirsevimab and 1.5% - so five times as many in the standard care group - were hospitalized for RSV-associated lower respiratory tract infection, which corresponded to a nirsevimab efficacy of 83.2%.

Very severe RSV-associated lower respiratory tract infection occurred in five infants, so 0.1% in nirsevimab and 19% or 0.5% in the standard care, so another five-fold difference there, which translates into a nirsevimab efficacy of 75.7%. Now, a little different in different countries, the efficacy of nirsevimab against hospitalization for RSV-associated lower respiratory tract infection was 89.6% in France, 74.2% in Germany, 83.4% in the UK. All right, and looking at where are we with RSV, it does look like we're coming down off that peak, so a little good news here, maybe. All right, moving into influenza. OK, not such good news here. The influenza positive tests are going up.

We're now approaching 14%, the number of positive specimens up at about 14,000, so moving, and it's really, we've really come to learn about flu and the way flu spreads through our country, and I'll leave a link into a great site, the cdc.gov/flu/weekly map and you can actually see, you go back to sort of mid-November, we start seeing that activity down in the southeast, Louisiana, Georgia, Alabama, Florida, then it starts moving a little bit up, we start seeing some more activity, and then really you can see it just starting to spread to the rest of the country.

The state is always a little bit behind, so I anticipate in the next week or two we will basically see most of the country turning that dark red. Red is bad.

VR: In many ways, Daniel.

DG: [laughs] It's one of my favorite colors, but it's bad here. All right, COVID, how are we doing with COVID? Not well, unless you're the virus. New cases are up, number of people in the hospital are up, the number of people in the ICU are up, the new deaths are up. New deaths this last week was 1,785. Someone asked the other day, "Oh, I heard there's this new variant, three people died in India." I'm like, "Three people died in India probably per minute."

We're talking about hundreds of deaths a day here in the U.S. The wastewater, if you look at the wastewater, we're not on the way down. Wastewater is climbing. I talked about - A couple of weeks ago, they sort of raised the top bar from 1,200 to 1,500. The Northeast has already hit 1,500. I guess next week they'll have to have an even higher copies per mL of sewage just to allow this to be on the chart.

VR: Daniel, I just want to make a comment about this new variant.

DG: Is there a new variant? Of course, there's a new variant.

VR: Yes, there always is.

DG: There's always a new variant.

VR: The press likes to say, "Oh, it's worse, and it's bad, blah-blah-blah." It's not. It's just more fit, it's displacing the other one. It has no relevance to disease or anything. The only relevance may be if it evades immunity, and that could be a bit of a problem, but there's no - It's about fitness. It has nothing to do with you folks.

DG: [laughs] It is. It is. What a coincidence that the rates go up every December and January, and there's a new variant.

VR: Yes.

DG: Yes. All right. Now, COVID children, other vulnerable populations. This might seem obvious, but the article, "School Absenteeism as a Marker for Community COVID-19 Rates," was recently published in *JPIDS*. Here the authors performed an observational study of North Carolina. It's actually a lot of North Carolina data in this issue of *JPIDS*, looking kindergarten through 12th grade schools participating in the ABC Science Collaborative that offered in-school instruction and contributed severe acute respiratory syndrome coronavirus 2 data for at least two of four weeks monthly in the 2021-2022 academic year.

What an interesting science collaborative. You're going to learn all about science. I'm going to test you for COVID. Additionally, they analyzed publicly available databases including the North Carolina Department of Public Instruction, CDCP COVID-19 Data Repository, and National Center for Educational Statistics. They described community and school COVID-19 infection rates compared with student monthly absenteeism rates to determine if the relationship between community COVID-19 infection rates and student absenteeism varied over time.

They reported for every 1% increase in community infection percentage, they found a 1.68% increase in absenteeism. For every one month change in time, they found a 0.12% increase in absenteeism. Yes, imagine this, when the kids are home sick, the kids are home sick. With COVID on the rise, yes. It's not a disciplinary problem. It's a medical problem. I sometimes worry about that, right? With like, sometimes at the high schools and elementary schools, like when a kid has a medical problem, the first knee-jerk is it's a disciplinary thing, but yes, yes. I mean, kids should stay home when they're sick.

All right. I know that's going to get some comments because that's really out there. What a crazy idea, people like staying home from school or work when they're sick. Anyway, the article, "Impact of the COVID-19 Pandemic on Pediatric Preventive Health Care among North Carolina Children Enrolled in Medicaid," published in *JPIDS*. Here the authors used an administrative claims database from North Carolina Medicaid to evaluate the rates of well-child visits and immunization administration for children less than 14 months of age. They're looking during the pandemic period. They're comparing it to the pre-pandemic period.

They included 83,442 children during the pre-pandemic period, 96,634 during the pandemic period. They're defining the pandemic period here as March 15, 2020 through March 15, 2021, just to point out, during the pre-pandemic period, 405,295 well-child visits and 715,100 immunization administrations were billed. During the pandemic period, that 405,000 dropped to 287,000 and that 715,000 immunizations dropped to 457,000. The rates of well-

child visits dropped about 36%. The vaccine administrations dropped about 45%. Really lower during the pandemic than pre-pandemic, but what do you make of this?

It's a pandemic. Are you taking your child out for a well-child visit? Are you getting those immunizations during this one year? Are you going to kind of wait until after things settle? Or is this just an issue of the anti-science making inroads here? I think we're really going to have to keep an eye on this going forward. A concern is the article that we discussed back in November suggesting that coincident with this are an increased number of exemptions being granted.

All right. Ventilation and transmission. Earlier this month, the article, "Digital Measurement of SARS-CoV-2 Transmission Risk from 7 Million Contacts," was published in *Nature*. Here the investigators analyzed 7 million contacts notified by the NHS COVID-19 app in England and Wales. They found that transmission typically resulted from exposures lasting one to several hours with actually a mean time, a median time of six hours. They found that contact tracing would have identified 80% of contacts if the duration guidelines were one hour rather than that 15 minutes. They found that time and distance were critical factors, and they challenged that 15 minutes within six feet binary.

VR: Daniel, what are the - I don't understand how this works. They have an app, and you say whether you got infected somewhere?

DG: You get notified. I don't know if you used any of these apps during the pandemic, but you could put this app. It was like in New York City. It was sort of weird because it allowed you to anonymously - like if someone had COVID, they could put in like, "I got COVID," and then it would keep track of where you and these other people were, and then it would alert you like, "Hey, you've been around someone with COVID." Right?

VR: Yes.

DG: It was always weird like when you're staying home in your house, Vincent, all of a sudden the alert goes off, and you're like, "Who is it?" It's the one who sheepishly runs up to their room. It's -

VR: Well, it's funny. I did have one of those apps, and in all three years or whatever, I got notified once, and it's like I'm in a high-traffic area. I'm surprised.

DG: [laughs] Yes, that's a little odd, right? That you're like in New York City, in and out of like Columbia and the incubator and yes, but here - Their idea, you get this alert and then you actually get to put information in, figure out who that is. They're going to do contact tracing. Then they're going to figure out, OK, so you got your contacts who are exposed to this person who has COVID and then certain percent of those folks are going to end up getting COVID, right? There are transmission events and then this person is now sick.

Then you look at it and you say, well, 80% of those folks were not just doing this 15-minute, six feet. Eighty percent of those folks were spending at least an hour with that person. You start getting into the subtleties of if you are seven feet away from that person but you're living in the same household, that's an exposure and actually probably more of an exposure than 15 minutes within six feet of someone.

VR: Got it.

DG: All right. Time, distance, a lot of things matter. All right. COVID active vaccination immunity. Every week someone comments about my not spending enough time talking about survivor immunity. They call it something differently. I realize they really are saying they want to hear reassuring things about immunity obtained from prior infection and probably negative things about vaccines, just to be fully honest. There's some good news in this article, also some bad news, but, “Antibody Response and Risk of Reinfection Over Two Years among the First Wave of COVID-19 Patients,” published in *CMI*.

Here the investigators describe the dynamics and factors related with infection alone and hybrid humoral response among the severe acute respiratory syndrome coronavirus 2 and risk of reinfection among first wave patients. A prospective longitudinal study with periodic serological follow-up after acute onset of all recovered patients with SARS-CoV-2 infection cared for at Udine Hospital (March through May of 2020). They look at nucleocapsid, or N protein, and spike receptor-binding domain (S-RBD) antibody tests to distinguish this infection versus vaccine-induced responses. They end up with 153 patients. They're going to follow them for a median of 27.3 months.

First, seemingly the good news, first wave patients had durable humoral immunity in 40% and anti-S-RBD response in 100% up to two years after infection. Remember that, Vincent? When everyone wants it, like what's my antibodies? You almost wanted to know that, your social security number and your antibody levels, because people had this idea, well, if I've got these high antibody levels, well, then I'm going to be OK. Well, then we see reinfections occurred in 16.3% of the patients, mostly during Omicron circulation. Reinfection rates did not differ significantly between SARS-CoV-2 and IgG seronegative and seropositive patients: 15.7 versus 16.1.

Unvaccinated patients had a higher risk of reinfection. "Oh my." This natural survivor immunity, well, maybe it was kind of close. Unvaccinated patients had a higher risk of reinfection at 51.1% versus vaccinated at 14.4. Ooh, that's not even close. The humoral response induced by infection alone was not protective against reinfections with the Omicron SARS-CoV-2 variants, where vaccination actually was effective to reduce the risk of a new infection.

VR: Daniel, this is a two-year study, so people could have been assessed close to vaccination or far from vaccination, and that would impact whether you're infected or not, right? Because if you have low antibodies that go down after months, you're going to get infected, right? I'm not sure what this is telling us, frankly. The N protein, yes, I bet a lot of those people were assayed very long out, and so they didn't have high - You get infected and then you make a memory response and then that prevents severe disease, but you're still going to get infected. Getting infected I don't think is really a useful metric. That's what I'm saying.

DG: Yes. I mean, that's sort of this interesting idea. People have this idea, "OK, I'll get these vaccines periodically, and it'll boost my immunity, and I'll have this period of protection." The other approach seems to be, "I'll just get infected a lot, and then when I get infected, it'll protect me from getting reinfected for a few months."

VR: For a few months, maybe.

DG: But then you got infected to get that protection.

VR: Yes. There's a risk of dying, right? That's not worth it.

DG: Yes. The risk of dying and the risk of hospital. As we know, vaccination compared to infection, it's just - that is a true binary. The vaccinations are incredibly safe, people maybe get knocked down for a few days, but boy. Over this past weekend, actually today, I saw a gentleman, chest tube in, high-flow nasal cannula, non-rebreather, and this is not his first COVID infection, and it's just really a question of, do we involve palliative care? You don't see that after a vaccination.

VR: Yes.

DG: Probably preaching to the choir with our listeners, but maybe they'll air this piece on Fox News for us.

[laughter]

DG: All right. COVID early viral phase. This is an area where we spend a little time, start this section with the *MMWR,* "SARS-CoV-2 Rebound With and Without Use of COVID-19 Oral Antivirals." So much captured here in the abstract. Let's start with that. We read that early treatment with first-line therapy, first-line therapy Paxlovid or remdesivir, or second-line therapy molnupiravir, prevents hospitalization and death among patients with mild-to-moderate COVID-19 who are at risk for severe disease and is recommended by the NIH COVID-19 Treatment Guidelines.

Anyone who tells you otherwise, don't trust them. On May 25, 2023, the FDA approved Paxlovid for treatment of adults at high risk for severe disease. Although antiviral therapies are widely available, they are underutilized, possibly because of reports of SARS-CoV-2 rebound after treatment. To enhance current understanding of rebound, the CDC reviewed SARS-CoV-2 rebound studies published during February 1, 2020 through November 29, 2023. Overall, 7 of 23 studies that met inclusion criteria, one randomized trial, and six observational studies compared rebound for persons who received antiviral treatment with that for persons who did not receive antiviral treatment.

In four studies, including the randomized trial, no statistically significant difference in rebound rates was identified among persons receiving treatment and those not receiving treatment. Depending on the definition used, referring to that, the prevalence of rebound can vary. No hospitalizations or deaths were reported among outpatients who experienced this rebound because COVID-19 signs and symptoms were mild. They conclude by saying the potential for rebound should not deter clinicians from prescribing life-saving antiviral treatments when indicated to prevent morbidity and mortality from COVID-19.

VR: I would agree, [crosstalk]

DG: How many times? All right. We've got a second *MMWR*, "Evaluation of SARS-CoV-2 RNA Rebound After Nirmatrelvir/Ritonavir Treatment in Randomized, Double-Blind, Placebo-

Controlled Trials - United States and International Sites, 2021–2022." Here, viral RNA, they say shedding data, from two phase 2/3, randomized, double-blind, placebo-controlled clinical trials of nirmatrelvir/ritonavir. This is the Evaluation of Protease Inhibitor for COVID-19 in High-Risk Patients (EPIC-HR) and Evaluation of Protease Inhibition for COVID-19 in Standard Risks, that's the EPIC-SR, were analyzed to investigate the role of Paxlovid treatment in COVID-19 rebound.

Rates of rebound of SARS-CoV-2 RNA shedding, identified based on an increase in nasopharyngeal viral RNA levels from day five of end of treatment to day 10 or day 14 were similar between Paxlovid and placebo recipients. Among patients with a virological response through day five, viral rebound occurred in 6.4 to 8.4 in the Paxlovid, 5.9 to 6.5 of placebo across HR and the 2021 pre-Omicron and 2022 Omicron enrollment periods. Viral RNA rebound after Paxlovid was not associated with COVID-19-related hospitalization or death.

Data from randomized trials demonstrated that SARS-CoV-2 rebound can occur with or without antiviral treatment, supporting the FDA's determination of safety and efficacy of Paxlovid in eligible patients at high risk for severe COVID-19.

All right, why do I spend so much time talking about our most effective tool after vaccines? Well, the article, "Oral COVID-19 Antiviral Uptake among a Highly Vaccinated U.S. Cohort of Adults with SARS-CoV-2 Infection Between December 2021 and October 2022," was recently published in *Open Forum Infectious Diseases*. We read that between 12/2020 and 10/2022, Paxlovid uptake was only 13.6% among 1,594 participants and molnupiravir uptake was 1.4%.

The highest uptake in this study was among those age 65 and over, that was about 30%, which is similar to a study conducted in Massachusetts and New Hampshire. Only about a third of the eligible participants with SARS-CoV-2 infection in this study, over 65, received Paxlovid. Usage does seem to be slowly increasing, but we have a long way to go. I want to point out, we are seeing over 200 deaths a day. As the Surgeon General pointed out, as I'm going to point out, these are mostly preventable.

The article, "Azvudine and Nirmatrelvir-Ritonavir in Hospitalized Patients with Moderate-to-Severe COVID-19: Emulation of a Randomized Target Trial," was just published in the *Journal of Medical Virology*. We've talked about azvudine before, right? It's that Chinese drug, that pro-drug that can be intracellularly converted into FNC triphosphate. It's a nucleoside analog and it gets incorporated into the RNA and it's chain-terminating. Think of some of our HIV drugs, have a similar mechanism.

Well, these results from a target trial with a multicenter retrospective cohort of hospitalized patients. These are hospitalized patients with moderate-to-severe COVID-19 without contraindications to getting the drugs. This is between December 1, 2022 and January 19, 2023. The primary composite endpoint (all-cause death and initiation of mechanical ventilation) among 2,262 patients admitted to non-ICU departments with confirmed moderate-to-severe COVID-19 around hospital admission. The primary analysis included 1,154 participants. We end up with 311 receiving the azvudine, 165 Paxlovid, 678 not getting any treatment.

Of the 1,154, 27.2% were severe cases. In the intent-to-treat analysis, azvudine reduced all-cause death by about 69% and its composite with invasive mechanical ventilation. Paxlovid reduced mechanical ventilation by about 58% and its composite with all-cause death by about 62%, so pretty effective. I will say of note, the median days from symptom onset to receiving treatment was actually eight days. This was a little bit long. This was a little bit late. Still seeing some pretty impressive data even when you've sort of missed that first five days.

Hypertension affected 37.3% of participants. About a quarter of the folks had diabetes, about one in five with cardiovascular disease, about 10% with COPD at baseline, these were sick folks. Eighty-six percent were receiving respiratory support when they were started on the antivirals. Most of them were getting antibiotics; 25% got anticoagulants, probably low. Remember, this is China. About 7% were getting NSAIDs. About 48% were treated with steroids. I would expect that number to be higher. This is really a study in vaccinated folks.

As I will point out, over 90% of Chinese adults have been vaccinated before December 2022, so these likely represent the effect of these two drugs in vaccinated, hospitalized people. The advantages for azvudine is it's a 5 mg tablet once a day, five days, no renal adjustments, minimal drug-drug interactions. Currently, we have Paxlovid. Be nice to have this second option. Number two, we have remdesivir. Number three, as we talked about, NIH guidelines, second-line therapy molnupiravir. For some folks, convalescent plasma. Let's avoid doing those harmful things.

Now, what about week two? That's actually what we were talking about in this, even though we're jumping in with the antivirals. That was a little bit late. Like to jump in with those the first week. If people progress, end up in the hospital. Steroids at the right time. Anticoagulation guidelines, pulmonary support. Remdesivir, if we're still in the first 10 days. Immunomodulation, possibly with tocilizumab. Avoiding those unnecessary and unproven therapies.

Here, I'm going to say it's important to publish and share negative data. There was an august hospital healthcare system. I'm not sure how to refer to it, but I'll just leave it there. One of our premier academic centers where the standard of care was to give everyone statins. Well, I think sometimes when we get the data, it helps shape our perspective and perhaps even provide us with a bit of humility.

The article, “Simvastatin in Critically Ill Patients with COVID-19,” was published in *The New England Journal of Medicine,* more from the REMAP-CAP Investigators. These results are from the ongoing international, multifactorial, adaptive platform, randomized controlled trial where they evaluated simvastatin (80 mg daily) with no statin in critically ill patients with COVID-19 who were not receiving statins at baseline.

The primary outcome was respiratory and cardiovascular organ support-free days, assessed on an ordinal scale combining in-hospital death and days free of organ support through day 21 in survivors. On January 8, 2023, enrollment was closed. The median number of organ support-free days was 11 in the simvastatin, seven in the control group. The posterior median adjusted odds ratio was 1.15 for simvastatin as compared with controls. Serious adverse events such as elevated levels of liver enzymes and creatine kinase were reported more frequently with simvastatin than with control.

You can sort of look at actually the organ support-free days. By the time you actually follow it out, you can basically see that the two lines overlap. Really not supporting the universal start of statins in these critically ill folks. All right, and we're going to get here to the late phase. This keeps coming up, so let me discuss the, “COVID-19 mRNA Vaccination Reduces the Occurrence of Post-COVID Conditions in U.S. Children Aged 5-17 Years Following Omicron SARS-CoV-2 Infection, July 2021-September 2022,” published end of November in *OFID*.

When this first came out, I sort of spent a little time looking it over, and people kept asking. I thought, well, let's go through it. These results are from a multi-site cohort of children enrolled July 21, 2021 through Sept. 1, 2022, who underwent weekly SARS-CoV-2 screening tests and were surveyed via self or parental report regarding post-COVID conditions (defined as greater than one new or ongoing symptoms lasting greater than one month after infection).

They did this multivariable logistic regression to estimate the occurrence of post-COVID conditions by vaccination status among children aged 5 through 17 whose first PCR confirmed SARS-CoV-2 infection occurred in-study with Omicron variant who completed the survey greater than 60 days from infection and who were vaccine age-eligible at time of infection per ACIP recommendations.

Vaccination status was characterized as vaccinated (at least primary series completed greater than 14 days before infection) or unvaccinated. Vaccination status was verified through vaccine registry and medical records. A few things here, is this really PCC? We're talking about greater than 60 days. We're talking about symptoms going more than a month. It's not technically PASC, but these are things continuing post-acute COVID. Of 622 participants surveyed, 5% met this criteria for PCC; 67% were vaccinated. Surveys were completed a median of 203.7 days after infection.

When they compared children with or without post-COVID conditions, COVID-19 mRNA vaccination was associated with a decreased likelihood of greater than one post-COVID condition symptom, 44% reduction. Greater than two, 48% reduction. Respiratory post-COVID symptoms, 47% reduction. I'm going to wrap it up there with our - before we get to our letters, as I've been saying for, well, almost four years, Vincent, no one is safe until everyone is safe.

We are getting near the end of our MicrobeTV fundraiser, where for the months of November, December, and January, we will double your donations up to a potential maximum donation of $20,000 to keep the lights on at MicrobeTV and all the other equipment. Go to parasiteswithoutborders.com, click on the ‘Donate’ button, and help us continue to do what we do and help us continue to support MicrobeTV.

VR: Thanks everyone for your support. Greatly appreciated. Lets us continue to do good science reporting. Time for your questions for Daniel. You can send them to daniel@microbe.tv.

Eric writes, "I've recently heard an eminent epidemiologist talk about how even norovirus is spread heavily via respiratory transmission, and it got me wondering, what does the research say about transmission via surfaces for most of the viruses common during the winter

months? Is it theoretical or proven? It seems clear that SARS-CoV-2 is passed overwhelmingly and perhaps exclusively via respiratory pathways, and the flu as well as the common cold have intriguing studies pointing to strong transmission via that pathway as well. Is it possible the medical establishment's appropriate focus on hand hygiene for bacterial and other contamination mitigation has contributed to confusion around the primary vector for most of seasonal respiratory pathogens? Thank you."

DG: I think this is great. You're always looking for what's going to be the silver lining that comes out of the pandemic or the many silver linings. One of them is hopefully that after 100-plus years, people are going to really say, let's talk honestly about the science behind all this transmission, right? We talked about, going into the pandemic, about this whole concept of droplet and the three to six feet, and it's sort of funny that the history of people gargling with Serratia and seeing like how far away it ends up on Petri dishes.

We really have a great amount of science on SARS-CoV-2 transmission. We just even talked a little bit more about how - there's no binary at six feet. Things are, they have to do with, it's like gravity, right? How far away, but then how much time you spend in that zone is going to be this cumulative thing. Now, norovirus certainly, and we have great examples of this on cruise ships where if someone vomits and then it actually gets sucked in through the ventilation system and circulated and you end up getting norovirus and you're not even in the same cabin with the vomiting person. There is in most cases a little bit more complexity to the transmission.

I am looking forward to updated CDC guidance on this. Remember, the CDC guidance is not going to be education for the public. It's going to be about what we do in healthcare settings, what we do in hospitals. Certain amount of things actually are transmitted through contact. SARS-CoV-2, not so much actually, but other certain, as we think of respiratory infections, you actually can acquire them by touching things and then touching your mouth, your eyes, your nose. The science for SARS-CoV-2 is fantastic. If you go back in history, it took a long time to even convince people that things like measles and particularly tuberculosis could be spread rather than just within that defined "contact of three to six feet."

VR: Marianne writes, "My grandbaby and her parents are recovering from COVID, but not in time for a Christmas visit. What's the protocol for being cleared to have elders visit? Adults had Paxlovid and had been vaccinated."

DG: I'll hit on this again, and this is great. This is, again, sort of when am I infectious, et cetera. The first five days, that's when people are the most infectious. That's when we see, and we talked of another transmission study there. That's when you're in that suburban home. It's the first five days. People are talking, they're singing, they're coughing, they're breathing. The virus is actually being exhaled. Once you get past day seven, really minimal transmission. It's really 10, is kind of the full. We talk about five days being the most contagious, and then day six through 10, a really rapid decrease in the risk of transmitting to others.

VR: Brian writes, "Working in a busy ED, I had a patient come in with seizure-like symptoms. The patient was recently prescribed Paxlovid, was on day two of the treatment. This patient had also ingested several THC gummies, and then several hours later had seizure-like symptoms. Any literature or guidance for this interaction?"

DG: OK. The THC, there is guidance here, Vincent, I don't know - I'd always worry when I start talking about the cannabinoids. People are going to realize that I spent too much time in Colorado and wonder why I know so much. Yes, so cannabis, actually the psychoactive component, the THC, is metabolized in several ways. There's some conjugation and excretion in the urine. There's actually some P450 metabolism in the liver. It's actually CYP2C9 mainly. There's only a minor part that is CYP3A4, but there is a component that's CYP3A4, so your ritonavir in your Paxlovid can actually increase your THC concentration.

You never know when someone said they just took two or three gummies, how many gummies they really took. Actually, it is in the guidance. If someone is a significant cannabis user, it can increase the THC concentrations, and actually elevated THC concentrations can reduce your seizure threshold.

VR: Louise writes, "I'm a family doctor from suburban Philadelphia, and I ask how soon can one give a second dose of Paxlovid? The patient took it in August, then had a second infection less than three months later. Her insurance said they would not pay for Paxlovid twice in fewer than 180 days. Any comments on the need to take it again and the payment? Thanks."

DG: Yes, that's annoying. When was the last time you heard people say good things about those health insurance companies? Ouch. OK. You can take and you should take Paxlovid as often as you get COVID. If you're a high-risk individual and you get COVID on November 1, and then you recover and then you go to that big party, and now December 1, you're sick again and you've got COVID and you're a high-risk individual, you should not limit your amount of Paxlovid you take. You should go ahead and take the Paxlovid again.

This reminds me, when they were trying to decide how many pills of Viagra do you get a month, right? Yes. The idea that the insurance company is going to limit the number of times that you can get appropriate, effective, NIH-recommended licensed drug treatment by withholding the payment when you've actually enrolled in a medical plan as part of your insurance. It's just wrong, and people need to push back against that.

VR: Jay writes, "I would appreciate it if you would address any research that does or does not support the use of these anti-COVID nasal sprays I've seen on the market. Nitric oxide is cited as the active ingredient. I know some folks who have come to rely on these as their COVID precautions in crowded, high-risk situations like cruises and mass transit. If there is evidence that this stuff works, I'm very interested in getting some, but it sounds too good to be true. I also realize that it's possible that in addition to being ineffective against SARS-CoV-2, they may cause harm. If you can point your listeners to reputable data about these, it would be helpful."

DG: Yes, so I'll start off with just the elevator, what you need to know, is we have yet to have any of these nasal sprays be really validated, compelling evidence that they work. They're being studied. There's ongoing trials. There's a study here or there that is interesting and encouraging, but we do not know. It's actually amazing, what people are spraying up their nose. If you've ever looked, Vincent, like you go ahead at some point in Google, like anti-COVID-19 nasal sprays, and people are spraying Betadine up there.

There's these nitric oxide things they're spraying up there. There's like a whole bunch of concoctions. Yes, you shouldn't be spraying stuff up your nose unless there's some compelling evidence that it is a helpful thing to be doing. Yes, just the state of the art right now being studied. We're looking into it. One day, maybe there will be something that is recommended based upon compelling science, but right now, it's still in the snake oil. There's people selling stuff without being sure whether or not it's helpful or harmful.

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

DG: Oh, thank you. Everyone, be safe and enjoy the holidays.

[music]