This Week in Virology

TWiV 1098 Clinical Update

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Aired 23 March 2024

pdf of this transcript available (link)

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 1098, recorded on March 21, 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: It's the third night in a row I've seen you, Daniel.

DG: I know. You and I are spending a lot of time together. [laughs]h

VR: Yes. Tuesday, New York Yacht Club to hear Craig Venter. Yesterday, office hours, and now, *TWiV* clinical update. Each time, a different bow tie. Let's see. No, I just can't see you. I don't know what you have there.

DG: Anthrax. I've got a couple anthrax bow ties.

VR: Oh, you're a fan of anthrax, eh?

DG: I like anthrax. It's an interesting disease.

VR: Someone on the live stream last night said they appreciate that I ask you what's on your bow tie because they like to find out.

DG: All right. Let's jump into it. We've got a lot to talk about today. Let us start with a rather lengthy quotation. "If, as a culture, we don't bear witness to grief, the burden of loss is placed entirely upon the bereaved, while the rest of us avert our eyes and wait for those in mourning to stop being sad, to let go, to move on, to cheer up. If they don't - if they have loved too deeply, if they do wake each morning thinking, I cannot continue to live - well, then we pathologize their pain; we call their suffering a disease. We do not help them: we tell them they need to get help."

That's from Cheryl Strayed from *Brave Enough*.

Let's move right into measles. Second week in a row that we're talking about measles. Last week, we discussed measles. This week, we have the *MMWR Notes from the Field*, "Measles outbreak - Cook County, Illinois, October-November 2023." I think this is a very interesting article when it comes to thinking about measles and transmission. Let's go through this. Now, during October 5 - November 1, 2023, five measles cases occurred in unvaccinated, vaccine-eligible children aged one to nine years who lived in the same apartment building but did not socialize with one another.

During the outbreak, approximately 400 persons were exposed to measles, including 13 children aged less than 1 year. I mentioned aged less than 1 year because here in the U.S., that's when we start our measles vaccination series in general. Sort of with things like this, I'm wondering if we need to start moving that to 6 months as we recommend for travelers. Here's the story. I know people will be thinking about how this virus spreads. October 10, 2023, the Cook County Department of Public Health in Illinois was notified by hospital A, a large pediatric facility, of a suspected measles case in a child aged 2.

This is patient A at hospital A. Now, this patient had immigrated from Yemen on September 29 and had no history of receipt of the MMR vaccine. The child visited hospital A's emergency department on October 5 with fever, cough, coryza, basically runny nose, and after receipt of COVID-19, influenza, and RSV test results, received a diagnosis of an unspecified viral illness. Just imagine how often this is happening every day, how many of these cases can so easily be missed. On October 8, the child visited hospital B's emergency department with worsening respiratory symptoms and received a positive rhino/enteroviral test result on a respiratory pathogen panel.

Now we know what's going on. After which the child was transferred back to hospital A and admitted for respiratory distress, bronchiolitis, underlying reactive airway disease. I don't know if people are thinking, the next day, right? So far, so good. No rash. The next day, the child develops this characteristic maculopapular rash. On October 10, this is two days after October 8 when they go to hospital B's ED. The child's family mentioned, by the way, before we got here, this child was exposed to someone with a clinical diagnosis of measles.

Measles is tested for, and on October 11, we get a diagnosis of measles. Just think about all the time that goes by here. We've got first visit to the first emergency room. Then we have the visit to the second hospital. Then we have transfer back to the first. Then we have this child in the hospital. Everyone thinking, oh, it's just a common cold. Then we find out this is a child with measles. It doesn't end there. It goes on. During the child's October 5 through 11 healthcare encounters, ends up with 247 healthcare workers and 177 patients and patient companions end up getting exposed.

I mentioned 13 children less than 1 year of age, five immunosuppressed children, one child aged over a year, but no vaccine, no history of MMR vaccination. This indexed patient's household contacts include two siblings, also no MMR vaccination. When they do serological testing, they're susceptible to measles. One sibling aged 4, we're going to call this patient B. Can you imagine why? They arrived in the U.S. at the same time as the indexed patient. We've got another sibling aged 9. That's going to be patient C. Both siblings end up developing measles.

Now, October 30, hospital A notifies the Cook County Department of Health that another child aged 2, now up to patient D, who was evaluated in the ED, fever, cough, coryza, then discharged. The family of that child lived in the same two-story apartment building as the indexed patient, but on a different floor. Patient D had no history of MMR vaccine. The child's parents reported objections to MMR vaccine based on personal beliefs, perceptions about vaccine side effects. Measles was confirmed in this child by PCR testing on the 30th. The rash doesn't develop until November 1. The families of patients A through C and patient D had different cultural backgrounds from one another, spoke different primary languages.

Both families reported no contact with the other family. Their apartments did not have shared ventilation. On October 31, testing was also performed for a sibling of patient D. Now we've got patient E, also with measles. Again, another child with no vaccination who had just isolated runny nose and was attending a child-care facility. Just this string of events of what happens here. Just the degree of transmission and the special status, I guess, we talk about with airborne, where not even in the same apartment, not even on the same floor, just being in the same building, seeing this transmission going on to the unvaccinated.

VR: Daniel, in the very beginning, they missed the diagnosis, that first ER visit. What should they have done?

DG: That's the really tough thing. It's like, how are you supposed to be thinking about this? Probably is a slightly better history. Here is a child who just arrived from Yemen. You got to be thinking, make-believe I'm in Yemen and I've got a child coming in with a rash, at this point not a rash, but fever, cough, runny nose, you might want to ask, so you're from Yemen. Any exposures to things I should be thinking about? You don't just treat this like a local child. Now we're going to have to start thinking about measles as part of our local milieu.

VR: Isn't measles virus part of the respiratory panel, like the BioFire Panel?

DG: It's not. not. What we're doing in a lot of facilities, and it looks like this is what happened at hospital A, we do this quad multiplex PCR testing. We're only looking for, as we saw here, we're only looking for COVID, flu A, flu B, and RSV. If those are negative, we say it's all we need to know. Moving on here. Then they go to hospital B where they actually do a broader respiratory pathogen panel where they pick up the entero rhinovirus. They put those together, same primers. No, measles is not on there. You got to be thinking separately and adding measles to your differential.

VR: Do you think that's the right way to go about this, or should we add -

DG: It's financial if you think about it.

VR: Of course.

DG: If you added a measles PCR to every workup of the child, we're talking about millions and millions of dollars.

VR: Now the cases are still pretty rare, but if we're in the middle of a huge measles outbreak, which could happen, then maybe we should do it.

DG: We're already up to, just landmark, we've already seen as many cases, diagnosed as many cases this year as we had all of last year. It's only March. It's really a challenge. Because so many clinicians, so many people are taught rash with fever, a febrile illness with rash. As we're seeing here, this transmission and this illness, the rash often comes later on when the immune system kicks in. A lot of transmission occurs before we even see that. Now, addressing the question, Vincent, you and I discussed last week, why? Why are we having a problem with measles?

We've got the article, "Measles Surge Driven by Gaps in Routine Vaccination Following COVID-19 Pandemic," published in the *Infectious Disease Advisor*. This isn't really as much a journal as a - I don't know exactly what you would call this, but they echo our concerns that this surge is being driven by largely unvaccinated U.S. travelers transmitting the virus to other unvaccinated individuals after returning home from countries where the virus is circulating. The case we read was about someone coming from Yemen, but a lot of times we have a U.S. citizen heading off, visiting the world, coming back, bringing back measles.

Measles diagnoses have also increased in the U.S. and globally because of disruptions in routine vaccination following the COVID-19 pandemic. In this article, they point out that - and I think these are numbers people have been asking about - up to 30% of children infecting with measles experience some degree of complication. Diarrhea, ear infections that can lead to permanent deafness, pneumonia, encephalitis. Moreover, approximately 25% of infected children require hospitalization. Interesting, right? Because was that what we experienced when measles was more common?

Are we doing this because it's measles and that's triggering the hospitalization? A big number here. Each hospitalization can cost over $100,000. This is something I talk about. People are like, oh, it's my choice whether or not I want to vaccinate my children. Yes, who's going to pay that bill, that $100,000? Forget about who's going to take care of these children who may end up with permanent deafness, who may end up with cognitive issues after inflammation of their brain. Now, MMR vaccination uptake is recommended to be 95% or higher to reduce the risk of transmission. To give a sense where are we in 2022? Only 83% of U.S. children were vaccinated against measles.

VR: That's bad.

DG: It's not good. I'm going to leave in a link here to the ID Society has a nice page, "Measles and Misinformation: The Impact on Public Health." This is one of those issues where we really need to do a much better job of information because there's plenty of people out there doing the misinformation. Now, we also got an alert from the CDC, “Increase in Global and Domestic Measles Cases and Outbreaks: Ensure Children in the United States and Those Traveling Internationally 6 Months and Older are Current on MMR Vaccination.” Just to mention, this is a recommendation.

Instead of waiting to 12 months of age, if you're going to be traveling internationally with a child between that 6 months to 12 months, you actually want to accelerate and get that measles vaccination at 6 months. Ideally, you can get a second one in before you go on your travels.

Now we have Mpox. We hadn't talked about that in a while, but we have news of Mpox in the Congo. I don't know, Vince, maybe I'm dating myself, it made me think of the Billy Joel song. *We Didn't Start the Fire*, but I don't know if this is because I'm a New Yorker, I used to live in Oyster Bay, I'm not sure.

We can read about this in the Rapid Communication in *Eurosurveillance*, "Ongoing Mpox Outbreak in Kamituga, South Kivu Province, Associated with Monkeypox Virus of a Novel Clade I Sub-lineage, Democratic Republic of the Congo, 2024." They throw Mpox and monkeypox in the same sentence. It's recommended that we not use monkeypox because of some racial concerns. Just bringing that up in your title, by the way. We can get more updated numbers from the WHO that there are over 14,000 suspected cases with over 600 deaths so far. You know what, people said, oh, Mpox, at least you're not going to die of it.

Four-point-five percent case fatality rate. Actually, Agam Rao, MD, of the CDC's U.S. Public Health Service, actually suggests that the CFR might be closer to 7.4%. A case fatality rate of 7.4%. I will point out important distinction perhaps between Clade I, as we're seeing here, and Clade II that spread through Europe and the U.S. During the 2022 Mpox outbreak, there were 1.3 Mpox-associated deaths per 1,000 cases. That gives us a CFR of less than one. It was 0.13. Quite a bit different. Forty deaths in total, as opposed to here where we've already seen 600 deaths so far. Not clear how much of that is a racial background, is an environmental background, is a nutrition, general health background, is a treatment access versus really Clade I versus Clade II intrinsic.

VR: By the way, Daniel, we got an email from a pox virologist in South America. She said, "The disease has been renamed Mpox by WHO for the reasons you stated, but the WHO does not control names of viruses. That is controlled by the International Committee on the Taxonomy of Viruses, the ICTV, and they choose to use monkeypox virus."

DG: That's helpful. We think we get to make all the decisions, but no, there's this international taxonomy group that meets, and as we learn more and more, things keep changing. RSV: This may be the last time we talk about it for a while because we really have come out the other side. Numbers are really, really down for RSV. Good news there, but not so good for flu. Influenza-positive tests are actually sitting pretty high. This is an interesting pattern that we've seen every so often. The classic is influenza rates go up, stay up for a period of time, and then they come down.

Sometimes we get a second hump. Sometimes, a few years back, we had this three hump, and that looks like we're headed towards that this year. We had an early peak, got a little better, had another peak, started to get a little better, and now we're headed towards a third peak this season. Again, it's regional. If you look at the maps, New York City is a little bit better than it was last week. Michigan is a little bit better than it was last week. Ohio, not so great. Nebraska, a few others. Part of what we're seeing here is also regional also. Check your local flu levels.

COVID. We keep saying things are going to get better, but we're still looking at over 13,000 in hospital. We're looking at average new deaths still over 200 deaths per day. It's starting to come down a little bit. Wastewater looks encouraging. I'm just waiting to see that translate into less folks in the hospital, less new deaths.

A few things to talk about this week with children and other vulnerable populations, really children. This week, we have the *MMWR*, “Notes from the Field: Surveillance for Multisystem Inflammatory Syndrome in Children - United States, 2023."

Just a reminder, the multisystem inflammatory syndrome in children is a particularly serious inflammatory condition that can occur two to six weeks after SARS-CoV-2 infection. It often involves the heart, the brain, the eyes, the lungs, other organ systems. This report describes the 2023 MIS-C cases and compares them with cases reported earlier in the COVID-19 pandemic. There were 117 cases, which the CDC suggests is only a subset of actual cases due to underreporting. Among the 117 MIS-C patients with illness onset in 2023 - deep breath - 58% had no underlying medical conditions.

We talked about last week how over 100 children have died of flu so far this year. To all apparent, they seemed completely fine. Same thing here. The majority of these children were otherwise healthy until this developed. Half of them required ICU-level care; 34% experienced shock, 27% experienced cardiac dysfunction. Three patients died. Three of these children did not survive. They made it through the acute COVID, but then during this multisystem inflammatory response, three of these children died. Ninety-six percent of the patients were age-eligible for COVID-19 vaccination; 82% had not been vaccinated.

Only 18% had actually gotten that COVID-19 vaccine, which I shall mention reduces the risk of this developing substantially. Among the 48 vaccine-eligible patients with underlying medical conditions, 19% had documented receipt of any COVID-19 vaccination. Among the 20 patients who had received COVID-19 vaccination, 60% received their last dose greater than 12 months before the onset.

Another one, maybe they're reminding people, this week we have the article, "Guidance for Prevention and Management of COVID-19 in Children and Adolescents: A Consensus Statement from the Pediatric Infectious Diseases Society, Pediatric COVID-19 Therapies Task Force," published in *JPIDS*.

I know I bemoan all the folks that don't follow the guidance for adult care, but it may be worse here. This is a nice article for all our pediatricians to look at. What is the guidance? Hopefully I've just reminded folks that children cannot only die from COVID-19, not only can children end up in the hospital, not only can children end up with Long COVID, we might get to that, but also we can have this multisystem inflammatory issue. Here they have a bunch of nice figures where they really guide you through what to do here and how to re-stratify these children.

As mentioned, remember, a lot of those folks that ended up with the multisystem inflammatory issue, they actually were completely healthy and probably would have ended up with low risk on this structure. They talk about some of the definite and probable risk factors that are associated, a really nice Figure 2, and just the odds ratio if there's an underlying cardiovascular or neurological, or seizure disorder, those can really have a high effect upon your risk of progression. Then when you start adding up more than one. Then they go through, basically, how to approach this.

Really striking is they're actually recommending treatment for those individuals that are at risk of progression. One-hundred-eighty-six references, so all very evidence-based. We'll leave in a link for folks to take a look at that.

Moving into COVID, early viral phase. We just had the treatment guidelines there from *JPIDS*. We also will leave in a link to the NIH COVID-19 treatment guidelines that were just updated on February 29th. Paxlovid, remdesivir, molnupiravir, convalescent plasma in some situations. Again, we'll leave links to the updated CDC's respiratory virus guidance, what to do when you are sick.

A little bit new here in week two. We have, number one, steroids at the right time in the right patient at the right dose. Number two, anticoagulation guidelines. Got some new ones coming out from American Society of Hematology. That's, I think, about all I'm allowed to say, but just I approved the manuscript. I think it looks good. Number three, pulmonary support. We have the article, "Lower versus Higher Oxygenation Target and Days Alive Without Life Support in COVID-19. The HOT-COVID Randomized Clinical Trial," published in *JAMA*. I like the title, the HOT-COVID title there.

These are the results of a multi-center, randomized trial where 726 patients in 11 ICUs in Europe with COVID-19 and severe hypoxemia were randomized to different targets. At 90 days, the median time alive without life support was 80 days in the lower oxygen group, and 72 days in the higher oxygen group. Death rate at 90 days was 30% in the lower oxygen group and 34.7% in the higher oxygen, giving us a risk ratio of 0.86, but overlapping confidence intervals. Let us not just get the headlines on this. Let's actually take a little closer look. There's a nice editorial on the study, which I think help tease apart what are we seeing, what might've happened here.

We have an editorial, “Oxygen Supplementation in COVID-19 - How Much is Enough?” Here, Richard M. Schwartzstein, MD, up at Harvard, writes that the less-is-more finding could be explained by a number of factors. More patients in the high-target group could have been intubated and started on mechanical ventilation because physicians could not achieve the target with noninvasive ventilation. Also comments that the observation that initiation of mechanical ventilation to achieve a high target PaO2 may have occurred is less a failing of the study design than a consequence of using a high PaO2 target.

A little concerning that this sort of study may have actually triggered unnecessary intubations to get people at this higher level. Not really clear to me that it was really the goal, higher level, or the forcing of perhaps some unnecessary intubations here and affecting these outcomes. We also have remdesivir still in the first 10 days, immune modulation.

I will move to a couple nice studies here in our Long COVID section. The article, "Prevalence of Orthostatic Intolerance in Long COVID Clinic Patients and Healthy Volunteers: A Multicenter Study," was published in the *Journal of Medical Virology*.

Perhaps a little bit of confirmation bias for what many of us treating Long COVID patients are seeing and doing in this article. Here, the authors investigated the prevalence of objective orthostatic intolerance in patients attending Long COVID clinics and healthy volunteers. They also looked at associations with OI, orthostatic intolerance symptoms, and comorbidities.

Participants with a diagnosis of Long COVID were recruited from eight UK Long COVID clinics and healthy volunteers from general population. All undertook standardized National Aeronautics and Space Administration Lean testing.

NASA Lean testing. Participants' history of typical OI, orthostatic intolerance symptoms, dizziness, palpitations before and during the NLT, the NASA Lean Test, were recorded. Two-hundred-seventy-seven Long COVID patients and 50 matched healthy volunteers were tested. Healthy volunteers had no history of these OI symptoms or symptoms during the NASA Lean test or PoTS. One-hundred-thirty, so 47%, just about half of the Long COVID patients had previous history of the OI symptoms; 52%, so about half, developed symptoms during the NASA Lean Test. Fifteen percent had an abnormal NASA Lean Test; 7% met criteria for PoTS, and 8% had orthostatic hypotension.

Of patients with an abnormal NASA Lean Test, 45% had no prior symptoms. When they relaxed the diagnostic threshold for POTS, they actually got to about 11% of the Long COVID patients pulling an additional 4%, but not pulling any of the healthy controls. More than half of the Long COVID patients experienced the orthostatic intolerance during the NASA Lean Test. More than one in 10 met the criteria for PoTS.

The investigators conclude by recommending that all patients attending Long COVID clinics are offered a NASA Lean Test, and appropriate management commenced. I'm going to make that a little bit broader. This may even be like a way for folks to screen, if they're concerned about, the diagnosis or not. I just wanted to spend a little time maybe sharing what is the NASA Lean Test? I was going to have you demonstrate for us, Vincent, but don't worry, I won't have you do that.

VR: I can pass it. It's no problem.

DG: You can pass. All right. It takes a little time. In the NASA, I always tell the people to buy one of those automatic, battery-powered sphygmomanometers, blood pressure machines. What you do is you put it on your arm. It's great if someone will help you with this. The participant is going to lie quietly for two to three minutes. You're going to get a couple readings while they're laying down. I often tell them just to get one. I don't want to overburden them because I'm going to make them do this a few times between appointments.

Record the pulse. Record the blood pressure. Maybe even ask someone, comment, how are you feeling? Then the participant slowly stands up. Don't jump up. We're not springing no acrobatics. You're going to stand up slowly. Now you're going to stand with your shoulders leaning against the wall for support. You're not slumping. You're really just leaning a little bit. What you're trying to do is hold the feet still about 15 centimeters from the wall. About 10 inches or so. Then you're going to do six further readings at about one-to-two-minute intervals. Basically pushing the machine, waiting, getting the numbers. You got to stop this prematurely if the participant has symptoms which really make it unable for them to complete it. They're like, I don't feel well. I feel like I might be dropping down. If you can do this for the full 10 minutes, that's great. Then you're going to look for any of these issues. Orthostatic intolerance is going to be, you have dizziness, lightheadedness, palpitations, chest

pain, tremulousness, and they get worse. Then improves, gets better when you lay back down.

The orthostatic hypotension is actually going to be when you have a fall in the systolic. That's the big number. Blood pressure within the first three readings of at least 20, or the diastolic, the low number falls by at least 10. This is with or without acute symptoms. The orthostatic tachycardia, it's a little bit easier, when you do this, is the heart rate just going to shoot up? A little higher threshold, 30 beats per minute. Maybe requiring this to be sustained a couple times depending upon your threshold. Then they go through a number of different other criteria you might be looking for.

I should mention the work that we're discussing here was part of the LOCOMOTION, the Long COVID Multidisciplinary Consortium Optimizing Treatment and Services across the NHS. It's a 36-month multi-site case study of 10 Long COVID clinics. Eight were participating in this sub-study. This was started back in 2021 and seeking to optimize Long COVID care across the clinics. One of the things I like about this is it's very objective. Patients can't stand up, and I'm going to voluntarily crank my heart rate up 30 points. I'm not going to drop my systolic blood pressure by 20. It takes a lot of the subjective out of it and gives us, I'll say, more objective validation for what these folks are experiencing. Also, we have a history of knowing how to treat people with orthostatic intolerance. We can actually start addressing this issue in a lot of these folks.

VR: Why does COVID exacerbate this?

DG: The whole idea is something about the post-COVID syndrome impacts the autonomic nervous system. Now, the exact mechanism, we're not sure about. We're seeing issues here with, normally when you stand up and the reason we're standing, relaxed legs, not moving, we don't want the muscles helping with venous return, you're expecting the autonomic nervous system to constrict the peripheral nervous system, peripheral vascular system. We made the tank smaller so that we can still get blood supply to our brain. Here is really objective evidence that we're having some autonomic dysfunction.

VR: I would suspect this is probably post-inflammatory, right?

DG: A lot of these individuals don't necessarily have this in that first week. A lot of times we see this develop two to three weeks, or even farther after the acute. It's not just COVID. We saw this in a lot of other post-infectious sequelae. Nice to have validation. We've been seeing this, we talk about it, but as I like to say, the plural of anecdote is not data. Here we've got data. Not only do we see deaths, hospitalization, and MIS-C, but we have ongoing issues with Long COVID in children.

What about autonomic issues in children? We have the article, "Autonomic Cardiac Function in Children and Adolescents with Long COVID: A Case-controlled Study," published in the *European Journal of Pediatrics*.

Now, prior studies like the one right above, focused on autonomic dysfunction primarily in adults. This study, the authors are looking at pediatric patients with Long COVID. Here we've got 56 Long COVID pediatric patients, mean age about 10, and 27 age-, sex-, and body surface area- matched healthy controls. They undergo a standard, 12-lead EKG, 24-hour EKG Holter

monitoring. Autonomic cardiac function was assessed. A comprehensive echocardiographic study was also obtained. Basically the data analysis showed that pediatric patients with Long COVID also had significant changes. We're seeing the autonomic dysfunction in the kids as well.

Last and least, to briefly mention the article, "Iron Dysregulation and Inflammatory Stress Erythropoiesis Associates with Long-term Outcome of COVID-19," published in *Nature Immunology*. In this investigation that assessed 214 individuals infected with SARS-CoV-2 with varying disease severity, they found unresolving inflammation, anemia, low serum iron, altered iron hemeostasis gene expression. Really, I'm going to say an anemia of chronic inflammation. Before everyone starts taking iron supplements, I also want to share the University of Cambridge research post, a couple nice quotations from there.

"When the body has an infection, it responds by removing iron from the bloodstream. This protects us from potentially lethal bacteria that capture the iron in the bloodstream and grow rapidly. It's an evolutionary response that redistributes iron in the body and the blood plasma becomes an iron desert. It isn't necessarily the case that individuals don't have enough iron in their body. It's just that it's trapped in the wrong place. What we need is a way to remobilize the iron and pull it back into the bloodstream where it becomes more useful to the red blood cells."

We don't really know if iron supplementation is helpful, and this study does not tell us that answer. I will finish as we've been finishing for over four years. No one is safe until everyone is safe. I want everyone to pause recording right here. Go to parasiteswithoutborders.com and click on the 'Donate' button. Even a small amount helps. We are now doing our American Society of Tropical Medicine and Hygiene fundraiser where for February, March, and April, we double your donations up to a potential maximum donation of $20,000. A portion of these funds will go to providing travel awards for two female qualified students, earlier-career investigators. Those applications, I guess, are going in right now for these folks.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Jeff writes, "I am a general pediatrician and I would love to hear your thoughts on applying the new CDC guidance for COVID and other respiratory illnesses to children who often have mild symptoms, particularly as it relates to return-to-school recommendations. I saw a 5-year-old recently with two days of congestion and slight cough. She had a COVID exposure and tested positive. When does she go back to school?

"She never felt particularly ill, so maybe the guidance doesn't apply. Most children at this stage will not reliably wear a well-fitted mask for any length of time. Perhaps instead she should be excluded longer for that reason. Since the guidance is intended to be more general, does it mean that all children with runny noses should be masking at school, or perhaps only those that have had fevers? I'm not sure what that would mean for the lunchroom or gym class where masking is not a serious option for most children. Any thought you have would be greatly appreciated."

DG: This is really great. We really need to have these discussions. How do we go forward? How have we addressed this in the past? How do we want to address this in the future? Do we want to make it such that getting that positive COVID test becomes something associated

with a punitive restriction? It's really tough. For a lot of children, let's say they're low-risk and the test is not necessarily going to affect how you manage them clinically. They're not maybe going to be a person who ends up on antivirals, then it becomes one question.

If it's an individual who maybe is higher risk, and we talked about the fact that there's a nice guidance publication on, what puts individuals at higher risk, so where they may actually end up with treatment. This is really tough. We know that the virus is such that an infected person is contagious for those, really the first five days and a little bit into the second five days. The reality you bring up is children are not going to wear a properly fitting mask while they're eating lunch, while they're in the gymnasium. We have a society that is structured where you really can't miss a week every time you end up having an issue.

We shut down most of the remote learning options in a lot of settings. I think there's a lot of bigger public health questions that we need to ask as a society. How are we going to go forward? I think the previous CDC guidance was often ignored, and in a situation like this, I don't think there's going to be a lot of parents that are going to be excited to have their child miss a full week of learning opportunities, and for them, maybe whoever the caregiver is, having that impact on work to keep a seemingly minimally impacted child at home to protect society.

VR: J writes, "I know you enjoy using data to set the record straight when rumors get going, so I thought you might be interested in sharing your two cents about the following situation. There has been some conversation in wildlife management circles about people's rabies antibody titers falling off precipitously after being sick with COVID-19. These are folks who have rabies pre-exposure vaccination due to anticipated wildlife encounters and who get their titers checked regularly to determine if and when they need a rabies booster. Is there any mechanism that would explain a causal effect of SARS-CoV-2 infection/COVID illness on rabies titers in a rabies-vaccinated person?

DG: Interesting. I'm not familiar with any sort of literature showing this. It sounds like this would be a very interesting study to maybe follow a number of people and see what the normal contraction trajectory is, the kinetics there, and then see if there's any kind of impact here with a case of COVID-19, with a SARS-CoV-2 infection. It came up on our live stream that certain situations like a measles infection can be associated with a loss of memory, and some interesting things we've learned about that, the ability of that virus to actually target memory cells, particular receptor on the memory cells, and thinking, that makes sense.

That's probably what's going on. There is some growing evidence about all the post-COVID impacts on B cells and T cells. I would be thinking about something along those lines if we really confirm this association. Interesting. I should mention, just because we're on rabies and I really like rabies, and I need a rabies bow tie, so if anyone knows where I can get a really nice rabies tie and modify it, what is a protective titer against rabies? Because we have a lot of these, you go to the lab and there's some kind of a cutoff. Working with vets, I was mentioning I spent a lot of time in Fort Collins, Colorado.

People who are exposed either in zoos or veterinary situations will get their titers checked. There's an idea that there's a threshold, a protective titer. I don't know how true that is. If you actually look at, so where do we get the data on this? Some of the data comes from

animals. There's a nice study on vaccinated raccoons where what they did is they actually grouped them into three categories. They had a bunch of the vaccinated raccoons who had negative titers. It didn't pick anything up, so below the measurable titer. About 40% of them survived.

Then they looked at the group that had higher antibody levels, and OK, 90% of them survived. Then they had ones that had this really high titer, 100% survival. Suggestive that there are certain correlations there between the antibodies. Maybe better is almost to, you get the rabies exposure and how quickly the amnestic antibody response comes up. Just interesting stuff here. I'd love to see if this pans out, if this is a real issue, and if you need to start rushing out and getting all those folks revaccinated for rabies.

VR: There is a CDC page on this. It says there's no protective titer against rabies, but the ACIP recommends neutralization of rabies virus at a serum dilution of one to five as minimum evidence of circulating antibodies. If it's lower than that, then you get revaccinated.

DG: You get another shot, yes.

VR: Eli writes, "Is there any evidence that giving COVID vaccine after COVID infection and recovery gives more protection against reinfection?"

DG: Yes. There is. We call this hybrid immunity. We've often talked about how if you get an infection, waiting the three months before you get your vaccination. I always joke one of the best ways to not get COVID is to get COVID. If you had COVID, and it's three months later and you want to reduce your chance of getting it, getting a vaccination on top of that actually can reduce your chance below what it would be if you didn't add that vaccination on top of a prior infection.

VR: Brendan writes, "Sorry if you've discussed this already, I see in this study," so the study that Brendan sends is "COVID-19 Rebound after VV116 versus Nirmatrelvir/ritonavir Treatment: A Randomized Clinical Trial," in *JAMA Network Open*. "The authors noted that viral load increases as part of some rebounds, which has me concerned about giving patients dexamethasone in the second week.

Can you please ask Dr. Griffin," yes, I'm asking him, "what we should do with this knowledge and what sort of testing is available for patients and clinicians to know if it's a viral rebound or just the inflammatory phase? Would a RAT show, or could the mucous membranes already have defeated the virus, so no positive tests then, yet instead the battle rages on somewhere else?"

DG: I'm going to actually discuss that article on our next *TWiV*. I already put it in my show notes, and so I recognize the study you're talking about. A nice thing I can actually quote from that study, not quote but I paraphrase because I'm not sure I remember exactly, but they make a point that there was no correlation between a return of symptoms in that second week and an increase in the virus, so in the PCR, in the quantitative PCR that they're doing there. That's the first thing to point out. Because that's what clinicians tell us they're seeing.

Oh, I saw this patient and they started to get better. In the second week, they got worse. I just want to point out that the majority of time, those people that are having symptoms in

the second week, there's no virological rebound. That is the early inflammatory phase. That's part of the disease process. Whether you treat them or not, we're still going to potentially see that. If you treat them with the oral remdesivir, the VV116, or with Paxlovid, the severity of that early inflammatory phase is going to be decreased markedly. The chance of them ending up hypoxic or in the hospital is going to go down markedly.

Here's the other thing which I think is interesting. What do you really want to know? Do you want to know, when they're having symptoms, if there is an increase in that PCR level? Do you really want to know that because you're going to do something about it? I want to point out we have years of evidence that jumping in late is not helpful. You're just throwing unnecessary antivirals at someone when they're now in the inflammatory phase. That gets in, I think, to your second question, oh my gosh, what if we give these folks steroids during that second week?

Let's say we have an indication that saturation is below 94% on room air. We have the recover data, but now we have a growing number of other studies showing that there can actually be a mortality benefit to treating these folks with steroids. If we follow those folks out and keep doing PCRs, folks that get the steroids, are they going to have a longer period of PCR positivity?

Yes, the odds ratio to that is probably about three to four. You will, by giving the steroids, you'll save their lives, about a 25% mortality reduction if you quote the recover data. It's equivalent to being overweight, having a BMI of greater than 30, also has an odds ratio of four for ongoing PCR positivity out past that day 10. It's one of those things that I'm not sure that it clinically would be any reason to withhold, potentially as a life-saving intervention, the steroids. Certainly nothing in here suggesting that more antivirals is appropriate.

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

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

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