This Week in Virology

TWiV 1106 Clinical Update

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Guest: Daniel Griffin

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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 1106, recorded on April 17, 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: I can never guess what you've got on your tie. I guess you have to wait till you cycle through all of them.

DG: Then that'll be a test. That'll be a memory test. This one's a little tough, and I'm pretty sure that I have never worn this on a MicrobeTV recorded cast, YouTube, whatever, any of the productions. This is actually more of a disease bow tie. It's hepatitis, and these are inflamed hepatocytes.

VR: Yes, I think you wore that before. You said hepatitis B virus. How many do you have? Just so I know how many I'm going to have to learn.

DG: I have about 100 bow ties.

VR: Oh, my gosh. All with viruses?

DG: Yes, it's a variation. I've got climate change. I've got sailboats. I've got ectoparasites. I've got viruses. I've got spirochetes. Yes, I've got quite the range.

VR: All right. If you didn't wear a tie, I wouldn't have anything to ask you. I'd have to ask something else.

DG: We'd have to talk about science. Imagine that.

VR: Yes.

DG: All right. Let's jump into it. For those watching, I'm going to apologize for the lighting. You'll notice I think my light has finally died after three or four years. Just not figuratively, just mechanically. I've got to buy a new light, but my light is still - Anyway. OK. Let's start off with a quotation. Hello, everyone. Let's do H.G. Wells this time. “Human history becomes more and more a race between education and catastrophe.” Sometimes I wonder, Vincent, I think some people just listen for the quotations and then that's the high point of the show and they tune off. You don't get credit apparently if they don't keep listening.

VR: I don't know how many minutes it takes.

DG: Yes. Maybe if I delay my quotation, we'll figure that out. Let's jump right into it. I keep updating everyone on what's going on with measles because the numbers keep rising. As of April 11, we always record just before the next update comes up, but as of April 11, about six, seven days ago, we were already up to a total of 121 measles cases reported so far for 2024. Not great. Now, flu activity is down, but I have an article that I thought was worth discussing. “The Number of Influenza Risk Factors Informs an Adult's Increased Potential of Severe Influenza Outcomes: A Multi-season Cohort Study from 2015 to 2020.” This was recently published in *Open Forum Infectious Diseases.*

As I mentioned, I really think this is a good conversation starter, so I'm warning you, Vincent. I'm going to pull you into a conversation on this.

VR: OK.

DG: The point of this study was to assess the impact of multiple risk factors on a person's risk of getting hospitalized due to influenza. My point here is that with many maladies, there really is a person-by-person customized assessment of risk and thus benefits of different interventions. In this study of patients greater than 18 years of age in the United States, evaluated retrospectively in five seasonal cohorts during the 2015 through 2020 influenza seasons, they're going to look at patient-level electronic medical records linked to pharmacy and medical claims.

They're going to be doing multivariable logistic regression. They're going to be looking at codes. They're going to look at sex, race, ethnicity, geographic region, baseline healthcare resource utilization, vaccination status, specific high-risk comorbidities, number of influenza risk factors, BMI, smoking status, and then they're going to do these odds ratios. There's really a lot in here, so consider this just a summary. Now, the season cohorts ranged from 887,260 up to 3,628,168 individuals. Of all patient characteristics evaluated, the cumulative number of CDC-defined high-risk influenza conditions that an individual had was most predictive of increased probability of having, I'm going to say, a bad outcome.

We might be looking at hospitalization in most of these situations, but we can see that range from a low of about 1.8 for one risk factor up to greater than six-fold for those folks with four or more risk factors. The folks are going to conclude by saying that these results show that a simple measure like the number of influenza risk factors can be highly informative of an adult's potential for severe influenza outcomes.

VR: What were the top ones, Daniel? Are there some top ones?

DG: Yes. Actually, I knew you were going to ask, so I leave my link here so I could jump right into it because they have a really nice table, and you can go through the table and see what are these. A lot of them are, I'm going to say, the usual suspects, one of my favorite movies. Although, when I had my wife watch it, she said, you have just spent two hours of my life that are now wasted and I will never get back. No, these usual suspects here are actually, I will say, more informative maybe than that movie. Let me go to the risks they've got here in their list. OK. Unfortunately, for me, it's coming up as one of these accepted manuscripts.

Yes, let's just go through it a few. Age is a strong predictor. Let's see what else we can find here. I mentioned BMI, so that's increased body mass index. Interesting in here, smoker status was actually something they identified. Let's see some of the other ones they've got here. There are actually differences in racial groups. Interesting that they're putting that into their comparisons.

VR: Geography.

DG: Yes. Geography is also, which is, I think we can guess on where geography leads us, right? We talked a little bit about, depending upon where you live, access to health care, we're going to see differences there. Yes, really a number. I think where I want to go with this as far as the message, what is the message we're after? I talk with my colleagues about when you see a patient and they say, "oh, this is just simple and straightforward." I say, "Is it really?" Would you really make a recommendation for a patient if you didn't know their full history? If you didn't know, do you have heart failure? Do you have chronic lung disease? Sort of adding more of these high-risk factors.

Is your body mass index greater than 30? How old are you? Have you ever ended up in the hospital before for this issue? Because that's actually quite predictive. You have a family history of people having issues, which is really interesting. We think of family history for cardiovascular. Infectious disease, the family history is even more compelling. A lot of this is when you have that conversation with a patient, you get a call, "It's Mr. Jones, Mrs. Jones. I just tested positive for influenza." A lot of our conversations can actually be customized. As we're seeing here, huge difference, six-, seven-fold increased risk of ending up in the hospital based upon who you are in those risk factors.

VR: I think you already do that most likely, Dan. You look at people who are older, high BMI, a smoker, et cetera, and you're already thinking to yourself, this could be a problem, right?

DG: I think we need to. I think we need to. Even if it's like flu, we don't have the most robust medicines, but let's say it's the first day or two and the person is considering Tamiflu, which is, I wish we had a more effective medication there that we used. The person says, "I'm 84. I've got chronic lung disease." Then you're like, "Listen, I don't know how much Tamiflu is going to do, but the little bit that it may do, it's worth you running out and getting started on that or maybe having someone run out and get that for you." You get a call from a 23-year-old and maybe it's day two or three. They're otherwise healthy. I'm not really sure that there's much risk that we're going to mitigate in that situation.

VR: Don't forget baloxavir. It's an effective antiviral for influenza.

DG: That was why I made that last comment of that we use because I think that's like a Sanofi product that they just never marketed particularly well. Despite the fact that maybe that actually might be a medicine with a little more efficacy, it's really just ridiculous how little that actually gets pulled out.

Moving straight into COVID, looking at the percentage of provisional deaths by territory. This is sort of helpful. How are we doing in general? I would like to see that we get to the point where it's really less than 1% of all deaths across the country are due to COVID. That's actually true in most of the country.

There still are some areas, I'm going to say that the hotspot we see is Tennessee, where it's really between 2% to 4% of deaths, one in 51 and 25 are due to COVID. That shouldn't be happening in April. There are still a number of states where, it's under 2%, but still above 1%. Places like Texas, Florida, I hate to say, New York, a number of other states as well. COVID activity is on the way down. We're continuing to see that nice drop in the wastewater. We'll keep track of that. I have to say in the hospital, we're seeing less COVID, seeing actually more human metapneumovirus, parainfluenza 3, a few of the other viral pathogens seem to be filling in the gaps.

All right. Now, tongue in cheek for the next article. It's the article, "Systematic Analysis of the Factors Influencing Sperm Quality in Patients with SARS-CoV-2 Infection," published in *Scientific Reports*. Now, I say this is perhaps a fun article for all the sailors or those in the Navy, because we're going to, we're going to be studying semen. Now, I joke about that, because that was a Mark Crislip, whatever he would have an article about semen, I think he would think it was spelled S-E-A-M-E-N, as opposed to S-E-M-E-N. This is also, I think, one of those areas where people might still be concerned.

The authors are investigating the impact of SARS-CoV-2 on semen, and more specifically, sperm. They're going to conduct a prospective cohort study, initially included 122 men with SARS-CoV-2 infection. They don't really get to track everyone. The longest time to track semen quality after infection was 112 days, ultimately end up with 58 eligible patients included in the study. A few dozen, but not as many as we initially thought we were going to read about. They're going to analyze the semen parameters at different time points before and after SARS-CoV-2 infection.

Now, I was a little annoyed with, I guess, this abstract. I'm just going to sort of say straight up front and where they give us the results, because you have to go to a table and find out the measurements, like what are these numbers. Just going to comment that right up front. We're going to learn that semen parameters were significantly reduced after SARS-CoV-2 infection. We hear that total sperm count dropped from 211 to 167. Now, of course, count per what, right? You have to look at that sperm concentration from 69 down to 51. Total sperm motility is actually, you can look at the motility of sperm and there's a scale. It was 57.5 down to 51. About more than 10% drop.

Progressive motility, you'll see a drop there. The parameters displayed the greatest diminution within 30 days after SARS-CoV-2 infection. Then it's going to gradually recover thereafter. The semen parameters were significantly reduced after SARS-CoV-2 infection and fever severity during the SARS-CoV-2 infection seemed to be the main influencing factor in

reducing these semen parameters in the folks after recovery. Little encouragement here. The effect appeared to be reversible with the semen parameters gradually returning to normal with the realization of a new spermatogenic cycle. It seems like it may be impacting the cells that are then part of that acute spermatogenic cycle. I like that.

VR: Spermatogenesis is sensitive to heat.

DG: Yes. Yes.

VR: Right. This is not surprising. In fact, any infection that gave you a fever, I bet would have a similar effect, right?

DG: Yes. I actually think that would be a great comparison, right? This is all scary. Oh my gosh. I don't want to go out to get a natural infection because what will it do to my sperm, my semen? What does every fever do to our semen and sperm? Also, is it clinically significant, right? These parameters, is this really like if you and your partner are thinking, "Hey, it's time to maybe try to have a baby?" Is this going to be enough? Is it really that we're seeing like in the month after people get SARS-CoV-2 that they have the reduced ability?

I can imagine for the first week or two, you may not want to even engage in the effort because you're feeling crummy and sick. Just sort of a, I put this in as a fun, interesting study, but just to go through what we're seeing here.

All right, and we are going to move on to COVID active vaccination. Wednesday, February 28, 2024, the vaccine advisors to the CDC recommended that people age 65 and older receive an additional dose of the current monovalent single strain COVID-19 vaccine, spring 2024. CDC director jumped on board, endorsed that, Dr. Cohen.

I thought this was a perfect place for me to read an email that you forwarded to me, Vincent. Let me truncate it. I just pulled out the part that I thought was most relevant. Hi, Daniel and Vincent. ACP did review the vaccine effectiveness data for the '23-'24 COVID vaccine during their meeting on February 28. CDC did not wait to publish these data in *MMWR,* as you said in the clinical update. Enjoy, Daina or Dana, I'm not sure how to pronounce it, D-A-I-N-A, and she leaves a couple links. For clarity, I just thought we would go through the slides. She leaves a link, which is nice, and we can leave a link in our show notes.

There's a couple slides that are relevant. There is one slide. This is slide 19. This is where they actually are looking at the vaccine efficacy, 2023-2024 vaccine against hospitalization among immunocompetent adults aged 18 years of age or older by age group. We see, as we've talked about, this 40%, 50% holding steady vaccine efficacy. Remember, their discussion was a lot on the prior year's stuff. I will point out in the slide, in the small print, which I'll draw everyone's attention to, it says VE estimates adjusted for age, sex, race, ethnicity, geographic region, calendar time, *MMWR* to be published February 29, 2024.

I do want to point out that this data was actually not published until the day after the recommendations were made. Now the interesting thing, and this is, I think, where we've commented, they go ahead based on this data, and they give us three conclusions. This is on slide 20. Updated 2023-2024 COVID-19 vaccination provided increased protection against symptomatic SARS-CoV-2 infection and COVID-19 associated ED and urgent care visits and

hospitalizations compared to no updated vaccine dose. OK, endorsing that it seemed in retrospect that recommendation in the fall to have an update was associated with some benefit.

Receipt of updated 2023-2024 COVID-19 vaccine provides protection against JN.1 and other circulating variants, something we've reinforced. Then I guess this is the part that we've had a discussion about. These are relatively early estimates from all three vaccine efficacy studies with no substantial waning. However, waning is expected and CDC will continue monitoring vaccine efficacy. That's been our comment, that we saw waning last year with the bivalent. We're not sure if that waning was time-dependent or because there was a change in variant. Just try to be clear about the science when we discuss this recommendation.

VR: You can't give a booster every three months to account for that reduction in titer, right?

DG: I think it was interesting just to reference the last deep dive. I think it was a *TWiV* deep dive last Friday where it's not all just about antibodies, right? There's also T cell.

VR: That was a great paper where they made mice without antibodies. They have B cells, but no antibodies. They're completely protected against challenge, even with a different variant. I'll bet that's an age-dependent phenomenon, right? Because you're depending on T cells, which are not generated very well if you're over 65. I don't think you should keep vaccinating that age group. I think you should just give them Paxlovid or something else.

DG: That is a challenge and we'll keep hitting on that. We're being honest with the data. I think you have to be a little careful not to overdo it with the vaccines because we're already struggling with people starting to say, "If you're recommending a vaccine with a minimal benefit, I'm going to just start not wanting to get vaccines in general." We really have to be careful not to erode vaccine confidence by overpromising, over expecting. We don't know if waning is going to happen with the monovalent. We don't know if we're going to start to see a rise. If anything, the numbers of cases of COVID-19 are on the way down. The wastewater is on the way down. Just putting this in context.

OK, COVID passive vaccination. March 22, 2024, we heard about the emergency use authorization for a new Pemgarda, pre-exposure prophylaxis. Still waiting to hear about how we might actually access this, price, et cetera. Just make sure that's on the radar of everyone.

VR: You haven't got any yet, right?

DG: No, and nor have I heard how one might access it and how that's going to work out. Now that it's here and it's potentially effective against current variants, it would be great for those millions of folks that might be eligible to get this added protection.

OK, COVID early viral phase. I'm going to leave in both the NIH and the IDSA guidelines going forward. You can have people, you can share those with your less up-to-date colleagues. Number one, Paxlovid.

Last week, we mentioned the article, “Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with COVID-19,” published in *The New England Journal of Medicine,* where they had that crummy, we criticized their primary endpoint of complete symptom resolution. I

don't know if someone was sort of bullish on this, that it was only about a day earlier and there was reduction in hospitalization and death, but only 50% with overlapping confidence intervals. I did mention the concept of number needed to treat that was introduced in the 1988 *New England Journal of Medicine* article.

I think this is relevant as with the EPIC-HR study that looked at high-risk unvaccinated individuals, the number needed to treat to prevent one hospitalization or death was only about 20, where what we're seeing here is for standard or low-risk patients that number might be 50 to 100. This certainly changes the return on investment if you're running a socialized medical system or trying to avoid all the time and effort with reviewing medications and making adjustments. As I read many of the commentaries coming out, I must say you can't have it both ways.

Despite the questionable outcome of feeling all better, the people that got Paxlovid tended to get all better about a day sooner, with the most common reported issue being a bad taste in one's mouth. I've seen people refer to that as the number needed to harm and as if getting a bad taste in your mouth qualifies as a very significant harm. I think it's also worth mentioning that in this study, in the group that did not get Paxlovid, someone actually went ahead and died. Nobody who got Paxlovid survived. I mean nobody who got Paxlovid died. One-hundred percent survival with Paxlovid, a death in the patients that didn't get Paxlovid.

As we keep pointing out, being careful, if you've got a high-risk patient, if you've got a patient who has a non-zero chance of ending up in the hospital or ending up dying, you have a tool here where you can actually affect that. I'm thinking about that flu study as well as individualize your discussions. It's really not that hard in all honesty to sit down with a computer, run through the patient's medications and manage those interactions. It's all laid out. The Liverpool checker can tell you what to do. To spend a few minutes and potentially save someone's life or prevent a hospitalization seems like something a provider should be willing to do.

OK. I'm also realizing that we have another study, the article “Nirmatrelvir/ritonavir, and Remdesivir against Symptomatic Treatment in High-risk COVID-19 Outpatients to Prevent Hospitalization or Death during the Omicron Era: A Propensity Score Match Study,” recently published in *Therapeutic Advances in Infectious Disease*. I do want to point out, we now have hundreds of studies demonstrating the benefit of actually treating people who are sick. Here's another one of those. They range from observational, retrospective, randomized controlled prospective.

Let me start with their sobering comment. Even though worldwide death rates from coronavirus disease 2019, COVID-19 have decreased, the threat of disease progression and death for high-risk individuals continues. I somehow feel like people have taken the Josef Stalin quotation and reversed it. "The death of one man is a tragedy. The death of millions is a statistic." Now this has become the death of one man is not a tragedy because we are no longer seeing the millions of deaths. Yes, just because the statistics have gotten better, every time one person dies, it is still a tragedy. It is particularly a tragedy for the family, for the ones who care about them.

I should think for the provider who decides it wasn't worth the effort of managing drug-drug interactions and making a renal adjustment. All right, off my soapbox. The study included all high-risk outpatients with COVID-19 in a tertiary referral center in Mexico City from the first of January 2022 to the 31st of July 2023. The primary outcome was all-cause hospitalization or death 28 days after symptom onset. The secondary outcome was COVID-19-associated hospitalization or death 28 days after symptom onset. Of 1,566 patients analyzed, they split it roughly in half: 783 did not receive antiviral treatment, 451 received remdesivir, 332 received nirmatrelvir/ritonavir, Paxlovid.

The median age was 60 years, 62.5% were female, 97.8% had at least one comorbidity. Almost everyone had at least one comorbidity. The use of nirmatrelvir/ritonavir was associated with an absolute risk reduction of 8.8% and a relative risk reduction of 90% for all-cause hospitalization or death. The use of remdesivir was associated with an absolute risk reduction of 6.4% and a relative risk reduction of 66% for all-cause hospitalization or death. Now, why do I give you both those numbers? The absolute is going to help you with number needed to treat. About a 9% for the Paxlovid. That's going to be about 11 as the number of people needed to treat to benefit one person.

Remdesivir with about a 6%. It's going to be about one in 16, so 16 needed to treat. Both antivirals reduced the odds of 28-day all-cause hospitalization or death. About a 92% reduction there for Paxlovid. We have a 71% reduction for remdesivir. There really is a nice table we can actually go through. They break down the risk of hospitalization and death overall, the risk for hospitalization and death, and the numbers for COVID-19-related. Again, just to mention the actual numbers. If you look at the overall 1,566, let's look at the number that got no treatment. Twenty-eight people that got no treatment end up dying.

How many people that got Paxlovid died? Zero. That's pretty stark. I don't think it takes a statistician to say, "Wow." We've got 783 folks. We didn't treat any of them in that group, 28 of them are dead. Now we have over 300 people that we treat with Paxlovid. Zero died. All right. I'm not sure what the issue, right? It's not an industry-sponsored randomized control trial. Everyone's vaccinated. It's Omicron. How is this not applicable to the patients we're currently seeing?

OK. Moving on to number two, remdesivir, which we just covered there. Maybe I'll make the comment for remdesivir. Also quite effective. There we went from that 28 died with no treatment, reduced that in half to 14 in the folks that got remdesivir. Not a big reduction because we're talking about 3.6% versus 1%. Not quite as impressive as saving everyone with the Paxlovid.

All right. Number four, convalescent plasma. We've got something new here. “Outpatient Treatment with Concomitant Vaccine-boosted Convalescent Plasma for Patients with Immunosuppression and COVID-19,” published in *mBio.*

I was waiting for this to come out because I've been having conversations with folks out at the Mayo where they're doing this stuff. The context here is that monoclonal antibody therapy has been limited by the emergence of novel SARS-CoV-2 variants that have serially escaped neutralization. In this context, there's interest in understanding the clinical benefit associated with COVID-19 convalescent plasma collected from persons who have been both

infected with SARS-CoV-2 and vaccinated. They call it vax plasma, but I think they should call it hybrid vax plasma. That's just my suggestion, by the way.

Here, the authors report the clinical outcome of 386 immunocompromised outpatients, who were diagnosed with COVID-19 and who received contemporary COVID-19-specific therapeutics, that's their standard of care group, and a subgroup who also received concomitant treatment with very high titer vax plasma with a specific focus on hospitalization rates. The overall hospitalization rate was 2.2% in the vax plasma group and 6.2% in the standard of care group. Sort of interesting, just put this in context. So, 6%, that means, try to do this, about one in 16 people end up in the hospital if you do nothing. Now you're going to reduce that to one in 50.

Really, a relative risk reduction of 65% is of note, and I want to comment here, 94% of the patients who got COVID and were treated were vaccinated. We are looking at vaccinated people during the time of Omicron, and in vaccinated patients with immunosuppression and COVID-19, the addition of vax plasma and very high titer COVID-19 convalescent plasma to COVID-19-specific therapies reduced the risk of progression leading to hospitalization. This is doing both, and if you look through, you can look at the different groups in this nice table they had.

In the vax plasma group, we have some folks that were getting remdesivir, some folks that were getting Paxlovid, some folks that were getting molnupiravir. They even have the number of COVID vaccines they got.

All right. We have our isolation guidance for respiratory pathogens. I was going over that with a patient today. Then week two, remember, this is cytokine storm week, right? People keep talking about this rebound, and I just want to point out, there really is not a good correlation between symptom rebound and anything going on with your PCR results. Just keep that in mind.

During that second week, some folks end up in the hospital. We keep pointing out, yes, folks keep ending up in the hospital. Steroids at the right time in the right patient. We have anticoagulation guidelines, pulmonary support, remdesivir, if still in the first days from symptom onset. We're going to have some new stuff on remdesivir next week. Immune modulation.

Then moving on to Long COVID. Here I'm going to actually tell a story. I take care of patients, and I'm still just shocked at the - I'm sorry to say it, but the arrogance and dismissiveness of some of my colleagues.

I saw a woman today, and I've been taking care of her for a while, clearly meets criteria, right? She started to get sick. She continued to be ill after her acute bout of COVID. She had a very compelling clinical story, the chronic fatigue, the post-exertional malaise, documented orthostatic abnormalities, super high EBV serologies, greater than 600 off the charts, some other biochemical abnormalities. She had very consistent clinical history. She had both physiological and biochemical abnormalities consistent with her complaints. She saw a Yale-based physician who informed her, "Sorry, ma'am, Long COVID, it's not a thing." A little troubling there.

Now the next one hits a little closer to home. This is another patient I've been working with who has post-exertional malaise. We've been working and discussing about the balance between complete physical inactivity and the harms there, but also the harms of pushing things a little too hard with her activity and triggering that post-exertional malaise. Unfortunately, this patient went and saw one of our local docs, so in the area here on Long Island, and they basically informed her that none of this is true. There is no potential for harm with exercise, and that all of her problems were due to her lack of activity and deconditioning.

Just fortunately, both of these patients were able to bite their bottom lip, come back and see me, regroup, where we just went over the actual current science and understanding. Just troubling that that continues. All right, well, I will finish off this part, as I have for about four years now. No one is safe until everyone is safe. I want everyone to pause the recording right here, go to parasiteswithoutborders.com, and click 'Donate.' Even a small amount helps.

We are in the final weeks of our American Society of Tropical Medicine and Hygiene fundraiser, where for February, March, and just a couple more weeks of April, we will double your donations up to a potential maximum donation of $20,000, with a portion of these funds going to provide travel awards for two female qualified student early career investigators.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Eli writes, "How are the eyes of newborns protected from infection with *gonococcus* now that there is so much drug resistance? Do we go back to silver nitrate?"

DG: Actually, that's a concerning question, right? Now, I don't know if it's still a high dose or if we're starting to actually lose it. Yes, the erythromycin ointment, they put it in the eye, and it is felt to be ocular effective, ocular prophylaxis. It's the only agent available in the United States. Boy, if we get into trouble here, it's going to be a problem.

VR: Douglas writes, "Hello, Doc. I'm a 56-year-old living in London. I have type 2 diabetes managed with metformin and chronic plaque psoriasis managed with methotrexate. I have received an email from the National Health Service stating, "We're inviting you to book a spring COVID-19 vaccination appointment. This is because your NHS record suggests you may have a weakened immune system." I've had the recommended vaccinations and received a boost last autumn as well as having caught COVID at least once. My GP is prepared to dispense Paxlovid if I test positive. I think a boost in spring would be overkill. Your thoughts would be appreciated."

DG: OK, I like the way they worded that. I don't know how sensitive or how that came across. Your NHS record suggests you may have a weakened immune system. Hopefully, that was taken well. No, you are on methotrexate, 15 milligrams once a week. That's a solid amount of immune suppression, so that does put you into a higher risk category. In addition, you're over the age of 50. I hate to think that's a risk factor, but ouch. You also have type 2 diabetes. You are in a highest risk group.

We've talked about the issues, a couple of the issues here. One is that folks on methotrexate with the associated impact on the immune system are not going to develop as robust a response to the vaccination. We've also talked about the data we have, which is not on immunocompromised folks, about things seem to be holding pretty steady out to 120 days.

That's about four months. This is a weak recommendation, I guess, at this point. We talked about how the wording is “should” from the CDC recommending for those 65 and over. Actually, they are not talking about you specifically.

I think that dispensing Paxlovid, we continue to talk about that being a great option and whether or not you get that boost or not, the Paxlovid is a great option. You would be one of those people, if you're already saying, "I think that the boost in spring would be overkill." If there's already a little bit of hesitancy to go ahead with this, I don't think I'm going to push you very strong on going ahead with that vaccination boost.

VR: JoAnne writes, "I'm getting ready to take a transatlantic cruise and as a precautionary measure asked my doctor for a prescription for Paxlovid. I was told that the hospital group in which he works, a large New York City institution, has a policy of not prescribing Paxlovid unless the patient has COVID. I do not have COVID, but in case I was to contract the virus, I would like to be prepared. I'm a woman in my 70s with comorbidities. My question, is it possible to get a prescription for Paxlovid in this situation?"

DG: Yes, I almost want to call this doctor's bluff on this. Is that really true? Someone sat down at a large New York City institution and came up with a policy of not prescribing Paxlovid? I'm not sure that's true. Paxlovid is a licensed medication. It's approved for the treatment of COVID-19, just much like you might take azithromycin or some other prescription with you for the possibility of getting a disease when you're not going to have access to that medicine. I'm a little bit taken by this suggestion. Number one is going to be, yes, maybe you need to find a different provider, as I, unfortunately, say to the chagrin of my colleagues.

The other is if you don't, you might want to ask them, oh, is there any chance you could share that with me because I'd be really interested in seeing that because I would be really interested in seeing that. If you do get a copy, please send it our way. Now, the doctor, he's a licensed, he or she is a licensed, he or she, or however the gender is able to do this. Yes, I think that it actually is pretty reasonable if you're a person who is high-risk and who would benefit, you say, a woman in their 70s with comorbidities, yes, I think this would be not only reasonable but appropriate.

VR: Mark writes, “CDC recommends MMR vaccination in adults if they were born after 1957 and do not have presumptive evidence of measles immunity. I was born in '58, was curious what my measles antibody titers were, so I paid out of pocket, had them drawn. The levels were "very high", so I did not get another MMR. I have done no international travel in the past three years and there have been no measles outbreak locally in recent years. Why are measles titers so high? Did the titers remain high since my vaccination in the ‘60s? I raised four kids, all who had MMR vaccination. Did they shed virus after vaccination that provided a boost?

DG: OK, so I can answer some of your questions. The first is this last question is I raised four kids who all had MMR vaccination. Did they shed virus after vaccination that provided a boost? We don't think that's the case. We do not think that the MMR vaccination attenuated virus can actually infect other people and give them a boost. The other is why are your titers so high? Is there more measles out there that we don't know about? Is this something that's been somewhat under the radar? Have you had boosts over time? You didn't even notice

because you are vaccinated, so you're not going to get sick. I'm not really sure why yours are so high. Vincent, any thoughts on this?

VR: Mark is an MD, right?

DG: Yes.

VR: Maybe he has contact with patients who are infected and they don't know it, right?

DG: Yes, and I hate to say it, right? We miss diagnoses, right? We don't see a lot of these. There is a chance, Mark, over the years that unbeknownst to you may have actually seen some measles cases and just missed them.

VR: Yes. I have high poliovirus titers because I worked on it for so many years.

DG: You need to work on your infection control.

VR: Apparently. Finally, Ellie writes, "My cousin who has received all the boosters and suffers from tinnitus often on 'a lot,' in her words, said that the COVID vaccine causes tinnitus. Since you and the *TWiV* are the only ones I trust for the facts about COVID, have there been any studies done to see if this is true? I do plan to ask if her frequent tinnitus began since she received the COVID vaccines or also existed before." That would be a good question, wouldn't it?

DG: That would be good. I had it two years before, but still, I'm blaming it on the vaccine. This is great. This brings us into how do we assess causation between a vaccine and an outcome? Things get reported to VAERS. Certainly, people have reported tinnitus after a COVID vaccine. They've reported a lot of things, right? Car accidents after their COVID vaccine. All kinds of different. Wasn't there some kid who like got a marble stuck up his nose after a COVID vaccine, right? That got reported to VAERS.

Then what they do is they do these studies where they say, "Are we seeing any more cases of tinnitus after vaccine than we saw, as a background?" That's been looked at carefully. Yes, certainly a lot of people have had tinnitus after vaccine, but a lot of people get tinnitus. When they look specifically at this, other than the little bit of tinnitus that self-resolves after a few days post-COVID vaccine, long-term ongoing tinnitus, we are not seeing any signal of any causal connection with COVID vaccinations.

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

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

[music]

VR: Marble. COVID vaccine causes marbles up your nose.

DG: Yes, no, I think it was in one of the randomized control trials. Some kid stuck a marble up his nose, and that had to go into the adverse reactions.

[00:44:11] [END OF AUDIO]