This Week in Virology

TWiV 1018 Clinical Update

Host: Vincent Racaniello

Guest: Daniel Griffin

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

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From MicrobeTV, this is *TWiV, This Week in Virology*, Episode 1018, recorded on June 22, 2023. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today here at the incubator in New York, Daniel Griffin.

Daniel Griffin: Hello, everyone.

VR: Good to have you here, Daniel.

DG: It's nice to be here. The only thing is I just realized now because we're recording *This Week in Parasitism* later, my bow tie today is not a virus.

VR: What is it?

DG: It's bedbugs.

VR: It's bedbugs.

DG: Oh my gosh. [chuckles]

VR: It's OK. Look, this *is TWiV* clinical update, so bedbugs would fit, right?

DG: Yes, if we have a big clinical issue, we'll jump in with those. Let's get right into it because we have a fair amount to cover today. This won't be too bad. Let me start off with a quotation. I wonder if I've used this before, but I'm up on the wards at Columbia and one of the interns, freshly minted interns fresh out of medical school, brought up this quotation, and I just couldn't help myself. Thanks to Jareliz Diaz for this quotation, which is from William Osler, "To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all." I love that. Osler had a lot of great quotations. I don't agree with all the bloodletting he was a big fan of. Other than that, OK.

All right, polio. Vincent, we got polio right up front. Now, this one is really interesting. When I read this, it occurred to me as, wow. What is so interesting? The Centers for Disease Control

and Prevention, the CDCP, we've got to start saying that, get prevention in there, is urging travelers to practice enhanced precautions when traveling to 30 countries they have identified in a recently updated advisory with a Level 2 notice advising travelers to practice enhanced precautions. If a traveler is going to these identified destinations, the agency recommends children be up to date on their routine polio vaccine, and adults who are fully updated also get a one-time inactivated polio vaccine booster. You may need to show proof of vaccination when departing the country. Well, these countries include the obvious high-risk places such as Canada, the UK, Israel, and a number of others.

We'll have a link to the different DEFCON levels, DEFCON 1, practice usual precautions. Here we see DEFCON, Level 2, practice enhanced precautions. Level 3, reconsider non-essential travel, and then Level 4, avoid all travel.

VR: Daniel, this is because these countries have circulating poliovirus, probably also cases of polio, many, many cases in Africa, for example. The U.S. has circulating poliovirus quite clearly. If you want to visit the U.S., you probably should get vaccinated also. It's just only fair because as we saw last summer, there was circulating virus. There was virus in wastewater. Being a little facetious, but if you live in the U.S. and you're not polio vaccinated, you should get vaccinated, right?

DG: That is really clear. This is a threat to the unvaccinated. If you are unvaccinated, if your children are unvaccinated, we encourage across the board. All right. Speaking of vaccines, we'll move into RSV. On June 21, 2023, that just happened, the CDCP, vaccine advisory committee, the ACIP, recommended the newly approved RSV vaccines, so a couple of votes here. In the first vote, which passed nine to five, advisory said adults aged 65 and older may receive a single dose of the vaccine using shared clinical decision-making. In the second vote, little stronger, which passed with a 13 yes votes and one abstention, they said individual adults aged 60 to 64 may receive a single dose of RSV vaccine using shared clinical decision-making.

VR: All right, Daniel, I don't understand this at all. Can you explain?

DG: What does this mean? OK. We've talked a little bit about a couple of new RSV vaccines. We talked about the one for older individuals. We also talked about the one for pregnant individuals during that last trimester that might then lead to protection of the newborns. What they're saying here is based upon that data they looked at it, and this is an endorsement but not a wholehearted endorsement, and I think it's justified. Now, I'll go through why, why the data would support what they're saying. This would be the first rollout in a large population. There were some safety signals that we saw. What they're really saying here is use your judgment, particularly your higher-risk individuals, certainly this makes sense. We'll have that discussion, higher risk individuals, particularly 65 and older or 60 and older.

For individuals maybe closer to 65, maybe in that 60 to 64 range, otherwise healthy, lower risk, you may want to give it a year. You may want to see what the safety signal is. That's that shared decision-making, get a sense of, as we say, if the benefit relative to the unknown risk until we roll all this out makes sense for you to go one direction or the other.

VR: I don't understand the distinguish between individuals and adults. What does that mean?

DG: No, I think basically everyone over 60 I like to think is an adult, though they don't always act that way.

VR: Is Joe Rogan over 60?

[laughter]

Oh, sorry, sorry.

DG: All right, Vincent, moving on. [laughs] All right, I guess we don't have to be nice to Joe. Let's be nice to Dickson. All right, COVID update. I'm going to move right into the article, "Association of Culturable-Virus Detection and Household Transmission of SARS-CoV-2, California and Tennessee, 2020-2022," published in *JID.* Vincent, I think you're going to enjoy this. I think our listeners will know why because as they say here, we're not just doing those PCRs. We're not conflating RNA copy numbers. We're actually going to be looking at culturable virus. Here, the investigators combined two studies, conducting daily prospective follow-up of persons acutely infected with SARS-CoV-2 and their household contacts. They described the frequency and the duration of a culturable virus detection in primary cases and assessed whether the duration of culturable virus detection was associated with household transmission and the timing of secondary infection.

April 2020 through January 2022, two case-ascertained household transmission studies were conducted in Tennessee and San Francisco, California. Specimens meeting this prespecified cycle threshold, Ct cutoffs, they're doing less than 40 for nucleocapsid and envelope gene targets were actually inoculated onto Vero cells, so those are Vero E6-TMRPSS2 cells or without. A couple of different ways that they're doing this here is a nice figure. Now, the results were reported, so I get a little annoyed, as culture positive or culture negative. Oh, why a binary? Why not something quantitative? Where are those plaque assays?

VR: Too hard, Daniel. Too hard.

DG: Is it too hard? I've done plaque assays. If I can do plaque assays, people can do plaque assays.

VR: Yes, it's not really, but people say it's just too much work. That's it.

DG: Yes. Then the RT-PCR was used to confirm the SARS-CoV-2 in the presumptive positive cultures. Let us go through some of these results. Forty percent of household contacts of primary cases with culturable virus detected became infected, compared with 21% of household contacts of primary cases with no culturable virus detected. I think that's actually an interesting thing. I think this has something to do with the binary here.

We have this idea, if the person isn't shedding culturable virus, how could you possibly get infected? Here we have 21%. Whether you can culture it or not, we're looking at 40% versus 20%, wide confidence intervals here. They also report that there was a nonsignificant increase in a contact's risk of becoming infected with every additional day that a primary case had culturable virus.

VR: Daniel, the fact that 20% of people get infected or contacts got infected and they didn't detect virus means their assay is not sensitive enough, right?

DG: I think that's the problem, yes.

VR: Did they calibrate their assay? Did they tell you in the paper how much virus would give you a positive? Did they dilute it all the way down and say, "No, probably not?"

DG: There are a lot of problems.

[laughter]

I have several comments. One is I don't - I think everyone will not be surprised. I should say our regular listeners will not be surprised that I'm not happy with the binary of culturable versus not culturable. What about doing some sort of quantitative assays? Unfortunately what we're seeing here is even when they're not able to grow it, you're still getting transmission. Not only do you have to do it in a quantitative manner, but you need a more sensitive assay. You need to do a better job of picking that up.

There also was no information for me about any of the PCR data and whether or not they could culture a virus. I would love to see studies where you were looking at the PCR results, the CT values and the levels the quantitative, plaque assay results. They do write quantitative infectious viral load data inclusive of the peak will be necessary to understand the effects of virological dynamics on infectiousness and transmission in future studies.

VR: Makes you wonder, Daniel, why didn't they do that now instead of having to repeat it and republish it?

DG: I don't know. Are they publishing the smallest publishable unit? [crosstalk] I do not know. Probably. No. Probably. I will tell people it's worth looking at the figure. They have this figure where it's color coded. You can see culture positive, culture negative, specimen collected but not cultured. If you go through, one of the things I will say and I do recommend people take a look at this, you could really see the clustering days after symptom onset when you're able to culture virus and when that drops off, this would be more compelling if cultured negative people weren't also spreading to others.

VR: Right? This would be nice if it were in PFU per milliliter, right?

DG: That would be fantastic.

VR: Now, there is a, first of all, there's a widespread of days after symptom. It goes from one to 17 really in a few cases. Although most of them are from one to, I would say, eight or 10 days of culture positive, right?

DG: Yes. We have that one. It's 17 days out and we're still getting positive cultures, right?

VR: Yes. It's interesting. Although how much is there, is it enough to transmit?

DG: Again, as we saw even this binary, right? Even if someone was culture positive, 60% of the contacts were not getting infected. It is amazing to me. Here we are three years out and we still haven't really clarified this issue.

VR: Why do you think that is, Daniel?

DG: I don't know. Do you have a good idea? I think we're not doing the - we keep saying this is the science we would like to see. Even here, we're not seeing that.

VR: I think the right experiments aren't done. Obviously, this is a lot of work, right, to collect these specimens and do the binary even. It's not the right experiment. That's why we continue to not get the answers because we're not doing the right experiments.

DG: Yes. I think ultimately that's it. Why are we not doing the right experiment? That's a bigger conversation.

VR: Yes. I don't know the answer to this, you'd have to ask the authors, the head lead authors say, "Why didn't you do this?" I'm sure they'll make some reason. We didn't have the hands to do it, this or that.

DG: It could be funding, it could be the expertise. I hate to tell you, Vincent, but plaque assays may be a dying art.

VR: No, never.

DG: All right. COVID active vaccinations. I feel like we're returning to this topic, but yes, updated COVID-19 vaccinations for use in the United States beginning in fall 2023. We were recording right when there were some meetings going on last week and there was an advisory committee. During this meeting, the advisory committee was informed of the manufacturing timelines. I think it's important, you got to be realistic about when you ask for something. I remember when they gave advice about flu vaccines last season, of course, they waited until after everyone had put in their orders and then gave recommendations. It is important and I do applaud that, look at the real-world challenges when you're giving guidance and do it in a timely manner. They reviewed the available data on the circulation of SARS COVID two viral variants. They use the proper word there.

Current vaccine effectiveness. Human immunogenicity data of the current vaccines against recently circulating variants. The antigenic characterization of circulating virus variants, animal immunogenicity. Really a lot of data here including preliminary human immunogenicity data generated by one XBB point, 0.1, 0.5 candidate vaccine. They went ahead to say, based on the totality of evidence, the FDA has advised manufacturers who will be updating their COVID-19 vaccines, that they should develop vaccines with a monovalent XBB 0.1, 0.5 composition. Now I'll leave in a link if people are interested in the slides from the Technical Advisory Group on COVID-19 vaccines.

That's the TAG-CO-VAC for the WHO meeting, where they say, while currently approved COVID-19 vaccines, including those based on the index virus, continue to provide protection against severe disease, the TAG-CO-VAC advises moving away from the inclusion of the index virus in future formulations of COVID-19 vaccine. Now, I think this is a great time to revisit

this concept of original angiogenic sin. Before this becomes too entrenched, or I should say the misunderstanding of this becomes too entrenched. I know this has been covered on *Immune*, so I do recommend that our listeners, well everyone should listen to *Immune* whether you listen to us or not. There was some data that was pulled out and this was actually, what kind of neutralizing antibody might you get, comparing a monovalent to a bivalent boost.

Those entrenched in the myth would think, "Oh, if you get bivalent you're just really not going to see much to this new because of all this memory, you're going to basically just focus on what you've seen before. If you look at the data here, it's not a huge difference. You still are able to get a robust response to the XBB 0.1, 0.5 even when it is in the mix of a bivalent.

VR: Gee, wasn't that the reason for making a monovalent in the first place?

DG: I feel like we've gone back and forth and we need to just, be honest with the data here.

VR: It may be that XBB 1.5 is different enough that even if you have the ancestral in the mix in a bivalent, the lymph nodes will see the new one as well and make robust response.

DG: Yes, I agree with the decision. I just think it's really important that people don't get it in their head and people do have this in their head. Oh my gosh, I regret that I got those original vaccines because now I'm just not going to get a benefit, if I do fall into it, I'm going to say there are certain groups where, I think it's going to be a pretty clear consensus. You've got your 85 year-old gentleman with a number of medical problems, OK, boosting really is going to make sense. As I think Paul Offit and a number of other clear minds, I'm not sure what the right description is there. This is not necessarily going to be a vaccine that every single person on the planet needs to get a booster.

VR: That brings up my question. Paul Offit said the CDC is the one who will make the recommendation, but I'm wondering what you think. We will have now a monovalent vaccine. If you're now 6 six months of age, will that be the first vaccine you ever see, do you think?

DG: I think that's what we're moving towards. I think you're right. There is the two steps. One is what will be licensed and available. Then the second is what will be the CDC recommendations? What are we going to use?

VR: How many doses, let's say a 6-month-old is now getting monovalent XBB 1.5, how many doses do you think?

DG: Yes, so I always thought it was confusing that when you get to the, well yes, when you get to the youngest individuals, there's this, "Oh, but if it's this product it's two shots. If it's this product it's three shots." I do know that's sticking strictly with the science. I think it really would make a lot of sense all the way across the board for a primary series just to be three, spaced shots and particularly that third to be spaced well distanced, six months out.

VR: Yes. To harmonize among the manufacturers too, right?

DG: Otherwise, if you make it too hard, if you make it too confusing, if a patient goes to a provider and the provider seems confused, that's not helpful.

VR: Exactly, right. OK.

DG: OK. All right. Actually something in the COVID passive vaccination category this week, we have the article, "Prevention of Covid-19 Following a Single Intramuscular Administration of Adintrevimab," not a great name, "Results from a Phase 2/3 Randomized, Double-blind, Placebo-Controlled Trial (EVADE)," published in *OFID.* I mean EVADE. That's cool. They did well there. These are the results from the EVADE trial, which is a phase 2/3, multicenter, double-blind, randomized placebo control trial of a ADG20. We're going to call it that from now on. Extended half-life monoclonal antibody for post-exposure PEP and pre-exposure prophylaxis, PrEP, of symptomatic COVID-19.

So here eligible participants, this is interesting, vaccine-naive. These are folks, 12 and older who had never gotten a vaccine. They were randomized one-to-one to receive a single 300-milligram intramuscular injection of the monoclonal, the ADG20. They're going to look at some primary efficacy endpoints, so they're going to look at, are you ready for this? PCR confirmed symptomatic COVID-19 through day 28 in the PEP, that's the Post-Exposure Prophylaxis cohort. Through month three in the PrEP, the Pre-Exposure Prophylaxis cohort, so between the 27th of April, 2021 and the 11th of January, 2022, 2,582 participants were randomized.

In the primary efficacy analysis, RT-PCR confirmed symptomatic COVID-19 occurred in 1.7% of the treated versus 6.8% of the placebo participants so about a 75% relative risk reduction, so not bad actually. Then we move on to the other situation, the PrEP participants. There, we actually saw about a 71% relative reduction. In a pre-specified exploratory analysis, 428 PrEP participants randomized after emergence of Omicron, and I'll explain why. Reduced PCR confirmed symptomatic COVID-19 was down by about 41%. Well-tolerated. We have some nice figures where we can see this confidence interval for both PEP and PrEP.

Just a couple of things I want to point out, right? This was administered as a single 300-milligram intramuscular injection. The ADG20 was engineered from a survivor of a SARS-CoV infection, not SARS-CoV-2, but SARS-CoV, dare I say 1 infection.

VR: You're not supposed to say one.

DG: Yes, I'm not supposed to say one.

VR: It's like you're supposed to say Washington State either. [laughs]

DG: Yes. I guess I can't say World War I. No, I think we can. [laughs] Yes, we definitely can't say Washington State. We have to just say Washington.

VR: Remember Mark Crislip always used to complain about that?

DG: Yes. Oh, he would. Yes. Then engineered with a modified FC portion for extended half-life. While ADG20 has neutralized activity against the earlier variants, it had reduced neutralizing activity against BA.1 and BA.1.1 and lacked neutralizing activity against more recent Omicron variants. Based on that, they actually stopped enrollment in January, 2022, but interesting enough, we're still seeing some efficacy here. Part of it isn't clear. Was that

because they were still dealing with some of the earlier Omicron variants or is it because there may be some non-neutralizing mediated benefits?

VR: This is not a UA monoclonal, correct?

DG: No, no. I don't think it will. They stopped it at this point. The efficacy was not overwhelming. What you really need is, and what they actually say in the article is you really need a way to fast-track monoclonals that are appropriate for the current circulating variants. You can't take months and months and publish data a year after it would be useful.

VR: No. Once you do that, by that time the variants have moved on.

DG Yes, and I think that's a challenge. All right. We are moving into the COVID early viral upper respiratory non-hypoxic phase, and I'm going to start here with a little bit of a story and consider this a test. This is your chance to - Do I remember all that I have learned over the last three years? We're going to start with a case and we're going to go through it slowly and then our audience can be thinking, "Oh, what would I do in this situation?" Here we have a man in his 50s. He's admitted with an asthma exacerbation severe enough that requires well, hospital admission, bronchodilators and steroids.

He's been sick for about four days, and now his COVID test comes back positive. Let's peel the onion on this one. First week, what do we usually recommend in hospitalized patients? Well, you can do Paxlovid. We're mostly using that in the outpatient setting. We have to start looking at kidney function and drug-drug interactions. Number two, we have remdesivir. Perfect opportunity, right? This would be the PINETREE data, the early first seven days, the three-day, 87% reduction in progression. We're probably not going to use molnupiravir. We've already got our antiviral remdesivir on board.

He's already day four. He's hospitalized, he's non-immunocompromised so we're going to skip our convalescent plasma. Now, we're going to try to avoid doing anything harmful. Is there anything going on here which may significantly increase this individual's chance of progression?

VR: Daniel, would you pick remdesivir over Paxlovid in a hospitalized patient at day four?

DG: In the hospitalized patients, we tend to. The data is pretty similar, right? 86%, 88%. The remdesivir is an easy lift, well-tolerated, only three days versus five. The big issue here, I think, is he was given the steroids, right? People might go back and forth about it being only in his 50s, being close to that line, but once we put the steroids on board in that first week, which we were forced to do in this situation, we have really increased this gentleman's risk making the - Basically, the remdesivir is almost counteracting that increased risk we introduced with the steroids.

As we've talked about, and we'll get into this, hospitalized patients, we will move into some of the things that we do here which will be anticoagulation, et cetera. In the realm of convalescent plasma, we have another new publication. This is the article, "Coronavirus Disease 2019 Convalescent Plasma Outpatient Therapy to Prevent Outpatient Hospitalization. A Meta-Analysis of Individual Participant Data from Five Randomized Trials," published in *CID.*

Five included studies from four countries enrolled and transfused 2,620 adult patients. Comorbidities were present in 69%.

The virus-neutralizing antibody dilution titer levels ranged from 8 to 14,580 in diverse assays so comparing those apples and oranges, wide range. 160 of the 1,315 control patients were hospitalized versus 111 of the 1,305 convalescent treated patients, so plasma-treated patients. Just compare those numbers there. We've got 12.5% in the placebo versus 8.5% in the plasma treated. We're seeing a 3.7% absolute risk reduction. We're seeing a 30% relative risk reduction for all-cause hospitalization. The hospitalization reduction was greatest in those with both early transfusion and high titer.

No significant reduction in hospitalization was seen with treatment greater than five days after symptom onset, or those receiving CCP with antibody titers below this median titer level. A couple of comments, and I always think it's important when you have a meta-analysis to look at each individual study. Because what you really want to avoid is, is there some huge study here with a lot of participants? All this really is, is just a rehash of that one study. I will point out, if you go to table one and you look at the CSSC-004, you're really going to see that, well 1,225, so really a huge chunk of these patients are being contributed by that one study.

VR: Daniel, what would you do? Would you use convalescent plasma in certain situations?

DG: Well, there certainly are certain situations where I think the data make sense, right? I'm very comfortable with the ID Society of America recommendations which really are targeting immunocompromised individuals.

VR: Right.

DG: This routine use is not recommended, but if you are in that first five days, you don't have other options, which actually is part of their qualification there. They say at high risk for progression, we have no other treatment options. You're in that first week, but what are those people, right? They're going be hard-pressed to find. We say, "Oh, molnupiravir, it only gives us 30% reduction." That's all we're seeing here. It's about a 30% reduction. We are not using this in a lot of situations. There are a few centers that are doing this, but in general, it's not widely utilized.

What they do, they make a point. I think this is important for us to just think about because this is not the last pandemic. I was going to say, this is likely - No, I'm just going to say, this is not the last pandemic. It is one of those early out-of-the-gate options to be thinking about.

All right, so now we are actually moving into that second week, the early inflammatory, lower respiratory hypoxic phase, the period of the cytokine storm. We'll start off one, steroids, at the right time in the right patient.

Remember, these are individuals. It's the second week. They have oxygen saturations less than 94% on room air. That's where we jump in with dexamethasone, 6 mg a day times six days, or an equivalent steroid. We have the anticoagulation guidelines from a number of organizations, including American Society of Hematology. We move forward with pulmonary support. Remdesivir still might have a role if we're in the first 10 days. Immune modulation

and avoiding those unnecessary antibiotics and unproven therapies. All right, well, I am going to wrap it up here. Hopefully, that was a little shorter than some of our other ones.

Not so long, but not so much on Long COVID this week. I will say no one is safe until everyone is safe. I do want everyone to pause the recording right here and go to ParasitesWithoutBorders.com and click Donate. Even a small amount helps us. For us to continue to do this, we need your support. Right now, we are having our Foundation International Medical Relief of Children fundraiser. May, June, and July donations made to Parasites Without Borders will be matched and doubled up to a potential maximum donation of $20,000 from PWB to FIMRIC. I will say right now, I've been in touch with some of the folks in our clinic in Eastern Uganda. Tough times there, heavy rains, lots of mud slides, lots of malaria. They're going to need our help to continue to do that important work there.

VR: It's time for your questions for Daniel. You can send them to daniel@microbe.tv. Had a question on the live stream last night. Someone asked, "Is reactivation of herpes viruses, which we see in Long COVID sometimes, is it seen in other post-viral long syndromes?"

DG: I'm going to just say yes, start off with yes, and I think that's reasonable. There certainly is a lot of concern and a lot of research looking at that phenomenon. We're still trying to sort out the significance in the post-COVID conditions.

VR: Yes, like EBV and CMV reactivations, right?

DG: Yes. It's interesting because there's always been this controversy about their role. A lot of times in these individuals, you can actually detect significant levels of DNA in an EBV serum assay. There's a lot that we don't quite understand.

VR: Daniel writes, here you go again, writing to yourself, "As discussed last week, according to the subgroup analysis for the metformin trial, the only groups with a statistically significant benefit were those less than 45, the unvaccinated, and those with a BMI greater than 30. If you fall into one or two of these groups, should you get metformin or only if you fall into all three of these groups?"

DG: This is a challenge because, as we talked about, the concept of why this is working is the theoretical antiviral lactivity. It really raises the question, if you can jump in with something like, we'll say, Paxlovid and 86% to 88% reduction in progression, are you going to get maybe the same benefit? Are you maybe even going to get more of a benefit? Metformin is certainly not EU AID or FDA approved or recommended by any guideline society for the prevention of Long COVID. If that's the mechanism, and actually, part of the discussion was this was served for people who can't afford or get access to Paxlovid, which strikes a nerve for me.

I don't think that we should have that a hierarchy with health care. Yes, so at this point, I don't think this is routinely recommended. What's routinely recommended, and there is a bit of evidence that is growing, is that early antiviral activity, getting vaccinated, these are effective ways of reducing the risk of Long COVID.

VR: Courtenay writes, “I've been looking for the past few weeks for any evidence that suggests our vaccines we received back in the early fall are still protective against serious disease and death with current variants. Paxlovid is still super strictly controlled here, and Courtenay's

writing from Kamloops, BC, Canada. You have to be old and have other conditions to get it. I know you've said you're leaning toward people not needing another booster, but I just can't find the data to base that on, so I thought I'd reach out."

DG: I feel bad when they're talking about maybe metformin is for people that can't afford Paxlovid. Maybe they're talking about the Canadians, where they're not allowed to get Paxlovid. There is consistent data that we are continuing to get. Even the WHO in their recent meeting really reinforced the vaccines continue to give protection against severe disease, continue to give protection against hospitalization. We've talked about how boosters can boost. There are certain populations where it makes sense to get those neutralizing antibody levels up to a higher level for a period of time, preventing even infection.

We also have growing evidence of vaccines really reduced, not just hospitalization and death, but even your risk of getting Long COVID. I think this is one of those tough things. What do you do? You don't meet criteria. You can't get the Paxlovid. Maybe for you, the risk is Long COVID. Do you consider looking and having a discussion with your doctor about something like metformin? I'll just put that out there. That's something to discuss that is not recommended at this point by any society.

VR: Bob Krug writes - now, do you know who Bob Krug is, Daniel?

DG: It's a familiar name. Is this the Bob Krug?

VR: It's the Bob Krug who discovered the cap snatching endonuclease in influenza virus. He listened to our last update. "I certainly agree with Dr. Griffin's statements about antiviral Tamiflu, which has been used for about 25 years. Dr. Griffin reported results showing that Tamiflu did not significantly decrease hospitalization of flu patients, including people 65 years and older. In fact, a great deal of evidence over many years has shown that Tamiflu is not a particularly effective antiviral. It's not surprising because it's a weak inhibitor of virus. Tamiflu has to be taken twice daily for five days to sufficiently inhibit replication. For this reason, National Institute of Allergy and Infectious Diseases has provided a large amount of funds in the last 15 to 20 years for the development of more effective influenza antivirus. A very effective influenza antiviral called Xofluza was introduced in 2018.

Xofluza inhibits the cap-snatching step required for the initiation of viral mRNA synthesis. A single dose, it eliminates essentially all virus within 24 hours, reduces hospitalization better than Tamiflu because the patient doesn't produce virus within 24 hours. The spread to household members is reduced. This is a great benefit. Virus spread to the general population is also reduced. It's been estimated that administration of Xofluza to only 30% of infected individuals would avert about 6,000 flu deaths in the U.S. each year. Why did Dr. Griffin not mention Xofluza?"

DG: [laughs] OK. Dr. Krug, thank you for mentioning Xofluza. I didn't mention it, right, because we were discussing the article about Tamiflu, but this is a great segue. Is that how I pronounced that word?

VR: Yes. It's good.

DG: Segue? [chuckles] Apparently when I saw that written out, I called it segue or something, and everyone just started rolling their eyes, and I'm like, "What is that word?" Yes, so actually, this is great for our listeners to get this out in front of them. Maybe there'll be a paper published on this in the fall, just in time to get this on everyone's radar. Yes, in 2018, the FDA did approve Xofluza. There were a couple of RCTs, hundreds and hundreds. I think it was like 2,000 patients. You did see a significant shortening, statistically and clinically significant, in the shorter time to alleviation of symptoms. A couple of things have been brought up, and I'll just say maybe this is a marketing issue, Dr. Krug.

You may have to talk to your buddies at Big Pharma. There were about 2% mutation rate in the early studies that went up to 10 or 20% when you got to the phase 3. People started worrying about that. Then again, you've already given the dose. It's already had the impact. Is that onward transmission of mutated flu? Does it really matter? The other, it's a couple of hundred bucks, probably about $150 to $200 for that one pill that you have to take. No, I think when we talk about how limited and how less than compelling the Tamiflu data, nice to give a plug here for the Xofluza.

VR: Do you ever prescribe Xofluza thing?

DG: I have never prescribed Xofluza.

VR: But you have Tamiflu, right?

DG: We have used Tamiflu.

VR: Maybe you should consider Xofluza. I have no connection with whoever makes Xofluza, just to say. Finally, Chris writes, "Does airborne exposure to wildfire smoke particles of 2.5 microns that can potentially damage the lungs, render the victim to increased susceptibility to SARS COVID-2 infection, and lead to COVID-19 disease?"

DG: I do not know, but there are some interesting studies from flu, actually, where there's actually an association with a better penetration to the lower airways with the smoke fire. Yes, I don't know of any specific COVID-19 study where maybe the SARS COVID-2 virus might have somehow facilitated entry, or there might be some increase in susceptibility to SARS-COVID-2 infection, COVID-19. I do think that this is a great thing to be thinking about. I think we all should be thinking about the quality of our air and what we can do to improve it.

VR: There's a page on the CDC website called “Wildfire Smoke in Covid,” they say, you know, wildfire smoke can irritate your lungs and potentially make you more susceptible, but I don't know that we've had studies that would - It would be associations of course, right?

DG: Yes. It would make sense. I wouldn't be surprised. Yes, I have yet to see a good study and when we do have a good study, I'll certainly share it.

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

DG: Oh, thank you, and everyone, be safe. [music]

[[00:40:41] [END OF AUDIO]