This Week in Virology

TWiV 1100 Clinical Update

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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.

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From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 1100, 1,100? Got to figure out how to do that, recorded on March 28, 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: Should it be 1100 or 1,100, Daniel?

DG: I think both are OK. I don't know if there's any one that has precedence over the other.

VR: When you say 1958, it's not 1,958, 1958. It should be 1100.

DG: Yes. I think it'll be interesting because next time it'll be 1102. I'll say that. 1102 is a lot easier to say than 1,102. Just gets to be a little -

VR: When we were in 2,000, though, we said 2,000.

DG: Yes.

VR: Not 20. 2002. 20-aught or something.

DG: I guess we used to say, I remember my kids were born, 2,000, 2,002, 2,005. Now I would say, "Oh, so and so was born in 2024."

VR: Yes, that's much easier once you get into the 10s, 2010, 2011.

DG: When we get to 2,000, I think I know what we'll do.

VR: What's on your bow tie today, Daniel?

DG: This is very hard to see. I don't know if anyone's going to zoom in on it. It's supposed to be Strep pneumo. If anyone zooms in, there's these little gram-positive cocci. They're not really in pairs the way I would like. Sometimes the artist -

VR: They used to call it Diplococcus.

DG: Yes.

VR: Then they said, "Well, they're not all these pairs, so we better change the names."

DG: Yes, sometimes they're in strips.

VR: Good.

DG: All right. Let's jump right into it. “Our knowledge can only be finite while our ignorance must necessarily be infinite.” That's by Karl Popper. It's really funny because, my personal simplified quotation here has always been what we know is finite, what we do not know is infinite. I thought I would Google and see if someone else had already come up with a quotation along the same line just to make sure that I wasn't just quoting someone else unnecessarily. No, I think that this is this lesson in humility, even the most brilliant among us.

I remember when I went to the University of Miami for my first year of university, and there was a physician there, actually a professor there, Dr. Knobloch. The man was brilliant. Got his PhD when he was 21. He spoke 15 languages. He would teach without even books. You'd ask him a question and he would look around and point to the different editions and tell you which page, how many lines, and how many words in. At some point, I realized, "OK, yes, never going to be as bright as I think I am." I think it's really important in science and medicine to realize as much as we think we know, there's an infinite amount that we do not know.

Moving right into measles, and we talk about measles a little bit more. I was clicking on this link earlier today like, "When are you going to update the March 21, 2024 data?" because as of March 21, 2024, here we are on the 28th, a total of 64 measles cases had been reported here in the United States. Just to keep things updated, since they put that there, we had a reported case in New York City and we just had a confirmed case out here on Long Island, Nassau County. I probably won't go into too many specifics until that's - it was a big gathering, child ended up being sent to one of the local hospitals and confirmed measles.

I just thought I would talk a little bit about what is going on with measles. Over time, a low level and usually what we've seen is unvaccinated children in general. Maybe someone travels. Measles is a huge problem throughout the world. They bring it back. We get these outbreaks. Maybe one of these individuals goes to Florida or Disney or something. Then we've had a couple of outbreaks. A few years back, we had 600, 700 cases. Then we had that big outbreak in 2019. We had over 1,000 cases. We're really marching forward at this point.

I know that Vincent, on some of the other science shows, you always say, "OK, if you like what we do, consider supporting us." This is really a call to arms. There's a few of us out here really trying to spread the word, trying to educate, trying to do the science communication, but really, the other side is this billion-dollar industry that is focused on undermining science and leading to children getting quite sick, children developing lifelong issues with vision, with

hearing, with all kinds of other disabilities. Really call to action. We all need to be part of teaching the science.

Every time you get in that situation where someone starts spouting the anti-science, you've got to respond. It's worth our time to educate and spread accurate science information.

Moving on to the flu, a bit of good news here. We skipped right by RSV because things have really gone in the right direction there. Finally, we're really seeing flu numbers start to come down. I do think we're getting near the end of this season's flu season. This is happening in most parts of the country. There's a few hotspots still out there. I'm not planning on visiting Nebraska anytime soon after I look at this map. No, in general, I think we're really going in the right direction. Hopefully, as things get warmer, more time outdoors, we're going to be getting through.

Now, COVID, got to present this a little bit differently this week. Two ways, I've been sharing the BNO numbers where we're still - new deaths last week, over 1,000, still over 1,000 folks getting admitted to the ICU, still over 10,000 folks in hospital. The CDC actually has a map much like they do with the flu. It actually gives you the percentage of deaths due to COVID-19 in the past week. They break it down by region.

It's really interesting to see that there still are a few hotspots. Florida is going strong. Between 2% to 4% of all the deaths in the past week in Florida were due to COVID. Somewhere between one in 25 and one in 50, that's pretty solid. It also is going on for Tennessee and North Carolina, Ohio, Maryland. A few hotspots we're still seeing there.

VR: Daniel, do you think the Florida situation is because there are a lot of elderly people there or because of the anti-vaccine rhetoric?

DG: I worry it's the anti-vaccine, the anti-science rhetoric. I was on a call the other night. It was one of these three-and-a-half-hour Zoom meetings with a number of purported experts, I was there, on COVID. One of the participants was from the South, and just saying a lot of times they just give up. People are still asking for their hydroxychloroquine, their ivermectin, not wanting to get boosters, not really understanding the importance of early treatment. It's a combination of things. As I say, numbers are still high, but going in the right direction when it comes to COVID, and wastewater continues to trickle down. I like that imagery there. I think we're going in the right direction there. We seem to be settling into this pattern and we'll see of where we have our really high peak. December, January, February, things come down. We get this second peak in the summer. Going to be interesting to see if that is the establishing pattern. We'll know come summer. We have some pretty exciting news this week. Hot off the press. COVID passive vaccination. Maybe we'll talk a little bit more about this because I cheated this week. I usually don't look at the emails that got sent in, but I looked this time because I know someone has a question about this.

Dare I say, finally, an Evusheld replacement. On March 22, 2024, the FDA issued an emergency use authorization for Pemgarda (pemivibart). I'm going to put my glasses on here. This is a pre-exposure prophylaxis, or a monoclonal for pre-exposure prophylaxis of COVID-19 for certain adults and adolescents, 12 years of age and older. Pemgarda is authorized for individuals who are not currently infected. This is pre-exposure, who have not had a known

recent exposure, pre-exposure, and who are moderate to severely immune compromised or who have moderate to severe immune compromised due to medical condition or due to taking immunosuppressive medications or treatments and thus are unlikely to mount an adequate immune response.

I'll leave a link into the FDA announcement. Where did this come from? They based this approval on interim data from the ongoing CANOPY clinical trial. You can actually go to the company to Invivyd. It's I-N-V-I-V-Y-D, but that Y is a monoclonal antibody. It's cute. This product, this VYD222, is a neutralizing half-life extended monoclonal antibody, so a monoclonal antibody that lasts a bit longer, that is being investigated, so ongoing, for the prevention of COVID-19 in this population of immunocompromised adults and adolescents. It's designed to have this broad activity, and it has this in vitro neutralizing activity in pseudotype virus-like particle as well as actually authentic virus neutralization assays.

They've looked at this in pre-Omicron as well as Omicron variants, including, I think this is relevant, JN.1. A comment here, it's given via IV infusion. This isn't quite as easy as just getting that IM shot. We'll have to see if it can be delivered that way. We have some data. We have data looking at individuals. The first data we got was a median of 35 days follow-up. Looking at 306 folks, we saw 0% in the one group. We moved that out to 67 days, still 0% in the treatment group versus 3%. Then we actually have data out to day 90, where we're actually starting to see some folks end up.

I would love a little more data here. It's a little thin on the data. I'd love to see any outcomes here as we see just confirmed symptomatic COVID-19 with people progressing to severe disease. I think that there was a vacuum here. I don't know.

VR: I'm curious what the epitope is because it's conserved, obviously, Omicron and pre-Omicron. I couldn't find it in the few minutes that I've been looking here. You don't happen to know, do you?

DG: There's an interesting history here. This company, Invivyd, it's Adagio reincarnated. That was another company that at one point was trying to produce these monoclonals that apparently were variant-proof, sort of this holy grail. I don't know exactly where it's binding. A little bit less information than I would like for an FDA-approved drug. Moving on to COVID early -

VR: It's EUA. Not approved?

DG: Actually, I believe it's - let's take a look here. It says emergency use. Yes, EUA. Not approved. Yes.

COVID early viral phase. Keep those COVID-19 treatment guidelines right there to share. I even noticed on this call, there still is this - it's really a mentality that we have to move past is, these experts were saying that, "Oh, sometimes if they have a patient, the patient is hesitant about medication. They'll say, 'Well, why don't we see how you do over the next couple of days?'" You can imagine my reaction to that bit of advice. This is not a situation where you wait to see how you can do.

As we've seen repeatedly, those symptoms during the first week don't always predict the severity of the cytokine storm. Our goal that first week is to reduce your severity of the second week. Number one, Paxlovid. We've got another article, title threw me a little, but we're going to move through. “COVID-19 Rebound after VV116 versus Nirmatrelvir/ritonavir Treatment: A Randomized Clinical Trial,” published in *JAMA Network Open.* Some think of this VV116 as the oral remdesivir. This VV116, it's a prodrug of a nucleoside analog approved for use in Uzbekistan, that's curious, being used in clinical trials in China.

It is a deuterated form of remdesivir. Selective replacement of protium hydrogen isotope atoms in small molecules with deuterium hydrogen isotope atoms. Curious. Apparently, this deuterium replacement improves the pharmacokinetics. The biggest thing is that this has good oral bioavailability. It's absorbed well, good tissue distribution properties. Upon administration, the VV116 is metabolized into the parent nucleoside, which is then converted intracellularly into the active nucleoside triphosphate. Ultimately, basically, it's an RNA-dependent RNA polymerase inhibitor. It's oral remdesivir, I think you could say.

Now here we have the results of a single-center, investigator-blinded, randomized clinical trial conducted in Shanghai, China. Adult patients with mild to moderate COVID-19, that's when you want to treat them, within five days of SARS-CoV-2 infection were enrolled between December 20t 2022 and January 19, 2023, randomly allocated to receive either VV116 or nirmatrelvir/ritonavir. Participants in the VV116 treatment group received oral 600 milligrams VV116 tablets every 12 hours on day one and 300 milligrams every 12 hours on days two through five.

Maybe they can market this as a VPAC. All about the marketing. Participants in the nirmatrelvir/ritonavir treatment group received the oral nirmatrelvir/ritonavir tablets with 300 milligrams nirmatrolvir plus 100 milligrams of ritonavir. They get that twice a day for five days. Then the participants were followed up every other day until day 28, and then every week until day 60. What was the primary outcome? Viral load rebound, defined as a half-log increase in viral RNA copies per milliliter compared with treatment completion. Secondary outcomes, which were more interesting, included a reduction in the cycle threshold value of 1.5 or more.

Time until viral load rebound and symptom rebound defined as an increase of more than two points in symptom score compared with treatment completion.

VR: Daniel, half a log? In my lab, we don't care about half a log difference. That's ridiculous.

DG: I remember coming to one of your PhD students' presentations and someone was asking for statistics on something and you were basically, "If it's not black and white, if I need a statistician to tell me."

VR: That was Ian Lipkin. He said, "Where are the error bars?" I said, "Ian, there's a one- to two-log difference. You don't need error bars."

(Laughter)

DG: "Look, this is this, this is that."

VR: Quite clear.

DG: "Oh, you can't publish without p-value." I'm like, "Oh my gosh, I think we should stop publishing just because we have p-values."

VR: The thing is, in this paper, Daniel, they are already saying, "There is rebound and this is how we measure it," which seems to me that's not how you do an investigation.

DG: It's interesting. With this really narrow focus here, they're going to say, "Hey, we're going to see this 20% of the time depending upon who we look at," and then they're going to try to get a statistician to show them there's a difference. Basically, at the end of the day, they're saying, "Yes, it's the same and we're seeing it in both cases, and really not much of a difference here." I just thought it was an interesting way to put a study together.

It's interesting, "OK, here's some stuff," because now what's going to happen is no one's actually going to look through this and say, "OK, they used this really low bar for their - they redefined viral load rebound for us and then they found that it was 20% of the time with the VV116, about the same with Paxlovid and then the same about a quarter of the time, people get better and then they say, 'Hey, during the second week, I feel like I got a couple of symptoms coming back." What does this really mean? I'm not sure it means a lot actually as far as options on the horizon, eventually, we might get the VV116.

There's another Obeldesivir from Gilead, oral forms of remdesivir are looping them here, and also perhaps Ensitrelvir, Xocova, that's an oral protease inhibitor out of Japan from Shionogi. That's the Paxlovid alternative, but instead of the ritonavir boosting, you just take three pills on day one and then one pill a day for day, two, three, four, five. I'm going to call that the X-Pak. We're going to have our Z-Paks, which we shouldn't be giving, our V-Pak maybe, and then the X-Pak from Shionogi.

VR: There were no untreateds in this group.

DG: No. They're just comparing these two groups.

VR: Two drugs.

DG: No. Don't worry, it's going to get lots of press, lots of questions.

VR: Of course.

DG: I don't know what to make of it. Just a brief mention of the article, "Vaccination Effectiveness and Antiviral Drug Effectiveness for COVID-19: A Causal Inference Approach," published in the *International Journal of Infectious Diseases*. In the study, the investigators identified hospitalized adult patients, 18 and above, in Hong Kong with confirmed SARS-CoV-2 infection between March 16, 2022, and December 31, 2022.

An inverse probability-weighted Andersen-Gill model with time-dependent predictors was used. Basically, what they're trying to do is they're trying to erase that whole immortal time bias thing and really give us estimates for the protection effects of oral antivirals and vaccinations against severe COVID-19. They found that in this cohort of 61,105 patients, as

long as the antiviral was started within five days of confirmed infection, Paxlovid was more effective compared to molnupiravir against all-cause mortality and development of severe COVID-19.

Then they've got a decent table, number four, where you can look through different vaccines, one dose, two dose, three dose, four dose, and then the impact of the different antivirals. I'll just leave a link for folks to look through that. Number two, remdesivir, if you can get it. Number three, molnupiravir, convalescent plasma in some situations. There was a physician on the call from the Mayo, and they're still using that in some of their high-risk immunocompromised folks out there. Actually, sometimes in combination with antivirals. Then we have our updated CDC isolation guidance for respiratory virus infections.

Speaking of isolation guidance, we have the article, "Timing and Predictors of Loss of Infectivity among Healthcare Workers with Mild Primary and Recurrent COVID-19: A Prospective Observational Cohort Study," that came out in the latest edition of *CID*. This is a prospective observational cohort study with serial virus culture, rapid antigen detection testing, and RT-PCR nasopharyngeal specimens of healthcare workers with COVID-19. The primary outcome was viral culture positivity as indicative of infectivity. They're going to use infectivity all over. What they really mean here is viral culture positivity.

With all the limitations we talk about with using quantitative PCR and viral culture, binary as well as quantitative, not being the same as contact tracing and actual documented transmission, we read here that viral culture positivity decreased from 71.9% on day five of infections, pretty high, to 18.2% on day 10. Participants with recurrent COVID-19 had a lower likelihood of a positive culture than those with primary COVID-19 at each day. They give some comparisons there. Independent predictors of a positive culture included prior COVID-19, an RT-PCR cycle threshold of less than 23.This is really important; not symptom improvement and not a rapid antigen test result. Flying in the face of the recent, advice.

VR: Daniel, this doesn't really help because you don't know how much virus is there. It's a binary assay. Those people who are positive on day 10, 18% of them, maybe they have a few PFU coming out and it's not enough to transmit. Really what you want to know is how much they are shedding, not just yes or no.

DG: You got to do some kind of a transmission study where you actually validate, is your culture positivity correlated - Are these people contagious or you can just grow it in the lab? Are you really good at it? You're not really good at it?

VR: No, culture positivity is really not useful. PCR is not useful and neither is culture positivity. You need a quantitative assay.

DG: Yes. That quantitative assay has to be validated. I'm going to mention the *Immune* where they did that human exposure trial in the UK. What you really need to do is you need to track these folks and like, "Are you spreading it to others? If you had some sort of correlate of transmission, great, but you can't just make believe you do with viral culture positivity binary here. Do I really think people are transmitting on day 10? I really don't. We don't have data to demonstrate that.

VR: Probably not, but they would say, "Oh, 22 out of 120 are positive. We have to keep you at home." That's ridiculous.

DG: Yes. No, there's a burden of proof on that kind of an intervention. The next one, we also have the article “Household Transmission Dynamics of Asymptomatic SARS-CoV-2 Infected Children: A Multinational, Controlled Case-ascertained Prospective Study,” published in *CID.* I'm going to give this the short working title. “Scientists discover that sick kids can make you sick.”

VR: That's great.

(Laughter)

DG: Yes, scientists have stumbled onto something. Parents have suggested for some time that sick kids can get other people sick. All joking aside. Here, these investigators found that asymptomatic SARS-CoV-2-infected children, especially those less than 5, were important contributors to household transmission with about 10%, one in 10, exposed household contacts developing symptomatic illness within 14 days of exposure to an asymptomatic SARS-CoV-2 PCR-positive kid. The other, which was really more disturbing, these asymptomatic SARS-CoV-2 infected children, actually a percent of them, almost one in 13 went on to develop post-COVID conditions.

Not great because you wouldn't think to jump in or treat these kids like, "Oh, the kid's fine. They're doing fine. How many symptoms? He's got this positive test," but one in 13. That's not great.

VR: Daniel, I think you missed your calling as a headline writer.

DG: Yes, I think everyone would read that if I had that.

VR: Yes.

DG: What your doctor doesn't want you to know is that kids can make you sick. Cytokine storm week. This was something that came up on this discussion. I think we've got to keep hammering this in. This is not a disease where you say, "Oh, why don't we just see how you do?" What we're really worried about, people really tend not to die during that first week. People tend to die during the second, third, when the inflammatory cytokine storm kicks in. What are we doing during week two? Steroids at the right time in the right patient at the right dose. This is after that first week in patients with oxygen saturations less than 94%.

We have anticoagulation guidelines, pulmonary support, remdesivir still in the first 10 days, immune modulation, and really avoiding those unnecessary, unproven, potentially harmful therapies.

COVID, the late phase. A couple of things I'll say here. I'm currently working on an evidence-based Long COVID review. Boy, it's going to take me a while to get through this. I've got writer's block or something. There are so many publications out there which are my ideas about what causes Long COVID. Now I'm putting together the actual evidence behind each of these different possible mechanisms, evidence, and what we can do.

A big thing I want to say is that, this is for a lot of providers a tough area. We just don't feel as comfortable, as confident. None of us learned how to treat Long COVID in medical school. Maybe that will change going forward. We may be uncomfortable. Remember, our patients don't always understand all this science. We don't always understand all this science. One thing they do understand is kindness. Until we learn more, at least we can offer that. I did want to also plug *Immune* 78, which I listened to yesterday. There's some great stuff there, Vincent. I won't do it justice.

I'm going to basically tell people to go ahead and listen to *Immune* 78. One of the papers, "Gut Bacteria-Derived Serotonin Promotes Immune Tolerance in Early Life*,"* some very interesting ideas about serotonin actually coming from gut bacteria. Then the other paper, which was what we alluded to, the paper of, "Mucosal and Systemic Immune Correlates of Viral Control after SARS-CoV-2 Infection Challenge in Seronegative Adults." A number of things in there were fascinating. One is showing that it was actually the T cells coming in, which I thought was interesting. Then the immune response being associated with the cytokine stormssymptoms, really more of a correlation with the immune response than the viral load.

VR: The T-cells were correlates of protection. These are people with mild disease. It could be different for severe disease but for mild disease, when you get better, it's because of your T-cells and they say probably also antibodies but they didn't really have as good evidence of antibodies .

DG: They have to put those in. Before we get to emails, I will conclude as I have for a number of years now. No one is safe until everyone is safe. If you didn't pause the recording up front, pause it here, go to parasiteswithoutborders.com, and click on the 'Donate' button. Every small amount helps, every bit helps us to continue our work and really the work we're doing here, spreading the word, science communication, we're saving lives and if you contribute, you're part of that. We have a growing problem with orchestrated misinformation for the profit of those that dole it out.

In addition to what we do, we are doing our American Society of Tropical Medicine and Hygiene fundraiser where during February, March, and April, we're going to double your donations up to a potential maximum donation of $20,000 and a portion of these funds will go to providing travel awards for two female qualified students, early career investigators.

VR: It's time for your questions for Daniel. You can send yours to Daniel at microbe.tv. Rick writes, "I live in Denver, Colorado. It seems I'm hearing about more people having issues with gastroenteritis this winter season. Most have been affected for about a week. Are you seeing an uptick in viral gastroenteritis also? If so, is norovirus the most likely cause?"

DG: We are having a ton of norovirus. Can we quantify viruses as tons? It probably is a ton. Maybe the diarrhea is in the tonnage form. Norovirus is tough and actually, there was a *TWiV* special last week where one of the poor investigators had decided he would do some norovirus investigations. This is the one you recorded in the German castle, Vincent?

VR: That's right. It was in Heidelberg.

DG: In Heidelberg. This is a recurrent thing. There are so many different, I will say, antigenic variant noroviruses that this is not always a one-and-you're-done-with norovirus. You could

have it more than once. I was sharing on the *Puscast* with Sara about the time I had norovirus last winter and fell backwards down an escalator in my dehydrated, infirm state trying to travel to Arizona and vacation with the kids.

VR: Oh my God.

DG: We are seeing a lot of norovirus. One of the great things is actually now we're aware that we're seeing because we do these syndromic multiplex PCR panels. It's incredible. It just takes 10, 12 - very few virions to initiate infection, vomiting, diarrhea. When the person vomits, you can actually aerosolize this. This is the cruise ship disaster where people are vomiting. It's getting sucked through the air vents and blown into other people. We're seeing a lot of norovirus. That's the most common, but one of the great things about our new technologies is you can test and in short order find out, because if it's norovirus, not just using that alcohol, this year at Chipotle getting the good stuff, you've got to really get some good handwashing to keep this from spreading to everyone else.

VR: This week I gave a lecture on acute virus infections and norovirus is one of them. Here's a nice statistic I have for diarrhea, Daniel. In any 24-hour period, the amount of water passed by people who have gastroenteritis is equal - 200 million people have gastroenteritis in that time and the amount of water they pass is equal to the amount of water flowing over Victoria Falls in one minute which is 65 million liters. Sixty-five million liters of diarrhea in a 24-hour period. That's a lot of diarrhea.

DG: You have a slide with the visual where it turns brown for a minute?

VR: That would be good.

DG: You can have some bio-render do that for you.

VR: That would be good. Alan writes, in this post on Substack, Dr. Jeremy Faust expressed the satisfaction that a new monoclonal antibody Invivyd has been approved for SARS-CoV-2 infections and prophylaxis against COVID-19 and bemoans the 14-month gap following the FDA's withdrawal of its approval for Evusheld. He argues that Evusheld should never have been pulled from the market because the FDA's decision was based on lab data without looking at clinical data. Assuming that this is true, which I have no way to verify, he makes a fair point.

If mice lie and monkeys exaggerate, one imagines that Petri dishes probably aren't any more reliable as predictors of in vivo human outcomes. I would really appreciate your perspective on the article and the overall situation with FDA approvals in the ongoing campaign to rein in COVID-19.

DG: Yes, a great comment. This echoes back to some of the things we've talked about. A lot of our assays are just neutralizing assays. As we've mentioned, the neutralization is not the only way that these monoclonals, and antibodies in general, can work. Are there FC functions? Really, there was nothing there for these folks for this over-a-year gap. It really would make sense to look at clinical outcomes like, "OK, so now that we've lost neutralizing activity, and maybe it's a lesson for us going forward, are we starting to see a higher percent of these people progress? Are we seeing therapeutic failure?"

Maybe this is a call to folks like at the Mayo where they're sometimes using combination therapy in folks and start asking, "OK, your immunocompromised folks that you're giving this new product to, are you starting to see a lot of them get infected? Are you starting to see this fall off?" I do bemoan just using a neutralizing assay to pull something off the market when there's really nothing left in its place. Yes, good comments here.

VR: Philip writes, "I had an injected typhoid vaccine two years ago, and I'm due for another. My doctor prescribed Vivotif. My pharmacy is having a hard time getting it. Thinking of the polio vaccines, oral and injected, would an injected typhoid vaccine and an oral typhoid vaccine give both blood and gut immunity? Would that combination offer more protection?

DG: It's a great comment. Just say I don't know, but maybe give a little more background for people on this. A lot of times, we'll give the injectable in a lot of our travel clinics. It probably lasts a year or two. The idea is that oral works a little bit longer, but the oral, you've got to keep in the fridge. You've got to take it every other day. It's four doses. There's a period of time when you couldn't get it. It was off the market, not being produced. Now it's back on the market, but sometimes, as you can see, there can be issues with access.

It's really an interesting idea that you would do the injectable and the oral. I think it's a little different than with polio. We don't have this issue of this vaccine reverting, causing a small but a solid number of people having issues with symptomatic polio. Interesting comments. I'm not sure I know.

VR: Robert writes, "Use of PCR to guide antibiotic therapy. Laboratories are pushing for the use of PCR to identify microorganisms, including resistance patterns to allow earlier use of appropriate antibiotics. I see some literature that suggests use in diarrheal syndromes can be helpful, but I wonder if there is literature which validate use in other clinical syndromes. I would suspect that bacteremia with blood specimens would allow earlier identification to direct therapy. What about urine, sputum, wounds, et cetera."

DG: We are using this more and more in clinical practice. Let's go through a little bit. Thanks for opening up this box. Sara and I on the recent *Puscast* talked about a study. I talked about it. Sara is not as excited about the multiplex syndromic PCRs as I am. I'll just share. This is where they were using it in pediatric ERs, pretty robust study. In the pre-syndromic PCR era, they were only identifying the etiology of the diarrhea about 3% of the times. Now, once they introduced this, they were identifying the etiology of the diarrhea in 74% of the times.

That's significant, 3% versus 74%. Also, there was a significant increase in the appropriateness with which these children were managed. That's huge. They reduced the return visits in half, and Sara made the comment that she doesn't always need to know what the diarrhea is caused by, but the parents want to know. If they don't know, and the child is still having diarrhea, they're going to bring them back. If you can explain, OK, this is what it is, this is what we expect," if they know what's going on, and there's an expected natural history that you can educate them with, that's great.

You're going to reduce the inappropriate treatment significantly because so many people throw antibiotics at norovirus. That's something that came up. Now we're using this in other situations. I had a gentleman in the ICU this last week, a gentleman I know well. He's been in

and out of the hospital with a number of issues, and in the ICU, critically ill. We do blood cultures, and actually later that evening, first we get a positive blood culture, and then very quickly we get that the blood culture is positive for Proteus, Pseudomonas, and the ESBL genetic loci.

Very significantly changing our management, knowing I've got to adjust my antibiotics to cover extended-spectrum beta-lactamase organisms, I've got to cover Pseudomonas. These tests are really helping us. Now, unfortunately, you have to be careful because 80% of our counties have no infectious disease consultant to help.

A lot of folks get a respiratory viral pathogen panel or a respiratory pathogen panel. It turns out it's human metapneumovirus, there's no evidence of airspace disease. This is a classic situation where you can stop those antibiotics, manage them symptomatically off antibiotics. If you look at the literature, a lot of docs just continue that ceftriaxone, azithromycin, or whatever else they're throwing at them, the zosyn vancomycin.

The key to these new technologies is having an appropriately educated person respond and actually achieve that improved quality of care.

VR: Anne Sebo writes, "I'm a retired nephrologist. I've been a faithful listener to *TWiV* and your clinical updates since April 2020, *TWiV* 598. Who was that masked man?" That was Daniel. "Michael Schmidt, who is one of the hosts on *TWiM*, introduced me to *TWiV* and the other MicrobeTV podcasts. I utilize *TWiV* to provide me with the facts that I can then spread to my community and fellow physicians. I found your delineation of the phases of COVID-19 infection especially helpful in understanding the approaches to treatment.

One bit of confusion for me is the recommendation for remdesivir in both the early viral phase and the second week inflammatory or cytokine storm phase."

"Although Paxlovid and remdesivir have different modes of action, they're both antivirals. For that reason, recommendations for the inflammatory phase do not make sense to me. I imagine that the recommendations come from the early studies of remdesivir when it was given to hospitalized patients who were in the early inflammatory phase and showed some effectiveness.

I suppose that if we did similar studies on nirmatrelvir and ritonavir, we might get similar results. I would be interested in your comments to clear up confusion for physicians who share this kind of thinking. Thank you and the entire *TWiV* team on being a great trusted source of information on all things viral."

DG: Yes. This is great. I'll go through. We are using antivirals basically as antivirals. When there's still ongoing viral replication. Each different agent has a slightly different profile when it comes to the science behind it. With remdesivir, if you can get it in within the first seven days, that's the pine tree data, about a 90% reduction in the risk of progression. Great stuff. If you miss that first window and it's day eight, nine, or 10, there still is a little bit of benefit. We're seeing some reduction in mortality.

That's remdesivir. You're still going after that viral replication phase. You're not using it as an anti-inflammatory. Now we'll move on to Paxlovid. The data was the best for the first three

days. We still saw some benefits out to day five. We don't have really data showing us that day six, seven, eight, nine, and 10 are going to have benefit. That's where the science really pushes us to getting in early. Ensitrelvir, that's the Shionogi product I just mentioned a little bit earlier.

In there, you're really looking at only the first three days seeing any kind of benefit in the studies they were looking at. The concept is still there. You're trying to jump in, but each different product, each different antiviral has a window of opportunity.

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

DG: Thank you and everyone be safe.

[music]

[00:44:33] [END OF AUDIO]