COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Caroline Zeiss (Yale University), June 9, 2021

Title: *RAPID: An in vivo driven SEIRS (susceptible-exposed-infectious-recovered susceptible) model of coronaviral infection*

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YouTube Recording with Slides

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Hi everyone thanks for joining us. I'm going to follow on a previous talk, namely how long does how long does protection last after you've been exposed to COVID either naturally or via vaccination? And to study that we looked at an animal model. We didn't look at antibody levels but we did look at the amount of shedding and the capacity for that shedding - shed virus to reinfect naive animals.

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So we used a native rat virus called SDAV. This is a rat-specific beta coronavirus that is very closely related to the seasonal human coronaviruses we get. Its next closest neighbor is MERS and then the next one after that is SARS-2 and it causes a relatively mild interstitial pneumonia that is transient. The animal recovers in 10 to 14 days, so it's not a great model of lung injury. However, it is a good model of transmission because all of the essential features of SARS-CoV-2 transmission are replicated in this virus. So we used SDAV to model transmission of SARS-CoV-2. We also used another rat coronavirus, also quite closely related, to model vaccination and so the analogy here would be a live viral vaccination. Our intent for creating this data is then to put it all into an SEIRS model, which is a mathematical model, to model epidemic to endemic transition which is what we're doing now. All I'm going to present today is the in vivo data.

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So this is how we modeled initial exposure to SDAV. The capacity to generate an immune response is dependent not only on the individual but on the mode of exposure. So the higher the viral exposure generally the better the immune response. We wanted to model high risk and low risk exposures. We started off with inoculating rats with known amounts of virus and then exposed those to recipient rats via a couple of routes. The first was via direct contact and then our low-risk exposures were fomite exposures. One was a fomite cohabitation model where after the fomite exposure the recipients were co-housed so if one got it, it could give it to another via direct route. And in the other they were single housed and that was our lowest risk exposure. So we see that when we separate all of these recipients out, these are our positive controls throughout so these are animals that are inoculated that are red. We see that their PCR positivity rate- so these animals were swabbed for five days sequentially after exposure. Their PCR positivity rate is a hundred percent so pretty much similar between direct inoculation and direct contact and they also are converted. And then as we go down to our lower risk exposures, their PCR rates go down and so do their seropositive rates go down. Just to note the Cq- this is the cycle number: low is more, so this is the threshold at which you detect the virus and we see that with direct inoculation and direct exposure we're looking at around 28 to 29 cycles. And then the shed amount of shared virus is much lower with the lower risk exposures, which is what we expect to see. We also notice that shedding exceeds conversion, so the virus can replicate in the nose and be shed and be detected as a positive test but it doesn't penetrate the body enough to actually induce seroconversion.

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And the point of that is that even though you test positive to extrapolate to COVID, it doesn't mean you've developed immunity to the virus. This is what happens after a break of three and a half to four and a half months. After the initial exposure we have two populations we have seronegative rats that never seroconverted and seropositive rats. In the seronegative group, when we expose them with the same paradigm, we see very much the same results, so that's driven by the risk of exposure. And in our seropositive group, we see that even those animals that are seropositive that have seen the virus, that their immune systems have responded, a fair number of those overall, close to 60%, will shed the virus on re-exposure. And the group to look at is this group here, red. So these are animals that go to SDAV intranasally and then got the same dose intranasally again so they got the highest exposure, highest immunity, and then highest re-exposure, and even those animals still shed at about 40% however the cycle times are much higher which means that the amount of virus shed is much lower.

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Next, we looked at we whether these animals that were shedding, immune animals shedding virus, at low amounts could actually give the virus to naive animals. This is what we see on natural exposure. So these are animals that got one dose of SDAV intranasally, waited three and a half to four and a half months, got a second dose and then co-housed them with naive animals and almost a quarter of those animals, those naive animals, shed the virus and seroconverted. With vaccination, we vaccinated animals. Now we waited a shorter amount of time so that's analogous to what's happening now, re-

exposed those animals to naive animals. We up the bar so we expose them for seven days and we see that we only see 14% of infections and at that point the serial positivity is much lower so it means that they're shedding very low amounts of the virus that can transmit to animals but at a very low rate.

It's tempting to think vaccination is better and it's certainly more consistent, it's more controllable. However, we should also note that the time between vaccination exposure is much shorter here whereas in the top with the natural exposure paradigm it's a little bit longer so this really models what is happening currently, but your people that were exposed by natural infection and their immunity is probably waning at this point compared to people who are being vaccinated currently.

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So, to conclude, with natural exposure and re-exposure I think every piece of data produced by scientists that tells us that herd immunity via natural exposure is not a good way to go. Again, this is one more piece of data to say that. Natural exposure gives you very heterogeneous immunity and on re-exposure the risk of shedding is high across the diversity of immunity that you see with natural exposure. And that amount of shedding can cause transmission to a naive person. With vaccination, greater protection in the short term, but it is likely that that protection is also going to wane over time. So overall, I would say it looks likely that this disease is here to stay and probably requires revaccination on a regular basis. Currently, what we're doing is applying this data to our SEIRS model where we're going to introduce the notion of respiratory infection as well. That's a sort of low to high risk. The entire spectrum is housed within respiratory infection. So, I'd like to stop there and thank the NSF for funding this.