Dr. Julia Port

Behind The Mask

September 9, 2021

Barr: Good afternoon. Today is September 9, 2021. My name is Gabrielle Barr, and I'm the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Julia Port. Dr. Port is a postdoctoral visiting fellow in the Laboratory of Virology in the Division of Intramural Research at the National Institute of Allergy and Infectious Diseases (NIAID). Today, she is going to be speaking about her COVID research, which is quite a lot. Thank you very much, and I look forward to hearing about it.

Port: Thank you for having me.

Barr: To begin, you were a part of a study that looked at aerosol transmission for B117, the alpha variant, over the lineage A variant of SARS-CoV-2. Can you please talk about the premise of the study, and why it is so difficult to differentiate between large particles and true aerosols, which is something you've looked at in your studies?

Port: The study was built on previous work that we had done, which demonstrated that disease severity is increased for an aerosol exposure, and work that we had done—similar to what other people had also demonstrated—to show that over short distances, you can have transmission through the air in the Syrian hamster model. Most people do not look at droplet size that can travel at those distances, so it's basically airborne transmission, but it's not very clear what type of transmission it exactly is. We tried in our first study to determine that a little bit, but the setup didn't allow it. We then decided to go into more detail and really develop a setup that allows transmission through the air, but at different distances, including distances of one meter or two meters, which is the six feet that the CDC always keeps talking about. That was one thing we set out to do.

The second aspect of it is that there's a bit of a debate on what airborne transmission is and if aerosol transmission is a subsection of airborne transmission or if they're different—if large particle transmission means it really can only happen in shorter distances. We wanted to have a setup that also allowed us to differentiate. It's not really difficult to measure those particles, it's just that most virologists don't look at that specifically, so we wanted to have a set up where we could in detail—then afterwards say if transmission occurred over one meter distance, this is the particle profile that could have led to that transmission. A lot of relevance is always given to five micrometers as a droplet size under which you would consider it a true aerosol, but that is also up to debate. A true aerosol biologist would probably have a lot more details to offer there. What it means, though, is if a particle is smaller than five micrometers, it can definitely go into the depths of the lung, which was important for us. We

know that particles of that size can also stay in the air longer and really travel over these distances if they're occurring in a natural setting, such as a room—so that was the one premise of the study.

Once we had that going, the second thing that we were interested in was whether aerosol transmission would be different for different variants of SARS-CoV-2, because that's something that hasn't been figured out yet.

Barr: Can you talk a little bit about how you went about designing and validating the Syrian hamster transmission cages that you did for that study, and what considerations you put into it?

Port: The first thing you have to take into consideration is animal welfare, so the cages by design still have to adhere to the ethics and welfare considerations. They have to allow a certain amount of space per animal. You have to have bedding, drinking water, food, and a certain amount of air changes present, so that the hamster can be in optimal, or at least acceptable, conditions, and so that no stress is caused for the animal just by being in the cages. What we actually started out with is normal hamster cages that we got from a vendor called Lab Products. Then we started modifying them in such a way that we could connect two cages to each other at various distances but introduced metal grids so that the hamsters could not travel between cages. In addition to that—because of course with those changes the cages could not be used in the normal racks anymore—we had to hook up our own air pump system, which created negative pressure flowing through the cage so we could adhere to the 30 cage changes per hour that the animals would be okay with, and not create any kind of stale air situation and so on and so forth. Those were the two major considerations.

Barr: What were your findings from this study?

Port: We found that, in agreement with what has been previously shown, in these new cages we had really efficient transmission—over a 16-centimeter distance. We could also show that if sentinel hamsters are exposed to infected hamsters on the other side of the cages, we could have transmission at one meter and two-meter distance if the duration of exposure was indefinite. The sentinel hamsters started showing signs of themselves being infected by day one, too, so we know that transmission happened in the first 24 hours. Then we started reducing the time window of exposure and we could see that even with only one hour of exposure at two meters distance, we had quite efficient transmission. The second thing we found, also using these cages, is that it looked like B.1.1.7—the alpha variant—was perhaps a bit better at transmitting as compared to the original "WA1" strain.

Barr: Were you surprised about the hour window? Did you think it was going to be a shorter amount of time in terms of transmission, or did you have no ideas in mind of what it was going to be like?

Port: In another study, we also looked at 15 minutes at a very short distance, and we know that's hit or miss. Even if they're only one foot apart with 15 minutes of exposure, not all of them will become infected. We did not actually attempt anything shorter than one hour at the two meters distance because we were working under the hypothesis that we may still get some infection, but it's not going to be very efficient anymore. It wasn't that surprising it led us to that result based on our previous findings.

Barr: What percentage of the hamsters became infected within the one-hour window?

Port: Between 75 and 100.

Barr: That's a good many.

Port: It's quite efficient. We think it would probably drop to around 50 or even lower if you go less than an hour.

Barr: What is it about the other hamsters that they didn't get infected? Or is that one of the things you're trying to learn about?

Port: We think you need a certain amount of virus—even if it is very little—to cause an actual infection. There is a point where hamsters will still breathe in virus, but their immune system is strong enough to stop infection before it becomes systemic and what you would call a "real" infection. These hamsters, then, will not start shedding virus themselves. It a stochastic effect at that point because some hamsters just aren't exposed to the dose required anymore.

Barr: You did a similar study that investigated whether prior aerosol infection with lineage A SARS-CoV-2 variant protects hamsters from disease and reinfection with the B1351 SARS-CoV-2 variant. Can you share a little bit about how you went about conducting this study and what some of your findings were?

Port: I co-conducted that study with one of my colleagues, Claude Kwe Yinda, Ph.D., and we also based that study design on our very first study, which showed the differences in aerosol and fomite related disease manifestation. That study had two aims. One was to see how low the infectious dose would be for aerosol and fomite. We found that with aerosols the hamsters are incredibly susceptible, while with fomite, if we go to lower doses infection is not really efficient anymore. While we were conducting that

study, the B.1.351 variant became quite prevalent and was a variant of concern, so we were interested if these kind of natural exposures—as contrasted to an intranasal exposure—would also be protective, which was basically showing two things that hadn't been shown before. One, whether a natural exposure by aerosol would be protective against the re-challenge by itself; and two, whether it will be protective against a heterologous free challenge. Once we had these hamsters that became infected by aerosols but cleared disease, we re-challenged them with B.1.351. We found that, while you still observe some shedding in the re-infected hamsters, it was much milder as compared to the first initial infection. More importantly, these hamsters were not able to transmit virus to a new hamster again. The previous challenge basically stopped onwards transmission.

Barr: Do you think that would hold true for some of the other variants? It seems like the variants all behave quite differently from each other—some are worse than others.

Port: It will hold true to a certain extent, exactly as it will hold true that the vaccines will provide protection to a certain extent. But basically, unless it's tested, it's really difficult to make a hypothesis on that, because the further away the variants go from the initial infection, the trickier it becomes.

Barr: How did you contribute to the study that determined that the B1427/1429—the epsilon SARS-CoV-2 variants—are more virulent than the ancestral B1 variant in Syrian hamsters? In what ways are they more virulent and why?

Port: The real first author of that study would probably be a better person to ask on that second part of your question—because we contributed to the assessment of whether they are more easily transmitted through the air, and that was building on the fact that we first published on having rodent cages that had a divider in the middle, which allowed only air but no fomite or contact transmission. We collaborated with them on that study. We conducted the experiments just to investigate whether it's more transmissible through the air. We didn't see any striking differences between the variants. The authors found that the B.1.429 and 27 outcompeted the all-circulating variants in direct infection experiments. But those were parts of the studies that we were not involved with. Our focus was on the assessment of airborne transmission.

Barr: One of the major studies that you worked on was one that looked at the severity of SARS-CoV-2 disease and transmission efficiency in Syrian hamsters. Can you talk about how you designed it, your methodology, and how you went about evaluating your data? That was a really big study; it came out in an NIH press release.

Port: The Nature Communication Study. That is the study I was referring to. That was basically the first one that we designed. I come from a background of assessing immune responses depending on

exposure routes, so I basically set out to also assess for SARS-CoV-2 whether different routes of exposure will lead to different disease manifestations, immune responses, and also onwards transmission. We use the Syrian hamster. This study started out in March or April last year. At that point, not that much had been published, but we knew from work of our Chinese colleagues that the Syrian hamster was a really good model for moderate disease and also for transmission, so we decided to use that model. Up until that point, people had only looked at intranasal inoculation, which is not really a natural route of exposure. I was curious on whether aerosol and fomite exposure would present differently. The things you need to look at are the innate immune response, the adaptive immune response, disease manifestation, and viral shedding pathology. Those were the aspects we covered. Once we had a bit of an understanding of how the exposure routes affected disease, we also looked at whether airborne transmission and fomite transmission were equally efficient and presented with similar results in the sentinels themselves.

Barr: How did you go about evaluating the data from the study?

Port: We evaluated by comparing amongst the groups themselves in the study and then also matching that up with what had been described in the literature with intranasal inoculation. By the time we published, another group had also published on oral administration of SARS-CoV-2 in the hamsters. We compared with that. Of course, we also judged what we saw in the hamsters with what was known to happen in humans, to see how much of it is translatable.

Barr: What were some of the challenges that you experienced in conducting this study?

Port: I had only started work at NIH in February 2020 so those were literally the first studies I was running in a completely new lab. It was just challenging because, besides this being urgently needed data, it was also in-lab training for a new person. That was quite challenging. Then, of course, new cage design, new cage divider design, experimental design that hadn't as such been conducted before—but everybody was on board, and it was a great team effort. It was also a collaborative effort across different core facilities, including people at the Rocky Mountain Labs (RML). In the end, we pulled through and turned it into a really informative and descriptive study.

Barr: What do you think some of the ramifications have been or will be for people from this study?

Port: I hope that it really highlights that it wasn't wrong when we were told that washing our hands and disinfecting surfaces is important because it is important—especially in settings with people that may be immune suppressed or there's a lot of risk of contamination. On top of that, it highlights that focusing on mask wearing and aerosol transmission mitigation strategies—such as air filtrations, UV light, keeping distances, opening windows, simple things like that—can have a huge impact because we think

the main transmission of COVID now is occurring through the air. I would hope that people read this study and take from it that not only is it really likely that you can be infected through the air, but it might also increase your disease severity if you are.

Barr: Why is there such a degree of severity depending on the route of transmission?

Port: Depending on your initial site of exposure, your innate immune response will be different. If you imagine that your initial site of exposure is in your upper respiratory system—let's say your nose, nasal epithelium—your lungs aren't really involved yet. By the time the virus may come to the lungs, your immune response is already going. That will then present itself differently in fighting the virus in the lungs, as opposed to via an aerosol, where the virus is directly deposited into your lower respiratory tract, which also means your initial immune response immediately occurs in the lungs. We haven't proven this yet, but we hypothesize that means the immune response also gets this additional over-activation just because it has to deal with the virus already there. It's not just a viral pathology, but also the immune response causing pathology. It's really how much time you have between the virus first entering your body and it being in the lungs, where it causes the most damage, or whether it even enters the lungs at all. It could be hypothesized that in asymptomatic cases, the infection is mostly in the upper respiratory tract. It has to do with how the virus disseminates and how fast and where your immune response starts.

Barr: Interesting. With fomites, is it mostly in the upper tract?

Port: That's the hypothesis that we're working under, because to enter the lower respiratory tracts directly, you really need those tiny droplet sizes that a fomite itself would not present with.

Barr: That makes sense. What are some next steps for you and others on this topic, based on that study?

Port: We're currently, of course, trying to get the aerosol transmission study officially published because as we're speaking, it's still only out as a preprint. Then building on that, I'm now conducting a comparison between alpha and delta variants to see which of them transmits better through the air and why it transmits better through the air. We know that a lot of other groups have really contributed valuable data and insights into changes in the furin cleavage or entry. That's not really our focus. We want to know whether that means aerosol stability is different and whether aerosol transmission is also different—not just as a function, but possibly the infectious dose being lower.

I'm currently conducting a study looking at whether breathing frequency patterns, breathing volume, and exhale particle size profiles are different between the variants, and if that has any impact on

shedding profiles and how much infectious virus we can detect in the air. This is, again, conducted in the Syrian hamster and then hopefully also linked back to pathology again. We're doing more of the direct competition experiments between different variants. We're still working with some mathematical modelers to figure out a good system that really recaptures real world situations because clearly, we can't run studies on a population level, because you'd need hundreds of animals and that's not ethically acceptable and also [is not] useful. We're trying to maximize the output of our current studies and really fine-tune the design of the studies.

The second thing my colleagues are looking into is in regard to environmental stability—whether the variants transmit differently if it's not done at room temperatures, but at different humidity and different temperatures more mimicking of pure summer or winter conditions.

Barr: That sounds very interesting—a lot in the works! Can you talk about some of the other COVID research that you've been involved with? You've been involved a little bit with the vaccines and some other topics. Do you mind sharing?

Port: I've been initially involved with some of the early vaccine studies that we conducted in hamsters and non-human primates with the AstraZeneca vaccine—not a 100% perfect vaccine—but it works quite well in those models. We're also now involved with transmission studies, using some of those transmission setups that I developed in actual vaccine studies. This isn't out yet, but we're currently looking into transmission efficiencies between vaccinated and vaccinated animals, or naïve and naïve, or previously infected and previously infected, to tease apart whether vaccination is different from previous infection, and how we can make vaccination more closely mimic previous infection. We've conducted studies on intramuscular versus intranasal vaccinations and found that to stop shedding in the upper respiratory tract, that intranasal vaccination is better. I've also been involved with a study that looks at, in a non-human primate model, whether age is a factor of increasing disease severity. There, we look at young versus old macaques and this is mostly a pure immunological analysis in that model. I've been a bit involved with the environmental studies. We're also looking at other counter measures, such as UV light to stop transmission. The last thing that I was really involved with was a study looking at whether a high fat, high sugar diet can increase disease severity in the Syrian hamster. We found that to a certain degree, it changes the disease phenomenon, but we think that the Syrian hamster is not necessarily the most suitable model for that, because they do not develop a classical obesity phenotype.

Barr: So really a wide variety of things.

Port: Yeah, our lab is trying to tackle problems from a holistic approach. We're a very colorful bunch of people that were mixed together and coming from different specialties and backgrounds, but it's great because it allows these studies that focus on a lot of different aspects and at the end, we come together to give a nice comprehensive overview.

Barr: What expertise do you feel like you add to your lab and a lot of the studies you've been involved with or have led?

Port: By training, I'm a tropical medicine scientist and immunologist, so I come with a bit of an epidemiology, public-health focused research background. My questions are always driven in that direction and having that applicability back to whatever human situation we're currently facing. My expertise comes in the form of my immunological background and being able to address the differences in transmission from the angle of how that impacts the immune response.

Barr: That makes sense. Can you speak a little bit about what it was like to come to NIH around the time the pandemic began? I'm sure that was quite a transition for you—you had to jump into all these projects even though in your mind you were set to do another set of studies.

Port: I came in February 2020 after having finished my Ph.D. I'm originally from Germany. I spent the last 10 years living in bigger cities. Coming to Hamilton was a harsh cut compared to that. I knew it was coming, but I didn't know it was going to be like this. Basically, social life and everything just stopped because of the pandemic, so that wasn't necessarily the nicest introduction to the U.S. I also hadn't been here before so that was definitely interesting. This year has been much better, but it's still of course problematic. From a personal perspective, it's not been the easiest because of visa issues and travel restrictions. I'm hopefully able next month to visit my family again after a year and a half of being stuck in this country. Fingers crossed on that. Other than that, RML is a very welcoming community and people have been incredibly helpful, but of course, it's not really been that easy to make new connections and build a life when most of the things you normally do you cannot do.

Barr: You came to RML with an interest in bat cellular and adaptive immunology. Have you been able to investigate any of that during your time at RML? I know you've been working a lot on the pandemic, but have you been allowed to sort of look into your own interests at all?

Port: I was allowed to do that for exactly one month, and then that stopped. It's not to say that what I'm doing right now are not my own interests, because it's the studies I design, it's the interests I have, and it definitely builds on the background I have. I initially wanted to do these transmission studies with Lassa virus, and I hope to be able to continue that next year. That's what I did for my Ph.D., and that's what I wanted to follow-up with. For the bat immunology part, that's now being revisited and is on the table again. We're hoping to develop a small bat model for SARS infection, so that's what I'm currently designing. Hopefully the studies can run by the end of the year or early next year, and that will have quite a heavy innate immunology part to it. I'm not sure how much I will be able to do the cellular adaptative immune response. I have plans to basically link together innate immune responses and

intestinal tract because that's where coronaviruses replicate in most bat species with changes in the microbiome and then maybe some changes of the adaptive responses as well. We'll see how it goes. It's really basically early stages for that project because there's only now been time opening up to look into that again.

Barr: How do you feel that your work on COVID-19 has made you a better scientist?

Port: It's helped me focus, prioritize, and strategize about experiments in more detail than was necessary before, just because the timelines are always pushing. I find it dangerous to say if it has made me a better scientist. I think it has made me a slightly different scientist than what I was before, just because the nature of the work has changed. Instead of you just publishing for yourself, you're also now publishing for the public, to a certain degree—which you always do, but during a pandemic you do it to a higher degree. The messages that our work sends out also have to always be considered in light of who will be looking at this and how it's received by the public. It has helped me to navigate and collaborate with different members of the team, different people around RML and also in other universities and NIH facilities in more detail. It's just been different because on top of this now being in a pandemic, it's also a new lab for me. I can't really compare what it would have been like had I been at NIH before the pandemic, so I can only compare it to what it was like when I was working at a tropical medicine institute, which is what I did before. Of course, there the focus is very different because I was working on human immunology; there was some animal work involved. I'm not sure it made me a better scientist, but it has broadened my horizons and has allowed me to also learn different new techniques and introduced different views and different approaches into how I look at problems.

Barr: Is there anything else that you would like to share about your work with COVID-19 or your experiences during COVID-19, both as a person and also as a scientist at NIH?

Port: What I would like to highlight is that these studies are always conducted with a team of people and that some of the most valuable people are the ones that you won't find high in the author list because they're technicians. Also, as we discussed before, a lot of it is collaborative work, so for that B.1.429 study, where we conducted the airborne transmission experiment, that doesn't mean that we are the ones who designed the rest of the study, or the ones driving that. When people look at publications and look at the output of a lab, it's also very valuable to look at everyone who contributed to that and understand that it's not just the PI [principal investigator] or the first author who put in a lot of work for a study, it's everyone who contributed.

Barr: That's a really great point, and there's just so many people at NIH and other places who've put forth a lot of effort to make it happen. I want to thank you so much for your time and for all the work that you're doing. I wish you continued success in all that you and your lab do. I hope that you get to visit some of your family and friends and have some time to recoup and things like that.

Port: Thank you.

Barr: Thank you.