Dr. Neeltje van Doremalen
Behind the Mask
September 17, 2021

Barr: Good afternoon. Today is September 17, 2021. My name is Gabrielle Barr, and I am the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Neeltje van Doremalen. Dr. van Doremalen is a staff scientist in the Laboratory of Virology in the Section of Virus Ecology, which is at the Rocky Mountain Laboratories out in [Hamilton,] Montana. [The Rocky Mountain Labs is part of the National Institute of Allergy and Infectious Diseases, NIAID]. Today, she's going to be speaking about a number of her COVID research initiatives. Thank you so much for being with me.

Van Doremalen: Yeah, absolutely.

Barr: To get an idea, you've been working a lot with COVID throughout this past year and a half, when did you begin transitioning to working on COVID-19 studies, and what was it like for you to suddenly shift focus last year?

Van Doremalen: I started working on coronaviruses in general when I started my position here in 2013. As soon as we heard of SARS-CoV-2—the name was not known yet at that point at the end of December 2019—we already started thinking about whether we thought this could be a virus that caused a pandemic and started thinking about potential experiments. So for me that focus on COVID-19 actually was very natural.

Barr: One of your first studies that you did was looking at aerosol and surface stability of SARS-CoV-2 compared with SARS-CoV-1. How did you and those that you worked with on this study select the five categories that you ended up testing, and how did you mimic with technology what human transmission would be like? That must be hard. [The five categories were: plastic, stainless steel, cardboard, copper, and aerosols.]

Van Doremalen: Yeah, it was. It is difficult, because of course, you're in a laboratory setting. By no means are we saying that if the virus survives on a surface in a lab for X amount of time, it would be exactly the same out there. We selected the surfaces because we had done this work with MERS-CoV [Middle East respiratory syndrome coronavirus] already. The plastic and the stainless steel are really common surfaces. And cardboard, a lot of people were worried about packaging that they were getting from China, because at that point, the virus was mainly in China. It hadn't arrived in the U.S. yet when we started these studies. For copper, we picked that one because with MERS-CoV we actually saw that it had reduced the amount of time that the virus was infectious on the surface. We wanted to confirm that it was the same for SARS-CoV-2, which it actually was. And then aerosols, that's pretty complicated equipment that we have in our laboratory. We have a really big drum [Goldberg drum] that basically aerosolizes the virus into it, and then it keeps on spinning. So it keeps the aerosols in the air. We also did work with other viruses with that. So again, it was a pretty natural transition for us to do [experiments] with SARS-CoV-2, as well.

Barr: Yeah. You did this very early in the pandemic. Would you tweak any part of this study based on what is known about the virus now and transmission now?

Van Doremalen: I think it's pretty clear. That was my hypothesis in the beginning as well—that the virus mainly transmits through the air and not so much by fomites, which would be virus on surfaces. I don't think I would adjust the study itself, but maybe I would emphasize that difference a little bit more because I think for some

people, it was taken out of context. I did try to emphasize that in interviews and say [that] we're not by any means saying that this is how the virus transmits. We're just reporting what we are seeing in the lab.

Barr: It could, [but] it doesn't necessarily mean that it did. That makes sense. With the study "Effect of Environmental Conditions on SARS-CoV-2 Stability in Human Nasal Mucus and Sputum," how much less stable was the virus in mucus or sputum than in culture? I thought that was really interesting.

Van Doremalen: Yeah, it is a cool difference. It's of course really important because the culture medium we used in the first study, that's not actually what the virus would be in. When you cough for example, you have the droplets landing on the surface. Jeremiah Matson led those studies. He used slightly different environmental conditions, but one of his environmental conditions was the same as what we used in the initial study. As a surface, he used plastic, which is also what we used. So if you compare these two—the half-life for our studies was around seven hours. For him, he used mucus or sputum, it was around three hours from the top of my head. So it really was reduced. We don't know for certain why that is, but it's likely because there's so many things in mucus and sputum that would actually break down the virus.

Barr: That's really interesting.

Van Doremalen: Yeah, it was a really cool study.

Barr: What was your contribution to the study "Mechanistic theory predicts the effects of temperature and humidity on inactivation of SARS-CoV-2 and other enveloped viruses?"

Van Doremalen: That was a continuation of the first study I did as well as Jeremiah's study because it looked at all these different environmental conditions. I didn't do any of the practical work myself. I was really there to help with the analysis and support people. Most of my studies at that point had focused on vaccine work.

Barr: Yes, that makes sense. How did you partake in some of the early studies that looked at the respiratory effects of SARS-CoV-2 on rhesus macaques? What are some of the challenges you experienced, and what did you find surprising or interesting?

Van Doremalen: As I said, we really early on in January 2020 decided what experiments we wanted to do. We really wanted to look at vaccines, of course, so what we would need for that is rhesus macaques for the nonhuman primate model. It was one of the very first experiments that we decided to do. We initially wanted to look at four different nonhuman primate models, but we decided to start off with rhesus macaques because the most [common] MERS-CoV nonhuman primate model is rhesus macaques. We just decided to replicate that. Indeed, we got lucky, because that worked straightaway, which was great. And, as you probably are aware, in the nonhuman primates—the rhesus macaque model, infected with SARS-CoV-2—the disease is not severe by any means. It's fairly mild so you have to take that into account when you do those studies. But if you think about it, that's what we see in humans as well. It's not like the majority of people will end up in a hospital. I think in that sense it was not surprising that we saw that. It's always almost a little bit easier if you get a more severe animal model [that develops a more severe disease]. But yeah, the rhesus macaque model is great at telling us what we can do with vaccines and treatments.

Barr: Are there animal models that do show more severe disease, or is it very challenging to find?

Van Doremalen: That's a good question; we work a lot with the Syrian hamster model, and that disease I still would not call severe. I think that's more of a moderate disease. When you look at the lungs of these animals

around day five, they show a lot of pathology, but those animals do survive. A postdoc in our lab, her name is Danielle Adney, did some work on mink, and in that, the conditions are severe. It's definitely a fatal model. Those animals all had to be euthanized, unfortunately.

Barr: That's interesting. What were your observations of the study that you are part of that looked at the subtle differences in pathogenicity of SARS-CoV-2 variants of concern, B.1.1.7 and B.1.351 in rhesus macaques? You had said you had looked at the variants with them.

Van Doremalen: Yeah. At the end of 2020, December 2020, it really started to become obvious that we were having all these variants of concern. We were worried about that. We also wanted to see if we could see any differences in the rhesus macaque model with those. Actually, one of the most challenging parts for those studies is getting good stocks of virus and growing them. You often get mutations in a virus stock, and if you've done a challenge with a nonhuman primate, you may get very different results than you would get with the original virus. I helped out a lot with that. I also helped with the actual animal experiments there too.

Barr: Have you continued to look at the different variants?

Van Doremalen: Yeah. We actually do quite a bit of work like that in the lab. I am particularly interested in vaccine efficacy with the variants of concern. Then Julia Port and Kwe Claude Yinda in our lab, both postdocs, looked at the aerosol transmission of those different variants. We combined these studies as well. We looked at the efficacy of the vaccine in transmission models. That's all in hamsters. That's not done in nonhuman primates.

Barr: Yeah, that makes sense. How did you contribute to the study that looked at the recovery from acute SARS-CoV-2 infection and development of anamnestic immune responses in T-cell-depleted rhesus macaques?

Van Doremalen: My involvement there was pretty limited. The main thing I did is look at serum samples and teach somebody else how to do those different assays.

Barr: Well, that's still important. It's important to teach. Now we're going get to the vaccine and therapeutics work, which you have done a lot of. When you are a part of a team looking at how rhesus macaques inoculated with SARS-CoV-2 responded to Remdesivir, what was the team's reaction to the fact that the drug does not reduce virus shedding, and are there potential drugs, perhaps, that could or can?

Van Doremalen: One of the things that we see a lot in rhesus macaques is that it's actually really difficult to reduce shedding. We see that in our hamsters as well. With Remdesivir, we did see a reduction in the lung titers and a reduction in the clinical signs. It definitely did have an effect, but even when we did our vaccine studies—and this has been reported by others as well—we didn't really see a reduction in this shedding of this SARS-CoV-2, which is really interesting. I am not aware of any treatments that would help with a reduction in shedding. One of the things that we are looking at is intranasal vaccination. In studies that we have done in nonhuman primates with that, it does strongly suggest that that would reduce the shedding of the virus.

Barr: Briefly, can you describe the AstraZeneca vaccine, because that is something you've worked a lot on these past couple of months, which is also known as ChAdOx1? How is it meant to work, and how does it differ from other vaccines that are available like Pfizer, and Moderna, and Johnson and Johnson?

Van Doremalen: It's actually really similar to the Johnson and Johnson vaccine. Both of those vaccines are based on an adenovirus. ChAdOx1 stands for "chimpanzee adenovirus Oxford-one" [developed at the University of

Oxford]. They have changed the adenovirus in such a way that it's not able to replicate in the cells anymore. We can infect the cells, but then it just stays there. It doesn't infect any other cells anymore. Then like pretty much any other vaccine that is approved, they used the spike protein of SARS-CoV-2. That is introduced in the genome of the adenovirus. Once cells are infected, the cells stop producing spike proteins, and then hopefully, your body will mount an immune response against the protein. With those antibodies that you form, they will neutralize the virus if you ever do get infected with it. That should really reduce the severity of disease.

Barr: When did you and others at NIH begin testing the AstraZeneca vaccine in animal models, and can you speak a little bit about some of the trials that you've been a part of that looked at its efficacy?

Van Doremalen: We actually started working with Oxford University. So this is Sarah Gilbert and Tess [Teresa] Lambe back in 2017. The first experiment we did was with MERS-CoV. We looked at the efficacy of basically the same vaccine, but then developed for MERS [Middle East respiratory syndrome] in a mouse model. From there, we got a big CEPI grant that allowed us to look at the MERS vaccine in nonhuman primates. We looked at the Nipah vaccine, which is another emerging virus, in hamsters and nonhuman primates. We looked again at Lassa virus in Guinea pigs and nonhuman primates. This is work mainly done by Bob [Robert] Fischer in our lab and Jyothi Purushotham, a Ph.D. student in our lab. Then the transition to SARS-CoV-2 was really natural because the MERS-CoV nonhuman primate study I did was in the last months of 2019, so we knew exactly what to do. We knew what we wanted to do. The only thing we needed was a nonhuman primate model that was working well. As soon as we had that developed in the lab, we started vaccinating the rhesus macaques.

Barr: This is maybe a little off topic, but was it hard to get nonhuman primate models to test on?

Van Doremalen: They do start to become a little bit rarer because so many people are doing nonhuman primate studies. I have never run into an issue. We don't use that many animals because of ethical reasons. We only do experiments when we really have a good question to ask. Thus far, we haven't had any issues yet.

Barr: Well, that's really great. What was the reason for testing the AstraZeneca vaccine intranasally as well as intramuscularly, and what did you and others who were a part of this protocol discover? What implications does this have for the way humans may take the vaccine?

Van Doremalen: This is one of my favorite projects. As I mentioned already, my immediate intramuscular vaccination in rhesus macaques study, which was the very first study we did early 2020. One of the things we noticed is that there wasn't really a difference in the shedding of the virus. Although the lungs were fully protected, we couldn't find any virus in their lungs in vaccinated animals; in our controls, we found a lot of virus; we still found a lot of shedding. If that would directly translate into the human population, which it probably cannot, but if you would think that it directly translates that would mean that even when people are vaccinated, they may still be shedding virus. That's actually something that we are seeing out there, because as you know, we are seeing breakthrough cases, and vaccinated people are sometimes able to shed and transmit the virus as well.

One of the things that we were thinking is that mucosal immunity is really important in trying to stop any virus in your upper respiratory tract. But if you just give a vaccination intramuscularly, you don't get any mucosal immunity at all. One of the theories is that if you give a vaccine in the nose, you do get mucosal immunity. What we did is that we took that same vaccine, we didn't change anything about it, and we literally just sprayed it up the nose of nonhuman primates. We did it in hamsters as well at first. In the hamsters, we saw a clear difference, which is significant; the shedding was really reduced. In nonhuman primates, we saw a difference as well, but it was not significant. We had only four animals per group. I think if we had six animals per group, it

would have been significant. But you know, with nonhuman primates, there's always the ethical question of how many animals you can use. Hindsight is 20-20, but it was really cool. I think that right now Oxford [University] is doing a clinical trial, a phase-one clinical trial, in which they are indeed investigating intranasal vaccination with their vaccine. I think that needs to be studied further because I think that's maybe something we should do for every respiratory virus.

Barr: That's really interesting. How come a lot of our vaccines are not given intranasally?

Van Doremalen: That's a really good question. I think probably the formulation of the vaccine needs to be a little bit different because the vaccine is encountering a completely different situation. I also think that it's we're just so used to giving it intramuscularly that it's a fairly new way of thinking of how to use a vaccine. Of course, FluMist is a vaccine that is given intranasally. That's an influenza vaccine. There are a few out there. I just think it's a fairly new way of thinking about vaccination.

Barr: Are there issues—this is so interesting—with enough of it going into humans, like through the nose? Is that a concern?

Van Doremalen: We really don't know because no clinical trials have been done yet. FluMist works really, really well. It should be okay. But yeah, definitely more research is needed. It's never been done on coronaviruses.

Barr: That will be really interesting to see. With the Syrian hamsters, you looked at the efficacy of the AstraZeneca vaccine against the UK and South African variants. Can you talk a little bit about how you went about conducting this study and how you've replicated this study with other variants?

Van Doremalen: Those names of the variants are old now. So those are [older] variants nowadays. The field changes really rapidly. It's hard to keep up at times. So of course, as soon as those variants came out, we were concerned about vaccine efficacy, especially the Beta variants. In the lab, where you look at the neutralization, neutralizing antibody titers were a little bit lower against that variant. So that suggests that vaccine efficacy may be a little bit lower. This variant was mainly present in South Africa. There was a reduction reported in vaccine efficacy.

We set out and wanted to test that in hamster models. What we found actually is that, even though in a hamster model, we've never seen a difference in shedding—so the shedding was still the same as it was in the control hamsters—but we didn't find any virus in the lungs of these animals. That's really what you try to do with these fixed vaccines is to try to prevent really severe disease. We have since done that with other viruses, specifically the Delta variants, which is, of course, the most prevalent variant in the U.S. right now and worldwide. Those studies are cooking right now, so I don't have results yet.

Barr: Is AstraZeneca working on perhaps changing the vaccine accordingly?

Van Doremalen: Yeah, they are. I don't know where they are with that right now. That is definitely in the works and so are Moderna and Pfizer. I think all the big vaccine companies are going down the same road.

Barr: Is AstraZeneca a two-shot situation with a booster, kind of like Pfizer and Moderna, or is it like Johnson and Johnson with just one shot?

Van Doremalen: No, they give two shots as well, but the timing interval is longer. In the UK, they increase the time interval to 12 weeks, actually.

Barr: Okay. Will you talk about NIAID's role in testing the CureVac mRNA vaccine on rhesus macaques? What differentiates this vaccine from the other vaccines, and why was its efficacy not as good as you found in some of the other vaccines that were on the market?

Van Doremalen: We started working with CureVac before the pandemic. This was a natural study for us to do because we already had a collaboration with them. There are two main differences between the CureVac vaccine and the Pfizer and Moderna vaccines, the first one being the dose. They go in with a fairly low dose; on humans, they used 12 micrograms. In our model, we used four micrograms. That would be about equivalent to a human dose of 12 micrograms. Pfizer and Moderna use 30 and 100 micrograms, respectively. The other thing that they do is that Pfizer and Moderna use modified mRNA, whereas the CureVac vaccine does not. It currently isn't really clear which one of those two factors played a role in the reduced efficacy that we saw in nonhuman primates, and they also saw in their phase three clinical trial.

Barr: Have you been involved in other protocols looking at other vaccines?

Van Doremalen: We currently are working on a study that Moderna and Bob [Robert] Seder from [NIAID's] Vaccine Research Center and [former Vaccine Research Center investigator] Kizzmekia Corbett, who's currently at Harvard, are involved in as well that is looking at variants of concern as well and at modified vaccines, and particularly in the context of transmission. This is a hamster model. You're looking at whether the virus can transmit from the donor hamsters to vaccinated hamsters.

The second study that we are working on is a mosaic vaccine. This is where Pamela Bjorkman and [postdoc] Alexander Cohen [both at Caltech's Mirkin Institute] developed a vaccine that is expressing eight different receptor-binding proteins that are part of the spike protein of coronaviruses. The idea would be that you would get a pan-coronavirus response. It wouldn't just protect against SARS-CoV-2, but also, for example, against SARS-CoV-1, and potentially—suppose we get another pandemic with a coronavirus, it could protect against that one as well. That would of course be ideal—If we would be able to develop a vaccine that would protect against a whole variety of different coronaviruses. If we indeed have a new outbreak with coronaviruses, we are already protected against it.

Barr: Both sound really interesting. The mosaic one sounds like it's just getting started. Have you guys been working on that before?

Van Doremalen: No, we just vaccinated mice. I think it's another three weeks, and then we do the challenge.

Barr: It will be interesting to get the data from that.

Van Doremalen: Fingers crossed.

Barr: We're going to now transition from you as a scientist to you as a person who's been living through this pandemic. How do you juggle so many COVID-19 studies occurring concurrently?

Van Doremalen: I think the main thing is that we have an amazing team here. None of these studies are done by me by myself. We've got the group that Vincent Munster leads; it's amazing. We've got two really good

technicians, Myndi Holbrook and Jonathan Schulz, and we've got so many other people in the lab that are helping with the different projects. So that is fantastic. Besides that, it's just really good time timing, really good time management, and lots of planning. It is a lot of work. It's a lot of hours you have to put in, but that's okay because I think one of the drivers there is that—you know, when I was able to do that rhesus macaques study with the AstraZeneca vaccine, the day after I gave Sarah Gilbert the results in the UK, they vaccinated their first volunteer. Now they think half a billion people got vaccinated with that vaccine. In a way you directly contribute to saving human lives, and that is such a massive driver. In a way I feel privileged to be able to do this work.

Barr: Have you ever had that experience where you've seen such a direct effect with your work because that's a really neat feeling?

Van Doremalen: No, it's crazy. The only other thing I can think of is that we went to Liberia when there was an Ebola outbreak there. All we did there was be in the lab and test samples of patients, but that was because the hospital was really nearby, so you could see the patients. That was also the first time that I was like, "Okay, I'm doing something that has a direct impact on people," whereas often you're just kind of in the lab doing your own thing, and it's not clear that we will ever have an effect on people. It is really nice to be able to do that.

Barr: That is really exciting. What aspect of understanding SARS-CoV-2 and how to tackle it would you like to study or delve deeper into?

Van Doremalen: Oh, gosh, so many. [Laughs.] I want to keep on working on vaccines, and specifically second-generation vaccines or pan-coronavirus vaccines. I think it makes more sense to be able to develop something like that. I really find the Delta variant interesting. It has a mutation in the spike protein that I think is the reason that it's so dominant right now. I would like to look a little bit into that. That has nothing to do with vaccines, which is kind of nice as well, to have this other topic you're working on. Then I always like transmission. I worked on transmission during my Ph.D. on influenza. I'd like to work a little bit more with that. That work is really spearheaded by Kwe [Kwe Claude Yinda] and Julia [Julia Port] and Bob Fischer, but it would be nice to be part of that as well.

Barr: Many, many things. How do you feel that you've grown as a scientist during the pandemic?

Van Doremalen: Oh yeah, I think I've definitely grown. I mean, you can't really not grow when you have to work that many hours, I think, on that many different things. I've learned a lot during the last almost two years now. And I keep on learning every day. I really enjoy that.

Barr: It's really nice. Personally, what have been some opportunities and challenges that COVID-19 has presented for you as an individual?

Van Doremalen: I think the biggest opportunity is, of course, my career because it really has lifted me basically, which is great. The pandemic is hard. I think at first, when people weren't really allowed to come in, that was really difficult because you have to work really hard, but you can't really interact with each other. Everybody was quite afraid to get infected. That was difficult. Then we had some personal things as well, like, my stepdad-in-law passed away. That was really difficult. Then little things like that made it even harder. We couldn't have a funeral for him because it was in the middle of the COVID pandemic. So that was really difficult. Then there were really good things as well, like we bought a new house in January 2020. So right before the pandemic really started. If that would have been a month later, I think I would have told my husband that we I couldn't do it because I was going to be too busy. It's been a lot of really good ups and also definitely some downs.

Barr: I'm sorry about your father-in-law passing away.

Van Doremalen: Thank you.

Barr: So I should mention that we talked about some of the major studies that you've been a part of. But if you briefly want to mention some of the other work that you have done with COVID. I know you've done a lot of transmission studies, and you've been part of other initiatives, as well. So if you just want to briefly mention it.

Van Doremalen: Yeah, so I think the other major aspect of my work is transmission. That would be direct-contact transmission as well as aerosol transmission. It would be nice to combine the vaccine aspect and the transmission aspect. There are some studies where those two are combined. I am moving a little bit away from the stability. That's really been taken over by Kwe [Kwe Claude Yinda] and Trenton Bushmaker in our lab. And yeah, I hope that's kind of it, to be honest, I think my plate is very full with all of those.

Barr: Definitely, yes. You definitely have enough going on. Well, is there anything else that you would like to share either about your research or your experiences during the pandemic?

Van Doremalen: Oh, I would tell everybody to please get vaccinated. That would really get us out of this pandemic.

Barr: That's a very true and important thing. Thank you very much, of course, for all your work and dedication. I think everyone at NIH really appreciates it, and I wish you and your family and your co-workers continued safety and continued success.

Van Doremalen: Thank you so much. This was really fun.

Barr: I'm so glad.

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