Dr. Emmie de Wit
Behind the Mask
June 22, 2021

Barr: Good afternoon. Today is June 22, 2021. My name is Gabrielle Barr, and I'm the archivist with the Office of NIH History and Stetten Museum, and today I have the pleasure of speaking with Dr. Emmie de Wit. Dr. de Wit is a Principal Investigator of the Molecular Pathogenesis Unit at the National Institute of Allergy and Infectious Diseases. She is on the Rocky Mountain Laboratories campus in Montana, and today she is going to speak about some of her COVID research and experiences. Thank you for being with me.

de Wit: Thank you for interviewing me about this.

Barr: You have always done so many things! When did you begin thinking about and working on COVID-related issues and what types of questions were going through your mind as a person who saw a lot of different types of infectious diseases in the early days of the pandemic?

de Wit: On my end, the pandemic did not officially start until sometime in March, but for us, of course, we became interested as soon as there was a message that there was a pneumonia outbreak in Wuhan, in China and no one knew what it was. Oftentimes, this can be nothing that is of my interest at least, but sometimes it is a new virus and these new viruses that cause respiratory disease are what I am interested in so, of course, I was curious right away. You immediately start thinking: What if this turns out to be this kind of virus? Would I be interested? What do I want to do? What work would I want to drop to work on this potentially new virus?

Then, after a few days, we started to hear that this might be a new coronavirus and coronavirus is something that my lab has experience with because we worked on the Middle East Respiratory Syndrome [MERS] coronavirus, when that emerged in 2012. Then, it becomes more interesting because then you have some expertise. You really start to think that if this is a new coronavirus, many of these viruses have the ability to spread from human to human so, that means that this is probably an outbreak that is going to spread. Many of these viruses, like SARS-CoV in 2003, or MERS-CoV, have caused larger outbreaks. SARS-CoV was actually a small pandemic, and with MERS-CoV we have seen these outbreaks basically, in hospital settings.

As this is becoming more and more clear, you are starting to think about things that you can contribute. One of the things that we have expertise in, here in my lab at Rocky Mountain Labs, is developing animal models for these viruses, to really model the respiratory disease and understand the disease better, and to then potentially be able to build on that, either to test antivirals or vaccines or really to just use that understanding of the virus to maybe think about different ways to treat the disease. All that is going through your mind as more and more information is slowly becoming available.

Early on, it looked like the cases were not really accumulating fast but then, on January 10th, I think, the first sequence came online and so it was definitely, a coronavirus. It was actually, quite a lot like the first SARS-CoV from 2003, and when we looked at the sequence, it looked like it would probably be using the same receptor to enter the cells as that SARS-CoV, and that is really important because that receptor is present on cells in humans. The virus comes in, and because the cell has this receptor [the virus] can bind to [the cell] and then, because [the virus] is bound to the cell, it can enter and replicate. This specific receptor is called ACE2 and like I said, SARS-CoV uses that receptor but also another coronavirus, NL63, uses that receptor. NL63 is a virus that is always present in humans and it causes the common cold. We knew that this new virus probably uses the same receptor that two other viruses use, causing either a small pandemic, or common cold.

Then, it becomes a little worrisome because then you start to think that this virus can probably spread between humans. One thing that we were thinking about is, of course, Ebola. A lot of people are scared of the Ebola virus because if you get Ebola virus the chance that you would die is really high, but on the other hand, it is a little irrational if you live in the U.S. because the chance that you would get the Ebola virus if you live in the U.S. is extremely small. So, although it seems really scary, the risk is very, very small unless you are in an area where there is an outbreak.

These viruses that do not cause severe disease, of course, it seems like they are not so scary, but then when a virus is able to spread efficiently between people, so many people get infected that although the chance that people get severe disease is really low, a lot of people will get really sick and, of course, that is exactly what happened this time. That is what we were thinking about based on the data from NL63 where this virus can spread widely but does not cause severe disease. Also, where SARS-CoV virus has managed to spread it was contained but caused more severe disease. It turns out that SARS-CoV-2 is somewhere in between those two but we did not really know this yet early on.

That was stuff that we were thinking about because, of course, when you think there is a big risk of this virus spreading on a large scale, it becomes really urgent to actually understand this virus and to develop vaccines and antivirals against it. These are some of the things that went through our mind but from a practical point, we were thinking already, early in January, that this is something that we need to work on, and we need to be prepared, in case this becomes a large outbreak. To be honest, I had not expected it to turn out the way it did, but I was expecting it to be more than just a few cases in China, definitely, with some international spread.

Barr: Do you expect it to be more like SARS-CoV-1, more contained?

de Wit: People did not really spread the [SARS] virus before they were sick so then it becomes possible to identify cases, isolate them, and then trace the contacts that they had, so that you can also isolate those people. But in the case of SARS-CoV-2 or COVID-19, some people spread the virus without showing any disease signs, so they do not even know they are infected and spreading this virus. And then of course, it becomes almost impossible to contain unless you lock everyone up.

Barr: What were some of the actions that you and others on your team did to prepare and how did you all pivot so well to being completely entrenched in COVID research?

de Wit: I have done some work in other outbreaks before so I think it is a combination of knowing what your strengths are in the lab, but also knowing that the only way you can do these things is if you can be really fast. You have to decide early on if this is something that you want to focus on. I decided that "Yes, my lab is going to completely focus on this." This is where our expertise is.

We made a list, although we did not have a virus at that moment that we could work with. We made a list of what we could do. Before even the sequence came out, we had a list of things that we would need if we were going to work with this virus. So, if you want to work with these viruses, you need certain reagents so that you can detect [the virus], and many of those you can already make or order as soon as you have a sequence. We just had a list of possibilities: if a sequence comes online, we are going to order these antibodies and these PCR reagents; if we get a virus, we want to do these experiments. Our expertise, amongst other things, is animal modeling so we were thinking what animal species would be suitable for this virus. We looked at SARS-CoV, the first SARS-CoV, because many different animal models were tried, and one that looked okay was the hamster so one of my colleagues focused on doing that, and then we focused on non-human primates. Next, you have to write an animal study protocol so we could already do that before we even had the virus because we were just designing a protocol based on our experience with other respiratory viruses, thinking that it might be like the MERS-CoV coronavirus. Let us infect the animals this way, let us take swabs to see if they are shedding virus, let us take x-rays to see if they get any infiltrates in their lungs, if they have pneumonia. All of that stuff you can already do really quickly and as soon as we had the virus sequence.

We got the virus from CDC in early February, and we were ready. We grew it up on a really large scale, right away sequenced it, and then we started out our animal studies right away because we had done all of the previous steps. It is really a matter of thinking what you are good at and how you can do it as fast as possible, and a matter of being willing to drop everything else that you were supposed to be doing.

Barr: Did you worry at all about accuracy because I know speed was such an important factor, but did you worry that you were sampling enough cases or leaving enough time to see effects?

de Wit: That is a matter of designing the experiments. You have to pick a number of animals to look at and of course if you do, like in our case, non-human primates you do not have an unlimited number of animals that you can sample. So then, you have to weigh what you think is an animal number that is justified to use versus what still generates the right data. We usually use groups of four because if you have four animals you can do decent statistics, and then the sampling is usually based on our understanding of the disease in humans at the time, which was not great. We did know that they would take swabs from people's noses and throats, that they would get samples, so then we decided to also do that kind of sampling. In terms of timing, you cannot leave these animals indefinitely, so you just have to pick an end for the experiment. We did two groups, one where we infected the animals and then we

euthanized them really early on, thinking that if they do not show disease, then at least we can see if the virus replicates because sometimes it is really hard to actually get an animal model that reflects the disease that is seen in humans. If you can show that the virus is replicating really well, you can also show that antivirals or a vaccine are stopping the virus from replicating which you would then have to assume that it also means it would not cause the disease. But just because you cannot see disease, it does not mean it is a completely useless animal model if you do not have anything else to go on. We had a second group [of animals] because in people it looked like most people were okay for about a week or so and then the people who progressed to severe disease did so in usually the second week of symptoms. We decided to leave one group of animals for three weeks so that we could see if they developed more severe symptoms of the disease, which they did not. That is really something that we have not figured out. In the non-human primates, different labs have tested different species, and we really do not see that severe disease. One thing is, of course, that most of the animals that we use are young and healthy and, of course, there we see less the severe disease. So, it could be a numbers game that we just have not infected enough animals, but I think it is, probably, something that is fundamentally different between how the virus works in a human and in a monkey.

Barr: So many humans were old or had underlying conditions. We are going to jump into your animal studies more in detail. Can you speak about how you and others that you collaborated with went about observing the effects of SARS-CoV-2 in rhesus macaques and what some of your findings were?

de Wit: There are two things. One side is really observing the animals, and so there we have one person who is dedicated to the whole study, and this person invests a lot of time before the study starts getting to know the animals so that you know how they normally behave because when they get sick, some animals become really quiet and other animals become really aggressive. It is really important to know how the animals behave before they go into a study. This person goes in twice a day and really spends a lot of time looking at the animals, seeing if their breathing pattern changes, which indicates that they may have a pneumonia; if they are more quiet than usual; and also the really simple stuff like are they actually eating or not? What we observed, was that the animals definitely show some signs of disease. It is not severe, but they become a little bit quieter; they do not eat as much, and also their respiratory patterns change slightly. That is what you can really observe.

We can also measure things. We do regular clinical exams and during these exams we take swabs, like I said, from the nose and the throat to see if the virus is replicating there. We also did bronchoalveolar lavages which means that you intubate the animal and then you put a little bit of fluid down in the lungs and then you suck that back up, and that is sort of an indication of what is going on in the lower respiratory tract to see if the virus is replicating in the lungs. We also take x-rays because in people, early on, for a while there were not enough reagents to test people and so they were just doing CT scans and x-rays to see if people had signs of pneumonia so that is something that we looked for, and that is also what we found.

At the end of the experiment, we euthanize the animals, and then we collect samples from all of their tissues to see if the virus is replicating there and also, if it is causing any damage. Early on, we did not

know as much about COVID-19 in people as we know now. We knew that it was a respiratory disease, there was a high amount of virus coming from the upper respiratory tract in swabs, and people had these infiltrates on x-rays or in CT scans. We actually also saw infiltrates in the nonhuman primates so although we did not see the severe disease it looked quite a bit like a person who had a not severe infection.

Barr: In addition to observing the rhesus macaques, you also did a study that tested [the therapeutic drug] remdesivir. Can you speak a little bit about what it was like to conduct that study?

de Wit: We had worked with remdesivir models before and so that is also why this was one of the things that we put on our list in early January. If this is a coronavirus, then this is one of the logical antiviral drugs to test because we had shown that it actually has an effect against the Middle East Respiratory Syndrome [MERS] coronavirus, at least in non-human primates, and actually this data was complete just before [SARS-CoV-2] popped up. In January, we sent out the findings, because our data had not been published yet, although they came out later that month, but we sent it out to people in the U.S. government and the WHO [World Health Organization], so that they could start thinking about using the data to potentially do clinical trials in humans, which of course is what they did.

For the remdesivir studies, we had decided early on to basically build the experiment on our experience. We tested it for MERS-CoV, but also for Nipah virus. Remdesivir is not an easy drug. It is very hard to use it in small animal models because the metabolism of the drug is different, but if you use non-human primates, then the metabolism is similar to humans. That is why we used non-human primates for these studies, and we basically based the study on what we knew from MERS-CoV as well as what we knew from that initial study that we did in the in the rhesus macaques that we infected with SARS-CoV-2. As soon as we were a week or so in [with our first SARS-CoV-2 study] and we knew that the virus was replicating in the upper and lower respiratory tract, and we were seeing some signs of disease, we immediately moved on and started the preparations for the remdesivir study.

Barr: What were your observations with how it worked in these non-human primates?

de Wit: In non-human primates we have the advantage that we can treat whenever we think it will have a big effect, right? So what we knew from that first experiment is that with these respiratory viruses you get the replication peaks really fast, and then it slows down, but the disease actually comes a little bit later after the peak of replication has already passed, which makes it really hard to treat with these antivirals. That is also what you see in humans: unless you treat them really early on with remdesivir, it does not really have an effect. But of course, we did not know that yet because the clinical trials had not been done yet, but based on our understanding of respiratory viruses, we did know that you do have to treat before the virus replication gets to that peak. I guess I should explain that what remdesivir does is blocks that replication. You can imagine that if the replication is already over the peak and slowing down already, just because of your own immune system, then, you can add remdesivir, but its effect is going

to be very limited because your body has already produced all of this virus that has already gotten your immune system all upset, which is what is causing the disease.

So, based on our very first data, we decided to treat 12 hours after we gave the monkeys the virus. Of course, this is very different. You cannot really compare that to a human because we go in with a very high dose of virus so, it is very hard to translate what that compares to in terms of how far along a human would be in the disease process. We were pretty sure that the peak of replication in the monkeys was probably at 24, maybe 36, hours so we really wanted to treat early. When we treated early, we saw that it did block the virus replication in the lungs, and already, 12 hours after we gave the first treatment, there was a lot less virus in the lungs of the animals that got remdesivir versus the control group. There is always a control group in a trial, because you have to compare it to what would happen if you do not give the drug. So in the control group there was much more virus in the lungs than in the animals that received remdesivir, and also in the control group we could see the clinical signs that I mentioned, they got a little bit more quiet and tired, they did not eat as well, and they had respiratory signs. We did not really see that in the treated animals and when we looked at their lungs, they also did not have the pneumonia that you see in the control animals.

Barr: Can you talk about the different areas of specialty that people brought to this study both from NIH but also Gilead who manufactures the drug and how you all work together?

de Wit: We had this existing relationship with Gilead because we tested remdesivir in other models before, and so already in January, I had been in touch with them about this new virus. Our expertise is really testing the virus in the animal models. They know how to make this drug and they also know how to dose that in humans so their expertise was really to provide the drug and to help us define a dosing schedule to be somewhat like what you would use in humans, otherwise of course, it is not very relevant. If you have given animals a hundred times more of the drug than you can ever give a human, it might be very effective in the animals, but you could never translate that back to humans so, that is their expertise. They sent us the drug and we did the whole experiment.

Barr: That is interesting. Can you speak a little bit about remdesivir and resistance mutations and do you think that could be an issue in the future?

de Wit: With any antiviral and the RNA virus there is always the risk of resistance mutations. We have seen that with most of the drugs, with all of the HIV drugs. If you give only one drug, there is resistance, so there is a chance that could happen with SARS-CoV-2. I do not know that there are any data that it has happened yet, but it could definitely happen so, it would be nice if we had more information. There is more data coming down the pipeline. Hopefully, we could do combination treatments because like with HIV, that really reduces the chance that the virus can escape because it has to escape two things at the same time.

Barr: Are you testing any other drugs currently? You said with remdesivir you have to catch it really early so are you testing any other drugs now that would help with patients?

de Wit: No, we are not. We have not done that because we do not have anything lined up that fits our unique expertise. There are a lot of labs that have done these massive drug screens so there are a lot of mechanisms that currently other labs are testing, but we are not.

Barr: You work more on the animal models, but it seems like you gave the animals remdesivir pretty early after you infected them; however, with a lot of the people, they do not really receive the drug until they are in the hospital, which is potentially several weeks after they have been infected. Can you speak a little bit about that?

de Wit: That is exactly the problem. One problem with remdesivir is that you cannot take it orally. So ideally, you would go to the testing site, you would be tested, and if you are positive, you walk out with a box of pills that you start taking right away. Since you have to administer remdesivir intravenously, that is really not an option. I know that Gilead is working on different formulations that you could take in a different way, but I think that right now the timing of remdesivir administration is one of the reasons why the effect is so minimal. Hypothetically—if you really wanted to—there would be ways to administer it intravenously more on an outpatient-based basis. They figured that out for the monoclonal [antibody] treatment, but the advantage of the monoclonal treatment is that although it is also done intravenously, you only need it once, whereas with remdesivir you will need another dose every day. It really comes down to refining how you can administer the drug, to get over that problem of being too late in the virus replication cycle.

Barr: That is interesting. You also looked at African green monkeys. Can you speak a little bit about that trial?

de Wit: That was really a combination of two things, and it was after we had done some of our initial studies, like developing the model, doing the remdesivir. We helped another group here to get the ChAdOx vaccine, that is now the AstraZeneca vaccine, through. We have done all of those studies and then, we decided what we wanted to do next. One of the things that was still open was the fact that there was no severe disease model yet. One option, therefore, would be to try a different species and see if they developed severe disease, but we had all of the data where we showed that the disease that we saw in the rhesus macaque, although it was similar, it was much milder [than in humans]. We did not really understand what was going on and why the virus was causing this disease.

Then we decided to infect African green monkeys or at least see if we could infect them, and one of the reasons we picked those was because I am also interested in Nipah virus which is a virus that also causes

acute respiratory distress which is what you see in the severe human cases [of COVID]. With Nipah virus, the African green monkeys are one of the few animal models, or at least non-human primate models, that you will see acute respiratory distress in so we were hoping that there was something in the genetics of the African green monkey that would make them more prone to developing this respiratory distress, and that maybe they would be a good model for severe [COVID] disease. At the same time, there is a risk that it does not work out, so you have to think about the other questions that you want to answer. One of them is, "How can I understand the disease process better?" That is why in this experiment we were able to include controls that we did not infect but we did inoculate them with inactivated virus—so we were putting virus in, but the virus cannot replicate. And because we did that, we had really good controls to look at what was happening in these animals other than what we had already seen in the rhesus that the virus is replicating, and you see pneumonia, but still look in more detail what was going on.

Barr: What were some of the things that you learned?

de Wit: One of the things that we learned was that because we did single cell sequencing, we could look at populations of specific cell types, when we look at the differences in the genes that are activated or deactivated when you get a virus infection. In the past, we had often done that, but really just looked at, for example, a whole piece of lung. If you have a piece of lung, there are all these different cell types that are in there so when you try to look at all of the genes that are expressed, that is a mix of all of these genes being expressed in different cell types, whereas all these different cell types might be doing different things. But when you do single cell sequencing, you can look at an individual cell type level of what is going on. Now we can not only see that the virus is replicating and is causing inflammation, but now we can see which cells are doing what. One of the things that was really surprising to me was that, based on what we saw in the rhesus macaque, the virus was replicating in the pneumocytes, but also a lot of the macrophages were positive. They had a lot of viral RNA in them, but they were not replicating the virus. It all makes sense because macrophages basically eat stuff all the time, so they are eating up infected cells that also contain RNA, but they do not produce new infectious viruses. But then on the other hand, the pneumocytes are sitting there and they are making all of this virus, the macrophages are responding to that and they are causing this huge inflammation so we can now start to tease apart what the individual cell types are doing and how they are all working together to make you sick.

Barr: What are some of the next steps with that research and some of the longer ramifications of the study?

de Wit: We have not really done much more with that because all of those variants of concern emerged, so we got distracted by that, but if you want to get deeper into all of the changes that we see in these individual cell types, you might be able to figure out new targets for treatment. These macrophages are causing inflammation, which is what makes you sick. I am sure you have heard that people are being treated with dexamethasone which is a really broad anti-inflammatory which

suppresses your immune system and is actually quite effective, but maybe there are better ways to do that, more sophisticated ways, because even with dexamethasone people die. Maybe if we really get into what is happening in all of these cells, maybe we can find new ways to treat the disease. That is really the long-term idea.

Barr: What challenges did you encounter with this study?

de Wit: With all of the studies during the pandemic, one of the main challenges was to make sure that they could keep going. We were really fortunate being able to work, but we were still really restricted in how many people can be in a certain space at the same time. In spite of all these rules, someone could still get COVID and have to go into isolation for two weeks or be exposed to someone and have to be quarantined, so one of the challenges was to make sure that we had all the people lined up. This was the first time when we made a schedule of who was doing what. And we also had a plan B for who would take over if this person was exposed or got COVID, and we had a third list with one or two last-resort people. It was practical things like that, and especially with these non-human primate studies.

Another challenge is always handling the stress. In general, when we do animal experiments you want to make sure that you do everything right but when you do non-human primate experiments, there is really zero room for error. Everything has to go smoothly and as planned and that makes it stressful which is a challenge that you have to deal with, unfortunately. It is really important that we do this type of work the best way that we can, and the stress comes with doing your job the right way.

Barr: Can you speak more in detail about how you contributed to the trial that looked at the ChAdOx1 nCoV-19, the AstraZeneca vaccine? Can you speak about how you contributed to that trial that looked at how it prevented SARS moving to pneumonia in mice as well as rhesus macaques?

de Wit: The study was run by Vincent Munster's lab who is upstairs here in the same building. My lab had this long-standing collaboration with Gilead for the remdesivir; his lab has a long-standing collaboration with the people at the Jenner Institute, Oxford, who developed this ChAdOx1 nCoV-19 vaccine. It was exactly the same that we did with remdesivir. They immediately talked about a new virus and the need to make a vaccine just in case this becomes something big. I was only involved on the sidelines because we just had so many studies. We wanted to do it really quickly and having to deal with working in the specific circumstances of the pandemic so when we did our remdesivir study [Vincent's lab] stepped in and helped on the days that we needed help, and that is what we did when they did the ChAdOx vaccine study. It was really just when these things happen, it does not matter that I am the PI [Principal Investigator]. Whatever needs to be done, needs to be done. If they need someone, I do not care what it is. We all help together at it, and because of that they were able to get these data really quickly. And actually in Oxford, where they were starting the first Phase One clinical trial in people with this vaccine, they were really waiting for us to show them the data. That was the main thing, of course, to see that the vaccine protects, but it was also a major safety question that they wanted to see

addressed before moving into people. Vincent Munster's lab sent them the data which was an essential part of information, and the next day they started the trial in people. It was very important to do the whole process as quickly as possible, which is why we stepped in and helped.

Barr: Did you work with others at Rocky Mountain lab, providing them help with any of their experiments?

de Wit: Yes. We also worked with Heinz Feldmann on hydroxychloroquine because we work mostly with BSL-4 pathogens, because we are a BSL-4 lab. This hydroxychloroquine story happened also when there was a big Ebola outbreak. In vitro somehow, it works really well to stop virus replication, but in animal models, it has not really panned out. So he was testing whether hydroxychloroquine actually worked in animal models, and we helped with that study as well. We have been working together with several other PIs. We are just making sure that we share all of our viruses and reagents whenever we can so that everyone can move through this as efficiently as possible.

Barr: In addition to some of your animal studies, you have participated in other kinds of studies, one of which is the aerosol surface stability of SARS-CoV-2 compared to SARS-CoV-1. Can you discuss your role and your findings of that study?

de Wit: This was on our very first list of things to do. The aerosol and the surface stability are always a question when you have a new virus because all of the public health agencies are really worried about how is this virus spreading, what is the danger, and what measures should we take. Imagine your colleague who is sitting at the desk next to you goes home with the sniffles, and then is diagnosed with COVID-19. Can you touch the stapler that you share if you know that your colleague has just used it? How well do we need to disinfect surfaces? Vincent Munster set up these experiments, and again we stepped in to help get that done as soon as possible, so that we could provide all of these public health people with some data to base their public health measures on. The N95 came a little bit after that because it was in response to the shortage of N95s for healthcare workers, and people having to reuse them. One of the important things that we showed is that you can decontaminate an N95 mask, and you can put it back on your face, but when you do that, and especially if you wear it for a while, the mask will just go bad, and it will not protect you anymore. So if you reuse a mask, ideally you would test and make sure that it still really fits tightly and is actually protecting you.

Barr: What are some of the COVID studies that you are involved in now and what are some of the types of studies you would like to be a part of?

de Wit: Right now, we are mainly researching all of the variants of concern. We have a study that we are finishing right now called the Alpha and the Beta variants. A lot of people have focused on: “Do the

vaccines still protect?" That is really important, but large parts of the world are not vaccinated yet, so it is also important to see, if these variants take over like the Alpha variant actually has, what the risk is. If you get an infection, are we going to see more people with severe disease or not? It doesn't really look like it. So that's one of the questions that we're working on.

What I think is really interesting, but is really complicated for us, is to look at the long COVID. To understand what's going on in people that months after an infection are still not feeling well and have all kinds of complications. I think that's really interesting but it's something that we haven't seen in animal models yet, and it is also difficult because we are trying to address all of these questions as fast as we can so and we haven't taken the time to infect animals and then leave them for a long time. And also, a lot of these things are really hard to measure. The fact that you are tired when you walk up the stairs, or you are just really tired all the time, or the brain fog—that's really hard to observe in an animal and know what is actually going on, but that would be really interesting to figure out, but probably, there are so many human cases that we might actually get more data from people who actually have long COVID, than we could get from animal models.

Barr: Have you seen any differences amongst the variants?

de Wit: We compared the Alpha and the Beta variants to a virus that was circulating in Montana because we got the virus here from a patient in Hamilton last summer. What we see is that the Alpha variant that was from the UK, we do not really understand why, would transmit better in humans than in the monkeys. In the monkeys, we do not really see any evidence that it would transmit other than that there is a different response in the nose. There is not more virus in the nose, but there is more inflammation, and if you have more inflammation, it could mean that maybe you are producing more snot and spreading more virus that way, but we do not know [if that is really what happens]. It is not causing more severe disease. The Beta variant, which was the South African variant before, is actually causing less severe disease so, we do see that the animals don't show as many disease signs and also, they have a lot less virus in their lungs, so that one actually looks like it would cause less severe disease than the virus that was circulating before.

Barr: Are you planning on looking at the Delta variant, the one from India?

de Wit: Right now we are not. These experiments are not so easy to do, and the viruses are not so easy to obtain. It has taken us a long time, and even though things have improved a lot, [virus] strain sharing is still a bit of a problem. Getting these viruses and then getting a clean stock is also sometimes problematic. One thing that we have seen is that at this point, we are generating data in the human population faster than we can keep up with in the animals. Regarding these variants of concern, the Alpha and the Beta, we know by now that the Alpha has completely taken over in certain areas of the world, but we are not really seeing more severe disease in people so that is what our experiments also show. Because we cannot keep up with the developments in humans in our animal models at the

moment, it becomes a question if it is worth doing the animal experiment to get these data [because] by the time you actually have the data you already know what is going on in people. It is only important to address these questions in animals if you cannot address them in people.

Barr: Have you been involved in any other COVID activities either at NIH, or outside of NIH, in the professional associations, or societies?

de Wit: I am part of a WHO working group for animal models, where we have weekly meetings and make sure that everyone has the most recent data on animal model development and what you can use these animal models for. I am also on the preclinical group for ACTIV [Accelerating COVID-19 Therapeutic Interventions and Vaccines] which is running all these clinical trials. They were getting so many requests from academics and also companies to have their drugs tested in people where a lot of the data were not complete, that they now have this pre-clinical group where we look at all of these proposals and identify if all of the important data are complete, or if more experiments need to be completed. If more experiments need to be done, we try to help these people to get those experiments done so that we can potentially move these treatments into clinical trials.

Barr: We are going to transition from you as a scientist to you as a person living through the pandemic. What have been some personal opportunities and challenges for you that COVID has presented?

de Wit: It sounds awful to say, but from a work perspective, it has been a great opportunity, because it is rare as a researcher that you do something that can have an immediate effect on public health, right? Normally, you sit in the lab, and you do your experiments and there are a few people that are really interested in what you are doing, but it takes forever to get from that lab experiment to maybe ever having a treatment, and oftentimes that never happens. But now, people are asking, “What about this?” “Can you do this?” “Have you looked at this?”, and to be able to help has been in that sense a very fulfilling time.

On the other hand, I had never expected this would happen and so at times it is also really difficult, because there is your scientific fascination with what is going on, but then there is also your personal worries about your friends and your family: ”Are they going to be okay? “Are they making sure they are not getting infected?” There is a lot more worrying that goes on in our lives. It has just been a really crazy time, but if you do not mind working hard, which I do not, and you have the feeling that what you are doing is important, it is actually not that hard to keep going. In that sense, our pandemic has probably been much better than most people's pandemic just because we were going to work every day and so were most of my colleagues, and although we were not allowed to all sit at a table and have lunch together, at least you are seeing people, and you have your set routine. You are just going to work and rather than being stuck at home in an apartment with a couple of kids. So, it has not been so bad for us.

Barr: Is there something that you enjoy that has made the pandemic more manageable? It sounds like you were working a lot.

de Wit: There is only so much you can do. This was going to take a long time. We knew this was not: "Let us just all work 16 hours a day for a month and then it will be over." No, it was pretty clear from the start that this was going to be long so you cannot always be working because then you are just going to break down and not be able to do anything. So we managed to keep a somewhat healthy work-life balance. We live out here in Montana, so in summer, when the weather is nice, I go home and I get on my bike and pedal up a mountain, and I feel much better when I get back home. In winter, we go skiing even if it is just cross-country skiing for an hour or so. You are out, you are in the mountains, it is beautiful, and you can just let go of all of the stress of the pandemic for a little bit.

Barr: This is a thought-provoking question. Towards the beginning of the pandemic you shared your thoughts on how controlling and monitoring the Nipah virus could inform our response to COVID-19. In what ways were your suggestions realized, and in what ways do you think there could have been or still can be some improvement?

de Wit: To be honest, I think it is still a little early to draw any big conclusions. One of our suggestions was that we need money, and a lot of money has been thrown at specifically the problem of the pandemic. It seems like more money is coming to invest more in being prepared for the next pandemic. How that is going to pan out is something that we will not know for a little while. Investing the money in the right places is definitely going to be important and we have to realize that these viruses can come from anywhere, so it is a global effort that is needed to make sure the world is ready for the next pandemic. Hopefully now that so many people are getting vaccinated, in a year or so we will hopefully be out of the pandemic. Maybe then, we can take a step back and look at everything that happened, and everything that was done, and where we could really make a huge difference next time, by being better prepared, by having certain infrastructure, or just having labs, or having stockpiles of certain things. It is too early, for me at least, to say now. It is all kind of one big blur of a lot of lab work so it would be nice to be a little bit further out, and actually look back and take all that money that we were now willing to spend and make sure we are spending it in the right places.

Barr: Is there anything else that you would like to share?

de Wit: No, I do not think so.

Barr: Well, thank you so much for all the work that you have been doing, and I wish you and your lab continued success, and of course, continued health.

deWit: Thank you. The same to you.