Dr. Nicole Doria-Rose
Behind the Mask
July 28, 2022

Barr: Good afternoon. Today is July 28, 2022. 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. Nicole Doria-Rose. Dr. Doria-Rose is the Chief of the Humoral Immunology Core at the Vaccine Research Center [VRC], which is in the National Institute of Allergy and Infectious Diseases, and today she is going to be speaking about her COVID-19 research and experiences. Thank you so much for being with me.

Doria-Rose: Thank you for having me.

Barr: When did you become involved in the mRNA-1273 vaccine, also known as the Moderna vaccine? What was it like to be part of that team that looked at its efficacy in primates to different ages in humans? What was the expertise you offered? You were a part of so many of those studies.

Doria-Rose: Let me start with my background. Most of my career was HIV research, and I was looking specifically at antibodies in HIV that are generated in people who are infected or in people or animals that get test vaccines. Specifically, my group had been looking at what's called neutralizing antibodies. Antibodies are proteins in your blood that fight off bacteria, viruses, and other germs. The antibodies that fight these germs can do it in different ways. They can just stick to the virus and coat them to make it easier for the body to clear them, they can directly kill the virus, or they can block the virus from infecting a new cell. Specifically, we look at neutralizing antibodies. Those are the ones that coat the virus and stop the virus from infecting their targets. My group had a lot of expertise on doing this in these standardized assays for 15 years. When COVID came around and there was this great need to do the analysis of blood samples from testing vaccines in animals or in people, my group got involved in doing this. There were already other labs at the Vaccine Research Center, where I am, that developed an assay, but it was not standardized. It wasn't as reliable as we wanted, and we couldn't run as many samples at a time as we wanted to. My group applied our expertise in doing this – more standardized, doing it faster, doing more at a time, sort of imposed the logic of the structure of it, some of the details of the way we do the lab tests and the way we handled the data. We adapted that for doing the COVID tests. We were asked to do that pretty early on. I'm at the Vaccine Research Center, and other groups at the Vaccine Research Center had worked with Moderna to develop that vaccine and so had already been doing that. Then we got called in to do it. We ended up looking at what groups were available to do what at the time, and my group ended up taking on running the samples from the Phase One clinical trial. That was the first time that this mRNA vaccine, the Modern vaccine, was tested in people.

Barr: That’s so exciting!

Doria-Rose: It was really cool. This was so important to do. We knew from the work that Kizzmekia Corbett and Lingshu Wang and the VRC had done that this looked pretty good in mice. It looked pretty good in mice. It even looked okay in monkeys, but you never know how it's going to look in people until you actually put it into people. So Moderna started what’s called a Phase One clinical trial. That's the first-in-human test. Groups of 15 people, and a group of maybe 10 people testing different doses and

then testing different age groups. We were kind of semi-blinded. We didn't always know which samples were which. They do that so that you're not biased when you are actually running the lab test and be like, “I really want this to work.” We didn't know but we could see that some of the samples were coming up positive and even looked as strong as in people who were actually infected. That was just so exciting, and we had to keep it a secret. We had confidentiality with the companies. For a while only we knew that it was working, and it was really exciting. We couldn't even tell our families. It was a high-pressure time because we really had to get it right. But it was really exciting to be able to contribute in that way.

Barr: How quickly did you have to do all this? You were part of multiple studies and tests. How quickly did you have to do all this – set it up and analyze the results?

Doria-Rose: We only had a few weeks to really get the assay, the lab test, into shape where it was good enough to use on those clinical trial samples. Normally, we would spend months optimizing all the different aspects of it. We didn't have that amount of time because we knew people were starting to get vaccinated [as part of the Phase One trial]. We knew when the samples were going to be coming in. We had to make any changes that we wanted to make and show that it was good enough and that was it. Then we were locked in. We couldn't change our procedures anymore after that. That was pretty stressful and high pressure to get it right. There were things we would have done differently if we had more time, but we got it to the point where we were confident that it was going to give us data that we could believe in.

Barr: That does sound really stressful. Can you speak about some of your work since the Phase One trial that has looked at the efficacy of the vaccine against the different variants such as the study convergent epitope specifications, gene usage, and public clones elicited by the primary exposure to SARS-CoV-2 variants that focus on the Washington Beta and Gamma variants, and the Omicron neutralization study that you have had an active role in? It's a very big question but, I guess, all your work on the variants.

Doria-Rose: Thank you for naming one of our favorites. We have done a lot of work looking at the variants. As soon as the variants Alpha and Beta started coming out there was early data from other groups showing that these variants were going to be a problem. That antibodies in people who were infected with the original strain of the virus or people who were vaccinated weren't – the antibodies response wasn’t as good. Their antibody responses weren't as good. We looked at a couple of different things. The paper that you mentioned looked at blood cell samples from people who were infected with different variants. The study that I really pushed for was one where we looked at those same samples from our clinical trial but looking over six months after people got their second dose of the Moderna vaccine and how well did they recognize all of these variants. We looked at it a bunch of different ways. My group used our lab tests that we had developed. We didn't know if that was going to tell the whole story. Other labs did it different ways. I actually brought together people of different labs who had different tests looking at different aspects of the antibody response. We all tested the same samples from the same four time points over the course of vaccination and six months after and looking at the same variants. What we found was that the variants responses were different between the different variants. The one that was the worst at the time was the Beta variant. The antibodies were about 10 times less potent depending on which lab test you did, almost 10 times less potent than they

were against the original. When you looked at the way different labs were doing different tests, some labs are looking at neutralization. Some labs are looking at just plain binding. Do the antibodies stick to different parts of the virus? There were also biochemical tests for antiviral activity. All of them gave basically the same answer: That it's not as good against the variants – at the time, Beta was the worst – and that you get this decrease over time as well. After the second dose, everybody's recognizing everything which was great, but it's six months out because the amount of antibody was going down over time. Half the people weren't recognizing the Beta variant at all. What was cool about this study is this got used as part of the decision-making by the U.S. government and others. That combined with the fact that the efficacy of the vaccines was starting to go down. That went into the decision to start giving people booster shots. This was in fall of 2021.

Barr: That's a great feeling.

Doria-Rose: It was. I know one of your later questions is about what some of the challenges in doing this. Part of the stress of all of this was – COVID just upended everybody's lives. My kids had to do online school. My kid got sent home from college. Everybody was working from home. There is also kind of a feeling of helplessness, like there is this outside thing and we are all subject to it. For us working in the lab and being able to contribute to this and seeing our work actually influence policy and shots going into people's arms. That was really, really rewarding and made it not as bad for mental health as it would have been.

Barr: Yeah, because your work is being used practically and making an active difference.

Doria-Rose: It was. On the other hand, it was a lot of stress to get it right. I had a little inspirational picture of hope over my desk that was a quote from RuPaul that was, "Don't F it up," basically. We knew we had to get it right. It was a lot of work and a lot of long hours and weekends, and the other thing that was hard about it was we had very limited in-person contact before vaccines. We were doing what we could to stop the spread and we really limited the number of people who could be in the laboratory at any one time. The people working with me, who were doing the actual lab tests, one of them worked early in the morning and the other worked late afternoon into the evening and through the night so that they didn't have to be in the lab at the same time -- to the point that one would be coming in at five in the morning and the other one would be just leaving at that point because he had been there all night. The hours they worked – I have to give tribute to Steve Schmidt and Sijy O'Dell. My team that did this just put in so much work and did such high-quality work under such awful circumstances. It was really great to work with them and to be able to do this.

Barr: Can you talk a little bit about the Omicron neutralization study that you have been a part of?

Doria-Rose: When we first saw the sequences coming out of South Africa – and I have to say that the scientists who do the sequencing are just tremendous – they sort of raised the early warning about Omicron. Everybody looked at the genetic sequence of this virus and said, "Uh-oh," because we could already see that it was going to be pretty bad. Nobody knew at first how bad it was going to be, but you could see it was going to be pretty bad just looking at the genetics of it. Those earlier variants that we talked about, Alpha, Gamma, and Beta, had about 10 changes in the spike protein, which is what the

antibodies target. They had 10 changes away from the original; Omicron had 30. Not only that, but we knew already which of the changes in Beta and Gamma were bad for antibody recognition and which of them helped make the virus spread faster. Omicron had the greatest hits from all of those or maybe the worst offenders from all those. We knew going into it that Omicron was going to be bad. People worked crazy hours to get the tools that we needed to test this in the laboratory. Then we tested it. We worked with a lab at Duke University, David Montefiori's lab, and we worked with all the samples again. We looked at people who had gotten two doses of the mRNA vaccine as most people had and saw that where before Beta was the worst one and it was about 10 times down. Here it was 20, 30, 40 times worse. A lot of people were not recognizing Omicron at all. The good news is people who had gotten their booster shot – then it wasn't as bad. It was only 6 times less, and everything was boosted by the boosters. At least right after people got the booster shots, their antibodies were back up in the range that we thought was going to be protective. What they told us was you got to get your booster shot, but it's going to be okay if you get your booster shot. That was really important information to see just how bad it was and that there was a way around it basically.

Barr: Can you talk about your study that looked to see if binding and neutralizing antibody responses to SARS-CoV-2 in very young children exceeded those in adults and discuss why that may be the case?

Doria-Rose: This was a study that we were asked to help with from Ruth Karron at Johns Hopkins. It was a really neat study. They were following families where one family member had COVID and then what happened in the rest of the family. [Inaudible] What we found is that the binding antibodies, the antibodies that stick to the virus, and then the neutralizing antibodies, the ones that block infection, are better in kids than in adults. One of the things that you have to look at is maybe it's just the virus they got infected with, but even within a family, if multiple family members got infected, the kids had better antibodies than their parents. You knew they had the exact same virus that they got infected with, but their antibodies were better than the parents. You see this too in kids who are infected and then you also see it in vaccines in kids. You can use a smaller dose of the vaccine and still get really good antibodies, and this is one of the reasons that the dose for kids for the Pfizer vaccine and the Moderna vaccine are smaller than the dose for adults. One of the things that was kind of interesting as well, usually you see higher antibodies when the cases are more severe, but here the kids didn't get really sick, and we know that kids don't get really sick. Maybe this is a reason why kids don't get really sick because they have better antibodies so they're better able to fight off the infection that they have when they get infected.

Barr: That is so interesting. Is it like that for other diseases too?

Doria-Rose: Not necessarily. In fact, for some diseases antibodies are not as good and there's been a lot of debate about whether this is similar to flu or similar to respiratory syncytial virus, RSV, or not. I'm not an expert on this, but I saw as we had conversations about that there was some surprise.

Barr: Usually kids get so much sicker than adults.

Doria-Rose: It depends actually. With chickenpox, little kids don't get very sick, but if you get it when you are an adult, you get really sick. If you get it for the first time when you are an adult or a teenager you

can get really sick. Really little kids can get sicker from things like respiratory syncytial virus or influenza. It was surprising, but this has been a thing with COVID all along. The people who get really sick are the oldest people, and in many other respiratory diseases, it's the oldest people but also the babies. Here it seems to really be the oldest people and not the babies. We are still trying to figure out why.

Barr: That is fascinating. What have been some takeaways from all these studies, and have they been applied to vaccine and therapeutic design?

Doria-Rose: Obviously the data from these studies has been presented to the FDA for getting approval for vaccines. All the work that our lab and other labs have done on the Omicron variants has led to the FDA recently stating that what they want the vaccine companies to work on is Omicron BA-5 matched vaccines. That comes from the work from many labs showing that that the original Omicron was bad, and BA-5 is even a little bit worse than that. We really want a vaccine. The booster shots that are going to be available should all go well. These studies are ongoing and I'm getting samples next week. Should everything go the way we think, the booster shots that will be available in the fall are going to be a mix based on the original virus and a product that is based on Omicron BA-5 so that you can get better antibodies against the BA-5.

Barr: What are some aspects of the immune response to the vaccine that you would like to probe deeper into at this point in the pandemic?

Doria-Rose: We have an ongoing study where we are looking at how the antibodies develop over time. We are trying to understand the mechanism of why that booster dose is so helpful. Why the antibodies are so much better after you get a booster dose in terms of how well they recognize Omicron and the other variants. We are doing some studies where we are looking at the white blood cells, the B-cells that make the antibodies, and we are looking at them over time to see what the mechanism is, why is it that that these booster shots are so important.

Barr: That is really interesting. Have you been involved in any other COVID-19 research or plan to be? Or initiatives as well because people do all kinds of things.

Doria-Rose: Right. One of the other things that has come out of the research at the VRC and many other institutes and companies is monoclonal antibodies that can be used for treatment or even for prevention. The drug that's bebtelovimab and the drug bamlanivimab. Those were some of the first monoclonal antibodies that were used as treatments. Those came out of research at the Vaccine Research Center. But many of these antibodies don't work as well or some of them don't work at all against Omicron and these other variants. We are continuing our work to try to discover new antibodies or engineer the antibodies so that they are better able to fight against the variants that there are now and potentially even variants that we don't know about yet. Because we don't know what the next variants are going to be, we are actually looking at related viruses that are in animals in different countries and even SARS-CoV-1. SARS-CoV-1 caused an outbreak in, I think, 2003 that killed a lot of people, and it is closely related to SARS-CoV-2 which causes COVID. If we can find antibodies that can react to both COVID and to that older virus, then maybe it will react to all the related viruses. It would

be something helpful when the next variants come out. That is the kind of work that we are doing – continuing to try to find these antibodies.

Barr: That's exciting. That's a lot. What are some things that you feel that you have learned from your research that you would apply to some of the other kinds of work that you do or just how you operate your lab?

Doria-Rose: Just sort of generally, we have had the taste of success which is really nice. You know after 30 years of HIV research we still do not have good vaccines. We keep hitting walls. To have a taste of success in a vaccine is actually invigorating. One of the things this has all done is jumpstart the mRNA vaccine field. There are some projects that many labs are doing now and something that I am planning for my own research, and that's using the power of mRNA vaccines because they can be made in such a standard way and can be made so quickly. That is definitely sort of the next wave of things that are going to be done for other viruses as well. The other thing that this has done sort of globally is we have seen what can happen when there is real urgency. We had what was called Operation Warp Speed, where everything was streamlined, where there was loads of money, where there was loads of urgency, where red tape was reduced. We have seen what that can do. That was part of why we got a vaccine in a year – it was because of that. We have seen what we can do, and we are thinking if there were that kind of urgency for HIV, where would we be now? Changes your whole thinking on it.

Barr: You have talked a lot about HIV and how you have applied what you have done with that, but you have also worked with other viruses like Zika. Can you talk a little bit about how you have applied some of your knowledge of working with those viruses to your COVID work?

Doria-Rose: One of the other reasons that we were able to get a COVID vaccine in a year is that the tools that we already had for looking at HIV, for looking at Zika, were able to be applied and adapted for COVID research. I was talking about discovering antibodies that could be used as drugs. That was technology that was already available, and we had been using for HIV and Zika. We have used multiple different technologies. There were several that were developed specifically for HIV, but already were being applied to other pathogens and viruses like malaria. A lot of that has been improved and refined over the past few years in working with COVID. Now we can apply those back to HIV and back to some of these other viruses too.

Barr: Where were you when you first found out about COVID-19 being in existence and secondly with Omicron? I know we were all kind of caught by surprise by that.

Doria-Rose: With COVID-19 I had heard some news reports that there was a new pneumonia in China. I actually was talking to a colleague who is from the Wuhan area, and he was talking to people back home. He had more information than was sometimes being made public, so we knew that this was going to have the potential to be something really bad. Then when everything shut down for two weeks – or we said it was going to only be for two weeks. The kids were sent home back in March of 2020. We were looking that this could be a lot worse than that. As soon as it looked like this was going to be a major public health problem, we started working on it at NIH and at the Vaccine Research Center. That was in 2020 and then the Omicron thing. Actually, it was funny. I told the story about this at a

conference recently and then I learned that everybody had a story about where you were when you found out about Omicron, so here's my story. It was Thanksgiving weekend when people started to realize how bad it was, and we had been working just crazy hours, super hard and not taking days off for a long time. In November 2021 my group and I decided that things were calm enough that we could actually take four days off or maybe even five days off at Thanksgiving. Cook and be with our families and whatever. I was starting to see news reports about Omicron. I probably have a lot of emails about this. It will be there on Monday. It will be fine. I made it all the way to Friday afternoon of Thanksgiving weekend. I was on a hike with my family and my teenage son says, “So Mom, I hear a new COVID dropped,” like it's a Beyonce album. All right, if my teenage son knows about this probably I should be checking my email, and at that point my phone starts ringing and it's not Beyonce. It's my colleague saying, “Do we have the right gene sequence for Omicron? What are we doing about Omicron?” I was like, “All right.” I got home from the hike and got back on my computer, and I had 100 emails about Omicron and that was the end of Thanksgiving weekend for me. That was that, and everybody has a story like this about what happened to their much needed four-day weekend when Omicron came out.

Barr: As a person you already said some of the challenges that COVID-19 has presented like your kids having to do school from home and things like that. Were there any opportunities for you?

Doria-Rose: Oh yeah. You know, given what a horrible thing this has been for the world, I'm always embarrassed that it has been good for my career. Having the opportunity to learn something new, to learn about a new virus, to be involved in clinical trials which I hadn't done very much of before, and then having a lot of really high impact papers, being able to be published in the New England Journal, being the senior author of a paper in Science. It has been a really great opportunity career-wise in that way. Just learning about a new virus, learning about and interacting with colleagues and new friends who I would not have interacted with before. A lot of the people who are working on COVID now – there weren't that many people working on coronaviruses before. There are now, but there weren't a lot of people working on coronaviruses, which COVID is a coronavirus. Most of the meetings that I'm in and Zoom calls that I'm on, everyone either worked on HIV before or influenza before. Now I know a lot more about influenza also because of working with those colleagues. It is really nice to grow as a scientist.

Barr: That's wonderful. Thank you for all of your work that you have been doing. I wish you continued success in all the studies that you are a part of.

Doria-Rose: Thank you very much and thank you for this opportunity.