Lindsey: With stay-at-home orders lifting and worldwide confirmed COVID-19 cases totaling in the millions and continuing to grow, scientists are pushing forward at “warp speed” to develop vaccines and treatments to slow the pandemic and lessen the disease’s damage.

Over the past decade, the scientific community and the vaccine industry have been asked to respond urgently to epidemics of the H1N1 influenza, Ebola, Zika, and now COVID-19. The H1N1 influenza vaccine, for example, progressed relatively quickly from discovery to distribution because the technology was already well developed. Now, we wait for the next break-through to possibly shorten development time in the case of a COVID-19 vaccine.

This is *The Antigen*, and I’m your host, Lindsey Dietschi.

On this special miniseries of The Antigen, we’re connecting with experts to give you accurate information on COVID-19. As you know, we’re working with our partner BioNtech on a potential vaccine for coronavirus. We have a global clinical development program underway and the first participants have been dosed. So today, we’re asking: what does the path to a vaccine actually look like?

For an accurate account of the journey from vaccine discovery to distribution, I’m speaking with Phil Dormitzer, Vice President and Chief Scientific Officer of Viral Vaccines at Pfizer. Of his many accomplishments, while formerly at Novartis, he led the research component of their response to the H1N1 influenza pandemic, supporting the development of three now licensed vaccines.

Lindsey: Phil, thank you so much for joining today. I'm really looking forward to the discussion and getting to speak to a scientist directly. For our listeners, what is the number one thing you'd want them to have in mind regarding vaccine development?

Phil: Well, that is a thorough process that is designed to show that a vaccine is both safe and effective. And on top of that, that we can manufacture consistently. Those sound like very simple things, but to demonstrate those things to the necessary level of certainty is a very big undertaking.

Lindsey: Yeah, absolutely. Very good point. When we're thinking about the whole landscape that's underway in vaccine development right now … I think a lot of us have read about there's some hundred vaccines in development and maybe about 10 or so that are in human testing. So, for the listeners, what really distinguishes those 10? What does it mean to be in human testing relative to maybe some of the other dozens of programs that are also underway?

Phil: With modern molecular biology, it's actually relatively straightforward to take a gene for a protein from a new virus and then express it, and create a vaccine candidate that, for example, you could test in a mouse. There are many, many groups that can do that, and can do it quickly and well. To take it from that stage, where you have your first genetic construct, your first test vaccine that's suitable for use in the laboratory, to something that is truly suitable to distribute to millions or hundreds of millions of people, is a very, very big undertaking that only a limited number of companies can do. Because to do that, you need to be able to define what you're making with great precision. To do a battery of preclinical tests, to make sure that it's safe and behaves in the laboratory in a way that you think means you will protect people, and then go into people.

In people, you need to initially test in small numbers, make sure that it's safe, that it elicits a certain immune response you want. Then in a very careful way you need to expand the numbers until you're in a large number of people who are representative of the population that will finally receive that vaccine, and demonstrate in that population that it really behaves in a way that makes it suitable to give to many currently healthy people. And then you need to be able to make the vaccine in large quantity, and be sure that every time you produce a batch it has equivalent quality so that everybody knows that if they're getting that vaccine they are getting something that is very similar to the stuff that was in the trial that showed that it was safe and effective.

It turns out that it takes not only a lot of, it's very expensive to do that, but that it has a huge infrastructure that's required. You need a lot of people who have a tremendous amount of expertise, sometimes in quite specialized areas, to be able to do that effectively.

Lindsey: Yeah. You can imagine the amount of expertise that it takes to do as you described. Create a safe vaccine that works, that can be produced at scale, manufactured at scale, and then used in a smaller group of healthy individuals. That really is the key about vaccines and the importance of getting that process right, since they're given to healthy people. So what's the typical vaccine development process and how does what's happening now differ from that?

Phil: The typical vaccine development process is lengthy. I think one example that's sometimes cited is the example of FluMist, where development started in the Eisenhower administration. It was decades to become a vaccine. Our example of something that happens relatively quickly in vaccines is the change that occurs as often as twice a year for a global company in both the Northern and Southern hemisphere, and the composition of the flu vaccine. It's not that it's developed from scratch every time, but at least there have to be changes frequently. And so there's a whole infrastructure from the science to the regulation to the manufacturing to the distribution that allows that to happen regularly.

Now, in the case of something like COVID-19, where a new virus arises, you can't start from zero, not knowing at all how to make this vaccine, and hope to make rapid progress. But what you can do is start with things that you know are working and adapt them to this new virus. What's being done now is to adapt vaccines that were either already in development, or in some cases that were in use elsewhere, and say, "What can we change to make it, now, not directed against another pathogen, like say influenza, but instead directed at this pathogen, SARS-CoV-2, which causes COVID-19?" Normally, over the long period of vaccine development, there are multiple projects that go on at once. And much of the process of vaccine development involves a lot of decisions about, "Are you going to prioritize this vaccine or that vaccine?" What's different now is because of the overwhelming impact of COVID-19 on health, on society, on the economy, that there is a focus on this project.

It also means that decisions about resource expenditures are focused. The example that gets cited a lot, and it's a very apt one, is normally you would go a long way through vaccine development. Make sure that a vaccine is working before you invest in the very large range of activities that are required to start manufacturing. But in this case, because it's so important to get this vaccine out, we see that we're going to start developing manufacturing and building our manufacturing capacity while we make sure that the vaccine is working. In smaller ways that kind of thinking is occurring throughout this vaccine development program. Where we do things that we would normally do sequentially, we do them at the same time. It doesn't mean that we don't do important things to determine safety and efficacy. We do them. But we do them at the same time, which involves a bigger expenditure of resource.

Lindsey: Yeah, absolutely. It sounds like the keys here are focus. Focus is enabling the timelines to be shortened. Things happening simultaneously to each other is allowing us to shorten those timeframes. And also the appetite to invest in these focused ways, in doing things like ramping up manufacturing capabilities and capacity. Putting this on the best path for this timeline to be well shortened compared to other situations we've been in. That's all very encouraging.

Phil: Yeah, yeah. I might add communication as well. There's a lot of communication that has to occur between clinical sites and ourselves, between ourselves and our collaborators and BioNTech, and between BioNTech and Pfizer and regulators, for example. Often we take a lot of time to do that communication. Now we communicate in real time, so that we really let the people who need to know to make decisions know what's happening as it's happening so that we reduce the time spent in communication. We communicate, but we communicate in real time.

Lindsey: Yeah. It's such an important point. We're actually seeing that in my team in global health partnerships as well. We're engaging with the global health partners to learn in days and weeks, instead of, as you said, being super buttoned up with a plan because we're all trying to figure this out

as quickly as possible. Really good point on the communications front and doing that in the interest of learning and getting things done quickly, and in an informed way for the people waiting for the vaccine. So, thinking about the technologies, you mentioned before, building on what we already know, and applying some of those insights to how we can develop a vaccine for COVID. Maybe you could go deeper into explaining the difference between messenger RNA, or mRNA vaccines, and DNA vaccines.

Phil: Sure. We've been working with our partners BioNTech on RNA vaccines since about August of 2018. We've been working with them on developing a RNA base flu vaccine. We've been interested in RNA because of its ability to respond quickly to changes. When a vaccine is based on say a virus or a protein, each new virus and each new protein can behave quite differently from others. Even others that are on the surface quite similar. It is true that molecules of RNA also can vary in their behavior, but one piece of RNA is a lot more similar to another piece of RNA in general, than a virus or protein is similar to another virus or protein. So that enables us to change quickly.

That's also true of DNA. DNA also can be changed quite readily. There was great hope a couple of decades ago that DNA vaccines would be sort of the new wave of vaccines because of this easy changeability, and because of their ability to elicit strong t-cell responses. What's found in DNA vaccines is they worked actually quite well in mice. But as they went through additional animal testing, even to larger animals or animals more closely related to humans, they stopped working so well. In humans, they can work, but typically you need to give a lot of DNA, and sometimes you even have to do a process called electroporation, using electricity, and as well as a shot to drive the DNA in.

It was found that with RNA, that's not necessary. They work in smaller quantities, and they work after simple injection in typically a lipid containing formulation that delivers the RNA into a cell where the RNA then creates a protein, which then elicits an immune response. Although no one knows for sure why that is, the most likely explanation is that DNA doesn't just need to get into a cell across the plasma membrane to get in the cytoplasm, but then needs to get from the cytoplasm into the nucleus. So it's another step. Whereas RNA only needs to go one step. It just needs to get into the cytoplasm. So it's thought that that's probably why it's easier to make an RNA vaccine with a relatively small quantity of RNA and a relatively straightforward delivery system than it is for DNA.

Lindsey: Okay. So the RNA going in and creating the protein that then elicits the immune response, that's really what makes it unique it sounds. So, as you are going through the vaccine clinical development process and thinking about what patient populations would be the right ones to immunize, maybe you can talk us through a bit about that. How do you identify which is the right patient population to immunize in this case to reduce the COVID-19 impact?

Phil: Sure. We do have an impact in this decision because we have to test the vaccine in populations like those who will receive the vaccine. But it's not entirely our decision. Because generally what happened in 2009 with the influenza pandemic was governments bought most of the vaccine, and then they made many of the decisions about distribution. But nevertheless, we do still have an important role to play here. When we think about this, we look at the older adults. Because you look at how hard this disease has hit older adults and it's clear that they're a priority population. Frontline healthcare workers are another very important population. There is a sense that you do want to get a high proportion of the population immunized. Because to stop the pandemic, it's going to be necessary to create what's called herd immunity, when a high proportion of the population is immune, so that even a person who is sick is unlikely to transmit to another susceptible person because most of the people around that person are already immune. So that argues for broader immunization.

There are special populations to think about. For example, the benefit-risk may be different for immunizing, say, children or pregnant women than it is for immunizing older adults or even healthy young adults who are neither pregnant or who are not children. Those are populations where more thought has to be put into what is the optimal policy towards immunizing those groups? And additional information will need to be generated to ensure the safety and efficacy of immunizing those populations.

Lindsey: It sounds like you and other scientists are starting to formulate some insight on, "Who could the target populations be in the short term?" Recognizing that as vaccines come to be available and are proven safe and effective, there might be some target populations that get immunized first. Elderly people, healthcare workers, all useful, those types of learnings. When you're thinking about seeing a vaccine going through clinical development as you are now, as a scientist, what are some of the signals that you're looking for as a vaccine is progressing through clinical development that help you see this has a chance to work, this has a chance to disrupt the transmission of COVID-19?

Phil: The first things that we look at when we first start testing in people, we first look at reactogenicity. Because you find that out right away. You find that out within a day or two of the injection. Saying, "Did it hurt? Did the person feel okay after they received the injection?" And then, after several weeks, you start to get information back on the immune response. Did they have a strong antibody response, or in some cases, a strong or t-cell response, or one that you think is going to be associated with protection? And then you move on from there. And after asking those questions, typically in healthy young adults, you start to expand the range of people in which you ask that question. You start to ask the question in elderly, and eventually, you expand to ask people who have more of the typical range of medical conditions as so many of us have, so that you start to get

a sense of, "How is this likely to behave in a real world situation where all kinds of people are going to get the vaccine?"

Lindsey: Got it. Starting with a population of healthy young adults, understanding the immune response that the vaccine might elicit, and then how that immune response might actually correlate to some level of protection against the virus. Really interesting. When we're thinking about this vaccine development program, and many, right, that we're reading about in the news, what do you think should really give people optimism about what you're seeing happen in vaccine development either at Pfizer or even more broadly?

Phil: Well, the range of approaches that people are taking is good because it's a very good thing in a situation like this to have many shots on goal. It's also encouraging to see some of the cooperation that's going on. At this point, it's too early to have actual efficacy data in humans on any vaccine. But we are starting to see, in animal models across the industry, signs that some of these vaccines actually can be effective in animal models. We'll have to see a lot more. We want to see peer reviewed publications so that everything undergoes rigorous scientific review, and ultimately rigorous regulatory review before any firm conclusions are drawn. But in the early days, looking broadly, there are signs that this is unlikely to be like HIV or hepatitis C, one of these viruses against we've tried and tried and tried and have been unable to come up with a vaccine. It's going to be challenging, yes, but there are early signs that this is a virus against which you can effectively immunize.

Lindsey: It sounds like you gain insights from a company perspective. You're seeing many companies gain those similar insights within animal models. And then that important step of a rigorous external peer review process on the data that's being gathered to really have an additional stamp, an additional understanding that what you're seeing is also aligned with what other experts would conclude in seeing the same kind of data sets.

Thinking a little bit about the bigger picture again. As you mentioned before, the enormous impact COVID has had on our daily lives, the economy, public health, et cetera. Curious, how has the international focus to quickly develop a vaccine, recognizing that it usually takes much longer to go through this process and now the timelines are much shorter given, as you said, the focus, the simultaneous things underway, the open communication, how has the international focus on developing a vaccine for COVID, or multiple, changed the way you and other researchers are working? Changes in scientific progress, or changes even in the attitude toward the work, or maybe even what your typical work schedule looks like?

Phil: Yeah. Well, I can certainly speak to what I'm seeing in my colleagues. I'm based, as are many of my colleagues, in Pearl River, New York, which is a New York metropolitan area. It is one of the

spots on the planet that has been most hit by this virus. The people coming into work every day are the same people who have family members very much in harms way, and sometimes directly affected by this. Some people can work from home. But if you're going to do laboratory bench work, that you cannot do at home, so you have to come into the lab.

There are about 350 people a day, come into the Pearl River site in the middle of the pandemic. They are taking the precautions. They're socially distancing at work. They're using protective gear when they need to. But nevertheless, they're coming in. They're not just coming in for ordinary hours, there have been weeks that people have worked, really, as long as they have stamina for, through the weekends, et cetera, to get this vaccine out. So, it has been a tremendous effort, often under challenging circumstances, for many people to be able to sustain this and to keep the progress going.

Lindsey: Yeah. I can only imagine the amount of dedication it's taking across all of the companies, academic institutions, public health partners that are focused on this. I mean, everybody is working at such an urgent pace. It's both encouraging and inspiring. I guess that leads me into my last question for you, which is really, seeing all this focus, seeing all this dedication, what's your sense of when might we have a vaccine to help address this?

Phil: I can certainly address the goals that have been set out for us by Albert Bourla, our CEO. The goal that he set for us at the very beginning is that he would like to see millions of doses of vaccine produced in 2020, and hundreds of millions of doses produced in 2021. That is the goal that we're working towards. The outcome depends on how well the vaccine works. One thing it depends on, for example, if you're going to demonstrate that the vaccine is effective in the traditional way, and that is immunizing a bunch of people and watching what happens to them, it depends on the attack rate. Will there be enough virus circulating by the time we're in very large studies to be able to observe people actually encounter the virus and get sick.

In a sense, we hope not. I mean, we hope there'll be successful containment. Which would mean that we have to use other means to demonstrate efficacy such as establishing a level of immunity associated with protection through studies in animals. So, there are aspects of this we control, and we're doing everything we can to make those aspects go quickly, smoothly, and effectively. There are aspects we don't control, such as what this virus is going to do. We are working very hard to reach the goal that Albert set for us.

Lindsey: That's great. Thank you very much, Phil. It's definitely really encouraging to hear how many people with the right scientific expertise are as dedicated as they are to this, and I'm sure inspiring for many others. Thank you so much for your time today and giving a chance for us to learn a little

bit more about how the vaccine development process looks, and how it looks different in this case. So, thanks a lot from taking time away from the lab to spend time here with us. Really appreciate it.

Phil: My pleasure. Thank you.

Lindsey: Thanks for tuning in to my conversation with Phil Dormitzer, Vice President and Chief Scientific Officer of Viral Vaccines at Pfizer.

Before we wrap up, I want to share with you what else is going on at Pfizer — As part of our broader COVID-19 response, we recently announced our partnership with Direct Relief, a humanitarian aid organization, on their "push pack" program. This program delivers critical medicines and supplies for hospitalized COVID-19 patients. Learn more about this life-saving work at pfizer.com/coronavirus.

Next time, on this special miniseries of *The Antigen*, we're discussing partnerships between pharma companies as well as the scientific and public health community, and how during these unique times, working together is vital.

In the meantime, please take a minute to rate, review and subscribe to *The Antigen* on Apple Podcasts, Spotify or wherever you listen to podcasts. It helps new listeners to find the show. Special thanks to *The Antigen* team at Pfizer and Wonder Media Network for producing this series. See you next time!