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114th Year
594th Meeting

Dr. Tal Zaks
Chief Medical Officer
Moderna

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Webinar

Moderator: Craig B. Thompson
President and Chief Executive Officer
Memorial Sloan Kettering Cancer Center

Welcome everyone. This is Barbara Van Allen, President of the Club, and we will be getting started in exactly one minute. Thank you.

Introduction

Chairman John C. Williams

Well, good afternoon, and welcome to the 594th meeting of The Economic Club of New York, and this is our 114th year. I'm John Williams. I'm the Chair of the Club, and I'm President and CEO of the Federal Reserve Bank of New York. As many of you know, The Economic Club of New York is the nation's leading nonpartisan forum for discussions on economic, social and political issues, and our mission is as important today as ever as we continue to bring people together as a catalyst for conversation and innovation.

A special welcome to members of The Economic Club of New York's 2021 Class of Fellows – a select group of very diverse, rising next-gen business thought leaders. And welcome to the graduate students from Manhattan College, the City University of New York Graduate Center, Brooklyn College, NYU Stern School of Business and Columbia Business School.

It's a pleasure for me now to welcome our special guest today, Tal Zaks. As Chief

Medical Officer, Tal oversees clinical development and regulatory affairs across Moderna. Prior to joining Moderna, Tal was Senior Vice President and Head of Global Oncology at Sanofi, where he was responsible for all aspects of oncology drug discovery, development and commercialization.

Tal began his industry career at GlaxoSmithKline in the genetics research group, where he built the oncology translational medicine team and led translational research. In addition to his industry work, Tal is Associate Professor of Medicine at the University of Pennsylvania and has served as a volunteer physician at the Philadelphia Veterans Administration Medical Center.

He received his MD and PhD from the Ben Gurion University in Israel and conducted post-doctoral research at the U.S. National Institutes of Health. He completed his clinical training in internal medicine at Temple University Hospital followed by a fellowship in medical oncology at the University of Pennsylvania.

So, today the format will be a conversation, and we're very fortunate to have President and CEO of Memorial Sloan Kettering Cancer Center and Club Trustee, Craig Thompson as our moderator. Now we'll end promptly at 2:45, and as a reminder this conversation is on the record as we do have media on the line. So without further ado, I'm going to hand the mike to you, Tal.

Conversation with Tal Zaks

TAL ZAKS: Thank you, John, and it's a real pleasure to be here with everybody today. And it's a special privilege to share the stage with Craig, whom I've known for a long time. By way of background, as you've heard from John, I'm one of these guys who ping-ponged in academia for many years and really my passion has been translating science into medicine. I've been at Moderna now for the past six years because it's a platform that caught my attention as one that should be amenable to rapid progress and really builds on the fantastic revolution we've had in science in the past several decades and an accelerated sense of ability to bring that into the forefront as actual medicines.

Last year, as many of you know, we were well positioned to start down the race to get a Covid vaccine. And I think we were well positioned because of the underlying technology, but also because really science has set us well in terms of understanding this virus and sharing of data. And so the ability to very rapidly build a vaccine to protect people was really predicated both on the investments that Moderna had made over the course of the preceding decade in bringing forward this technology and then connecting that to the scientific understanding of virology and immunology.

It's been a phenomenal year really of collaboration. First, I have to say the company itself, which I represent here today, has grown and matured throughout this period, but

with a lot of help from, and collaborations with various government and academic institutions without which we wouldn't be here today. If you just think back, you know, when we were, during the first Phase 1 and 2 trials, nobody actually could measure in the blood whether this vaccine was working because people had to set up the assays as fast as we had to develop the vaccine.

I'm fortunate to be here today really as a representative of a very large team, and the reason I can afford the time is because people better than me are actually at work doing the stuff that needs to get done. But one of the things that I've personally learned over the course of this journey is that translating the science into medicine, noble as it is, doesn't get you anywhere without actually translating that medicine into politics, if you will. And I use politics here as a positive word, as shared understanding and shared meaning of what this means.

And I think we have an opportunity to really, in the current era where people are curious and interested, to be transparent and bring that understanding that we are privileged to have of the science of what we're doing and share it with a much broader population than ever before. And so in that context, I think it's both a privilege and a duty for me to be here today, and I look forward to this conversation.

CRAIG THOMPSON: Well, thank you for agreeing to do this, Tal. As you said, we've

known each other for 20 years and I'm proud that it's a fellow oncologist that led these efforts, even though it took you far afield from your cancer training into the world of infectious disease. So I want to paint the stage for our members. You're a little too modest. Although the company has been an extraordinary success story, it was a relatively new biotech company just, actually when you joined still not a public company until a few years ago.

At the time you joined you were the Chief Medical Officer. In larger pharma companies, that's someone that interprets the products for the broader public and does the surveillance on the side effects. But in Moderna, because it was a relatively small company at the time, you were also in charge of all product development and all regulatory approval in a company that had never produced an FDA-approved product. So it's remarkable that you all, as a team, seized the opportunity to demonstrate that your mRNA vaccine technology that you had been developing for a number of years could stem the tide of the greatest pandemic the world has seen in the last 100 years.

The fastest, previous vaccine, just so our members understand, took five years to develop. And yet the challenge was to develop a vaccine, from when the first virus isolate was made and reported last January, a vaccine in the shortest possible time to stem the side effects. From start to finish you all achieved the production of an FDA-approved vaccine in 11 months. That's an extraordinary achievement and we are all in

your debt for that. There were many doubters and many vaccine skeptics from beginning to end. And yet the clinical trial, the Phase 3 trial, that followed those Phase 1 and Phase 2s that you talked about the difficulty of, demonstrated over 94% success in preventing infection and nearly complete protection from life-threatening illness from Covid-19.

So how did you guys do it? Why is mRNA vaccine, which had never been used in humans before, so successful and, as you said, your competitors/your fellow believers, the company in Germany, BioNTech, side by side built a similar vaccine with similar efficacy, against demonstrating the proof of scientific principle that this approach has the opportunity to rapidly allow us to respond to future infectious agents, not just Covid-19? What makes RNA vaccines different and why are they so successful?

TAL ZAKS: So there's several factors here that have come together, Craig. It's not just one. But the salient ones are the fact that, you know, think of this as an information drug. All of our products, whether they're vaccines or drugs or therapeutics, they are all basically the same molecule that contains the information of what we want the cell to encode. And so when that's your starting point, it took us only two days once the sequence was known to actually put the vaccine in production. And that allows you tremendous speed and flexibility. You know people ask me, well, am I going to get side effects of the virus? Well, we've never had the virus in the company. We don't know

what the virus looks like physically. We don't need to. It all starts from information.

The second element is that because we know to direct the attention of the immune system just to that antigen that's required, it ends up being a very clean approach, and I think that's important for the safety profile. So we teach the immune system how to specifically recognize only that piece of the virus that we know – based on science – matters for us to be able to prevent disease.

And I think the last element here has to do with something that, you know, physicians rarely pay attention to but is just as important which is manufacturing. It turns out that, you know, when you make an mRNA molecule, it's really all very fast, very easy synthetic biology compared to traditional recombinants. So the manufacturing processes here, while not straightforward and took us many years to get there, ultimately once you get there, it's reproducible, it's repeatable, and you can do it at a much faster scale than traditional technologies. And I think if you put all these three things together, that is what enabled us to really achieve that initial entry into the clinic.

Now, the progress through research...(Audio Issue) First, I think a lot of credit goes to FDA. They were operating in a very difficult political environment and yet they kept the true north in terms of insuring that the bar of evidence required for approval here was very conservative. However, they were always lockstep with industry in providing

guidance and looking at our data in a very fast turnaround time, much, much faster than they're able to operate normally. And I think that's what allowed us to shave time, so Phase 1, Phase 2, Phase 3, every phase could start once the initial phase was still ongoing as long as you had minimal data and that's critical.

And the last element of why we were able to go so fast here has to do with the pandemic. You know, to prove that you're preventing disease, you're preventing cases, you actually have to see cases happen on the placebo arm. So your speed is a function of transmission. And the paradox of vaccine development is that the worse the disease you're trying to prevent, the easier it is to demonstrate in your clinical trial. And so the clinical trials were initially designed to read out within six to twelve months and they read out in three. And the reason is that we were doing this in the U.S. during an era of very high transmission.

CRAIG THOMPSON: I just want to follow up on that, Tal, to be clear. The government dubbed the whole national effort for vaccine development, Project Warp Speed, and Moderna was able to achieve this in 11 months. That's led the critics to say someone must have cut corners. We mustn't have done the right safety checks. We must have not waited long enough. And I just wanted to give you a chance to answer that question about what allowed you to do this so much faster than anything else. I get the production issues, the specificity that's encoded, the mRNA that you talked about, but

were there regulatory changes or was this just getting the efficiency of everyone aligned and an ongoing and endemic infection as you said that allowed you to prove quickly in the vaccinated people that they were protected? Or did we really shorten this and that's why there's this emergency use approval rather than a full approval?

TAL ZAKS: So let me be clear. The reason that there's an emergency use rather than a full approval is the FDA's mechanism to ensure that they have time for all the follow-on paperwork, etc. to happen while being able to look first at the critical data. That's just a regulatory path. By the way, the proof of that is that globally if you look at Europe and other jurisdictions, there is conditional approval. So this emergency use is a unique FDA pathway, but the proof is really – and we had a lot of conversations on this – FDA set a more conservative bar than they needed to, and they did this on purpose.

In fact, if you'd ask me the first part of last year, you know, do you need to run a full Phase 3 trial to demonstrate this, I thought that if we show neutralizing antibodies to a very high level and, by the way, the levels that we achieve exceed those of natural infection on average, I thought that would be enough to get you an accelerated approval. It's just like in cancer. If your drug shrinks the tumor, you say, okay, that's probably a sign that survival is going to be better, right? You don't necessarily always wait for survival trials.

Well, here initially, even in July and August, we already knew. In May, we saw the Phase 1 data. We already knew that we had the right levels of neutralizing antibodies and that we were exceeding them. And yet FDA insisted, and in retrospect appropriately so, that we take a very conservative stance and we say, well, neutralizing antibodies is great, that's not good enough. Your technology is new. We've never actually proven that this can work. Prove to us in the gold standard of preventing infection, severe cases, hospitalizations, that indeed your vaccine does that.

And to ensure the veracity of this, what they did, which I welcomed with open arms, they actually assigned us a Data Safety Monitoring Board, a group of external experts that I didn't pick. The NIH picked them. And they're the same experts that oversaw the J&J, the AstraZeneca, etc., all the U.S.-funded studies. So we had a group of experts that were looking at this independently.

And the last piece I'd say is, you know, when you're a sponsor and you're in my shoes, you want to make sure that when you generate the data, the public believes you and that they're relevant to the public. So we had a lot of discussion on how do we ensure the veracity and the trust.

And at the end of the day I brought a group of external experts, including people like Art Kaplan from New York City and a friend of mine from my Sanofi days named Anne

Beal. Anne is an African American woman physician. She led PCORI back in the day. And I asked Anne, you know, how do we engage the community in the right way? And Anne said something that has sort of stuck and resonated with us internally. She said, Tal, I've been in your shoes. You're going to have to be transparent to the point of discomfort. And that's the only thing you can do.

And, by the way, yesterday it was announced, Anne has now been nominated to the Board of Directors of GlaxoSmithKline. And that sentence that she formulated sort of stuck in my mind. And when we were with the Phase 3 trial, we were the first ones to actually publish our Phase 3 trial on the web, unredacted, as the trial was ongoing. Something that pharma typically doesn't do and, in fact, I'm happy to say all the large companies followed suit within 72 hours and the protocols were out there.

So now the conversation shifted to, from what's the protocol, to actually explain to me the reasoning. How do the statistics work? Right? And we could shift the conversation with the public on the content, and I think that enabled people to understand what the trial was about, see the data for what they were. When the data were finalized, you know, we went in front of an FDA Advisory Committee, and it was all for the public to see. And I think that sense of transparency is where you can all be assured that indeed, you know, not only were no corners cut, but in fact this was a very rigorously conservatively designed and executed trial. And that's true of my colleagues in the other

companies as well.

CRAIG THOMPSON: So given that this emergency use approval is part of the regulatory process that the FDA goes through, when can we expect to have enough data to see the chance that it can be removed and be fully approved? Do we have a time line for that for Moderna or any of the vaccines?

TAL ZAKS: Yes, I think that's going to happen, by and large, by this summer or early fall is my expectation, at least the companies will submit the formal approval packages.

CRAIG THOMPSON: Well, that will certainly be good for the vaccine-hesitant as we go forward. Now, the other criticism that we sometimes hear is that in clinical trials everything always go better for any new drug and so that the 94% effectiveness is done in a very controlled, very specific, very defined role. Right now we've given out 168 million shots to people in the United States, so we've had a tremendous amount of real-world data. What's that real-world data telling you about the success rate of protection – given that we've had an ongoing third wave this winter– in terms of the Moderna vaccine as we've seen it roll out in the nation?

TAL ZAKS: Well, Craig, you bring up a really important point. I think, we always talk about real-world evidence generation, those of us who do trials. I think for the first time

I'm actually seeing a real impact of such data. So the CDC is collecting these data and is looking at various studies. The CDC, after the first month of safety, went out with a report in their weekly, morbidity and mortality weekly report, and they basically said, we looked at the safety of the first 10 million or so shots given. We do not see any worrisome signal for safety and that initial reactogenicity, the discomfort you feel particularly after the second dose, yep, the way it's been reported in the trials is what we see in the real world.

You remember there was a concern for anaphylaxis. They looked at it now that there's more experience and they said, well, we see about the same event rate as you see with the flu vaccine. It's a few cases per million. And so that seems to be the case. And so what it tells us is that the real-world evidence, the systems are actually in place to collect both safety and efficacy, and I'll come back to the efficacy, and to the degree that there are signals, they're being appropriately flagged and followed through.

On the efficacy, again CDC came out, and I'll just mention this. They came out, now last week or even this week, I saw the pre-print, where they did a study in the real world of 4,000 healthcare workers and they say, look, after the first shot already we're seeing 80% efficacy. After the second shot, which is the appropriate regimen, 90% efficacy and that holds. So you've seen data for, not our vaccine but Pfizer's vaccine in Israel, where they've vaccinated a large proportion of the country and that's where we got the first

sense of real-world evidence and indeed the pandemic wave there is turning its tide. Initially, after vaccination what they showed was the continued infection but not in those who were getting vaccinated. And now as vaccination rates have climbed, it's certainly turning the tide in the country at large and they're already talking about having, you know, open concerts and things of that nature.

So, the real-world evidence all points to the same level of efficacy that we've seen in the trial and more importantly that indeed vaccinating enough people will change, will turn the tide on this pandemic.

CRAIG THOMPSON: Given the studies that you just quoted about the protection after a week of just the first shot, why two shots? And why did both companies that developed mRNA vaccines choose two shots? Because we know the distribution has been difficult. No one is excited to get that second shot. We'll talk about side effects in a minute. But why two shots? Why did you both decide we needed a two-shot regimen?

TAL ZAKS: This is sort of basic immunology, Craig, which, you know, you taught me back in the day. You don't know this but we actually met before Penn when you came and gave a talk at the NIH and I was a post-doc and you were the, and that was all about immunology. Right? And going back to those days, we know that when you stimulate the immune system to see a foreign antigen and with a vaccine, with an

mRNA vaccine, the immune system will generate some antibodies. But if then the inciting event goes away, the immune system shrugs its shoulders and says, okay, solved the problem. If you come back a month later and you show it again to the immune system, then evolutionary we're wired in a such a way that we go, oh, hold on, that problem I thought I solved, I actually didn't. And so the quality of the immune response you get after that second dose, the speed is faster, the quantity is faster, and the quality of the neutralizing antibodies is much higher. And that's all borne out by the data.

And so, yes, you start to get the first sense of effect even after the first dose. We don't know how durable that is. And I suspect and I fear that if all you get is one shot of an mRNA vaccine, that will wane much faster than if you sort of come in a month later and cement that and remind the immune system to up its game to improve the level and quantity of antibodies that we have.

And the data that we have is thus all with two shots and I wouldn't recommend anybody just getting one shot and already think that they've achieved the full protection. By the way, as it relates to durability, the data are out this morning in the *New England Journal* with our vaccine showing that six months later you still have pretty nice antibodies, again after two shots.

CRAIG THOMPSON: Well, that's very comforting because my next question was going to be that several members asked me to ask, which was that right now the CDC only says there's three months of protection, so the fact that there's now published data out for six months of protection. Is there any idea about what the possibility that it will last even longer? I know I can't ask you to make any real prediction but what is the evidence that there will be longer-lasting protection from this virus?

TAL ZAKS: So, you know, there's a saying in my culture, "Since the destruction of the Second Temple, prophecy has been given to fools." So the degree you're asking me to give a prophecy, you consider me a fool?

CRAIG THOMPSON: Fair enough.

TAL ZAKS: I think if you look at the waning of the antibody responses, they'll probably hold for 12 months. So I would expect we'll be protected for at least 12 months. I think that's where you may start to see some variability in protection. It may be that people who are more vulnerable, protection will wane sooner. We'll talk about the variants I'm sure. It may be that we become more vulnerable to some of these variants sooner. But certainly I think up until that point, if you just look at the curves and continue the extrapolation, I think we should be good for the first year.

CRAIG THOMPSON: Great. That's very comforting for those of us that have taken the two vaccines that are hoping it gives us sustained protection for a long time, and we will look for the updates of your trial patients as we go forward. On the side effect side, we continue to hear the anecdotes that the second shot does give you side effects. You guys have done a great job, as you mentioned earlier, in warning us about that. Because of that secondary activation of the immune system, you will see some side effects that are flu-like symptoms and a sore arm, and many people have reported that. But there's also the rumor going around the fact that people that have previously had Covid have worse side effects on that second shot. And I just wondered, there's enough real-world evidence now of people, is that really true? Or is that just the anecdotes that are shared in the Zoom calls?

TAL ZAKS: So, my sense of the data is that you don't get a worse adverse event profile if you've been sick before and you get vaccinated. What you may see is more reactogenicity after the first dose, but then after the second, it doesn't get any worse. And, in fact, we had 300 people in the trial, in the Phase 3 trial, who we later figured out based on blood tests that they had been infected previously, before getting vaccinated. The side effect profile in that population was no different.

CRAIG THOMPSON: Okay, so we've got the first vaccine, the government announced this morning that by the end of the week half of adult Americans will actually have

initiated trials with one or the other of the mRNA vaccines because they are the ones that are available right now. What's the follow-on research going to be? Right now in the initial trials we don't have a clear indication of what pregnant women should do. And many women, I, in the workplace, I know it here in the hospital, the nurses that are thinking about becoming pregnant or are advising patients are very concerned about this issue. What do we know about the use of the vaccine in pregnant women?

TAL ZAKS: It's a great question. I think there is, there will be emerging data. CDC is collecting this information about outcomes for pregnancies to reassure people that so far, as far as we know, there's no adverse events. We have done the sort of proper toxicology study in animals to demonstrate that indeed you can expose animals and then they give live birth and everything is fine. We look very carefully for any adverse events. We don't find any. Scientifically, based on first principles, you wouldn't expect to find any. And there are emerging reports actually of infants who were born to moms who were vaccinated during pregnancy and the infants are already born with antibodies to SARS-CoV-2.

And I think whatever theoretical risk there is to pregnant women, and it is theoretical because we have no mechanism nor any evidence of such and nor do we expect it, but whatever such theoretical risk should be borne in light of the actual real risk to pregnant women and their children if they get infected with SARS-CoV-2 during pregnancy. And

so I think while there's not a clear recommendation by FDA on that because of the lack of data, if you look at OB-GYNs and you ask the professional organizations, I think they are in large recommending it. And our answer is, you know, it's a personal decision between the woman and her physician, but certainly the data do not preclude giving it to pregnant women and that's the formal stance on it.

CRAIG THOMPSON: Couples thinking about becoming pregnant have been coming to the doctor and asking the question, the vaccine contains nucleic acids. Can it damage our genomes? Can it be passed on to offspring? What's your answer to that?

TAL ZAKS: I love that question because it's an opportunity to talk about mRNA. So mRNA is nucleic acids but it is not the stuff that's in your DNA. Right? All of our cells have the same DNA. The DNA is in the nucleus. That's a walled-off part of our cell. And when the mRNA goes in, it's actually a very transient piece of nucleic acid information that doesn't go into the nucleus. It has nothing to do with our genetics per se. It has everything to do with just transiently instructing the cell how to make protein. So while technically it's nucleotides and therefore it's called genetic material, if you consider a gene to be hereditary, then mRNA is not genetic.

CRAIG THOMPSON: Thank you for that clarification. I think that will help a lot with some of the vaccine hesitancy that we're seeing here in New York and elsewhere. Now

the next question that comes up is what about children? Why was the age 18 chosen? It's not a physiologic age. It is an age of consent. But how did you guys choose that and what are you doing to expand it to kids and get ahead of this epidemic?

TAL ZAKS: So, age 18 is sort of, as you say it's an age of consent and it's also a regulatory threshold, so the way in which you conduct trials is often different. You know, if you go to people beneath 18, you have to go to pediatricians. So the whole infrastructure of how you conduct the research is different. So we chose upfront to conduct this in a separate trial and, in fact, we have two trials. One trial of adolescents, 12 to 18, that one has completed its accrual and we should see data in the coming weeks and months so data will come by the summer to enable vaccinating younger.

Now the younger age, under 12, that now becomes an age group that's not just vulnerable because of consent issues but actually the physiology now is different, and we have to make sure we get the right dose for them. So whereas, 12 to 18 I'm pretty certain is going to be the same dose as adults, in the very young I think you need to explore and see whether a lower dose may be optimal because their immune system tends to be a bit more reactive. So that's going to take us a bit longer. I expect to see those data by the end of the year. But certainly the 12 to 18 we anticipate all the data available and probably regulatory approvals by the fall, by the next school year so we can start to vaccinate them.

CRAIG THOMPSON: So that means high schoolers will have a chance for a vaccine prior to the new school year, which has been a big challenge for our public school system. But you also said that it's going to be a little longer for the rest of our school-age kids and the precautions the schools are taking as they open up and we get the economy started back up and the schools and education back started up. Am I correct on that?

TAL ZAKS: I think you're absolutely right. And I think, you know, the other piece of the challenge will be to continue to evaluate the risk-benefit. You know if we're very successful and the pandemic, by and large, goes away, then the benefit of the vaccine to the very young is lower than what it will be today, right, in a major metropolitan area. So we're going to have to carefully look at that and give the FDA the time and all the data required to make that judgment.

CRAIG THOMPSON: We've heard for years that other vaccines like for the flu and other vaccines that we take throughout life, that our ability to mount an immune response in response to the vaccine goes down over life. Yet there was remarkable efficacy in the older age groups in your patients. Is there any explanation for why this type of vaccine is so effective in the elderly? Does this portend that mRNA technologies will be spread to other preexisting vaccines and replace them?

TAL ZAKS: So the answer in a nutshell is yes in the sense that we have been working hard to engineer the understanding we have around the lipid nanoparticle that delivered technology here and the ability of cells to make this such that we retain a high level of efficacy across age groups. You've seen that already from the Phase 1 data that the error bars are tight even in the very old and they're consistent with what you see in younger age groups. You see that in the T-cell response, which is really what we need. It's the part of the immune system that ensures that we have durability and memory, and you see that come up irrespective of the age. So I do think it is an inherent feature of the way that this technology works, and I anticipate that will absolutely be relevant for flu, for other respiratory pathogens like RSV for which we don't have vaccines today. And indeed this has accelerated our R&D efforts towards those domains as well.

CRAIG THOMPSON: Great. That's great news. So then the other question that everyone wanted me to ask you is can vaccinated people still spread the virus, even though they don't become ill? What do we know about that?

TAL ZAKS: Not enough. And that's why I think we still need a modicum of caution. I think it's pretty clear if you look at the emerging data where there is, and if you just do the math of the decrease in transmission in the population, that you'll be able to back calculate that indeed being vaccinated decreases transmission. That being said, if you're vaccinated – and I'll give you a very simple explanation – it's really a function of

the sensitivity of our test. So if I'm walking up Broadway and I'm vaccinated and on 47th Street somebody sneezes a boatload of Covid on me and I keep walking up, and on 50th Street somebody now sticks a swab in my nose and tests for PCR, is it going to be positive? Probably yes. All right. Am I infectious? Well, that becomes a difficult question to answer. Right? It's easy to do it in hamster cages. It's much harder to do with people.

So the truth is we don't know yet and our general recommendation is to follow CDC and local jurisdiction guidance, public health officials who are monitoring transmission rates in the population. When I'm vaccinated I put on a mask. I put on a mask, not to protect myself. I put on a mask to protect my fellow human beings. And I think until transmission rates drop, that's probably the behavior that would be wise for all of us to adopt.

CRAIG THOMPSON: Great. Thank you for that clarification. I want to go back to an issue that you talked about before which has also driven some of the vaccine hesitancy. And that's the number of reports of difficulties in manufacturing of many of the other competitor vaccines that have been in development. We had just another news story in the papers today about another manufacturing issue around this.

Given that Moderna has never before gone to the kind of massive production, between you and the BioNTech-Pfizer, you've produced 168 million, almost equally, that have

been given to people, 168 million doses. Only 2% of that total, 168 million, has gone to the other vaccines that were not produced by the mRNA technology. And yet you're planning to produce half a billion to a billion doses going forward. How have you avoided the manufacturing defects? You weren't a manufacturing company. These big pharma companies, the J&Js, the AstraZenecas of the world, they're professional manufacturing organizations. What's the secret to that? Is it really that this is so simple to make, these mRNA vaccines, or is there something more to the process?

TAL ZAKS: No, I think the answer here is competence and dedication. So the CEO of our company, Stephane Bancel, is an engineer with a background in manufacturing. I can tell you that we, as a company, after the first vaccine positive result in the first Phase 1 trial back in 2016, he made the commitment to build a manufacturing plant for a company that just had their Phase 1 data. And the reason was, he foresaw the need to understand, learn and control the critical quality attributes of manufacturing.

And so most of the production that you've seen come out has actually come out of our own plant that has been up and running for a few years with our own people and our own know-how. The head of manufacturing is Juan Andres. Juan's prior job was leading, you know, 36,000 people across five continents at Novartis and managing all of their manufacturing infrastructure. So Stephane, I think, very astutely invested and brought in the right competence and the right team to be able to both build this, learn as

we go along, and then scale.

This year we're going to be with our first Phase 3 vaccine for CMV. Now we had foreseen that even before, years ago, and so the plans, the train tracks were laid to scaling up manufacturing well ahead of Covid, in planning and thought process and in the way Norwood was built. The way our manufacturing plant in the suburbs of Boston was built, it was built with an ability to expand. So it was all really thinking ahead, which I give a lot of credit to Stephane and Juan.

CRAIG THOMPSON: Great. So the President announced today that every adult American will be offered a vaccine by now April 19, moving up from May 1. Are you up to the challenge of being able to produce enough vaccines?

TAL ZAKS: Absolutely.

CRAIG THOMPSON: That is wonderful news to hear. So one of the advantages that you told us about for RNA vaccines is the speed of development. You've said that repetitively during this interview. We've heard a whole lot about the variants. I'd like you to now turn to addressing these variants. Are they a concern for the existing vaccines? And does the mRNA technology lend itself to newer booster kinds of shots for the developing variants if they become concerning and aren't covered by the existing

vaccines?

TAL ZAKS: Right. So, you know, since the start of the pandemic people have been worried about, is this virus going to evolve? And I think we've seen over the past year the evolution of the virus in a number of ways. And there are two important ways in which the virus can evolve. The first is to make it more infectious because, you know, it's the first contact with human beings and it's been such a wide and successful contact from the virus' standpoint that it gave it the opportunity to mutate and evolve. And we've seen a lot of the mutations accumulate over time that enabled the virus to just adhere better to cells and infect us better. And that's probably the genesis of what's called the UK variant, the 1.1.7.

But then there are additional spots in the virus, and especially in the way it binds to our body where it can mutate and avoid immune recognition. And these are the ones that I worry about. And the two variants that people are starting to look at and have concern are the ones that started in South Africa, the 351, and the one from Brazil, the P.1. Now these variants, if you look at the blood of somebody like me who has been immunized with the original strain vaccine, my blood can neutralize the original virus very well. It can still neutralize these variants but to a lesser degree.

And the question is, is that lesser degree worrisome? Well, in the immediate period after

vaccination, probably not. But a year or two out, it may, and so that's the fear. The fear is over time if there's a differential there, we will become susceptible to some of these variants that may have evolved partially to escape immune recognition. And if that's the case, then whether you've been sick last year or whether you've been vaccinated by my vaccine, the fear is that you will not be as protected as you should be.

Now, the initial data coming out are super reassuring in the sense that we are seeing protection rates even with some of the competitors' vaccines that have been done in South Africa and you see, by and large, that people are still protected, particularly against severe disease which is what we worry about. I should also mention that it requires a lower level of antibodies to protect against severe disease than it does to protect against the sniffles. So if immunity wanes and all I get is the sniffles, all right, no big deal. But if it puts me in the hospital, then I'm worried. So the good news here is that it requires less antibodies, therefore, we're more likely to be protected. Now, in a nutshell, what does it mean? Well, it means I'm still worried and I'm particularly worried towards the end of this year, beginning of next year if these variants continue to circulate.

So what do we do about it? That's where I think we're well-served by having the mRNA platform for two reasons. First, we can react very quickly and put a variant-matched vaccine into production and we now have the manufacturing infrastructure to actually be

able to do what we did last year in two months, to just do a Phase 1 study, here in two months we can get millions of doses out there. So that infrastructure can be put to use now for the variants.

But as importantly, we've learned over this year how to connect what we measure in the immune response to the ability to prevent disease. And so we can now do much faster and easier studies and prove that indeed if you've come in with a booster shot, a third dose six months after you got your initial series, can I boost the immune system in the right way to now be fully protected against these variants? We've started those trials already because we were able to put it in production quickly so the first people have already gotten dosed with a booster shot against the variant. And as soon as we have data, we'll share it. I expect we will see that the data, the booster shots give us a higher level of protection. We'll be showing some of the mice data that we already have next week. We have a Vaccine Day with the company so you'll be able to tune in and see that. But, by and large, I think we'll be in a good place to be able to provide a booster shot for protection should we need it by the end of this year.

CRAIG THOMPSON: So I'll ask you for your second prediction. What's your prediction? Are we going to be taking regular boosters as we go forward, just as we do in the flu, to continue our protection and quell this pandemic?

TAL ZAKS: If you look at other coronaviruses, the other four coronaviruses that circulate in the population, they tend to reinfect us anywhere between once every one to three years. And so if you assume that there's going to be some point where this new coronavirus kind of reverts to that normal behavior, then I think the future world will be one in which we will want to assure protection from respiratory viruses and that protection will get updated periodically.

Is it going to be every year like the flu? I don't know yet. Is it going to be every five to ten years because something new emerges? That's probably a more likely scenario and I think the truth will be in the middle. The beauty of this platform, from my perspective, is it's going to be really well-suited to combine on an annual or every two-year basis whatever you need to combine with to ensure protection.

CRAIG THOMPSON: Great. Well, listen, this has been an incredibly productive discussion. I want to end with one last question before turning it back to John so that we can actually do that. And that's to let the younger members of our audience know that you recently announced that you're going to step down as Chief Medical Officer of Moderna in September declaring victory on the amazing 18 months you've had. I want to let the younger members know this isn't the first time you've done this in your career.

As John mentioned earlier, at the peak of your leadership of precision medicine, when

you ran all of global oncology for Sanofi, a job most people would have killed for, for the rest of their careers, you stepped down to do this adventure with Moderna. And precision medicine that year that you stepped down was announced as the biggest advance that had been found in American medicine by President Obama. So what I want to know is what's the next adventure? You're an entrepreneur at heart. What are the emerging areas of biomedical research that match the excitement of precision medicine early in your career and RNA vaccines as you just told us about for a year?

TAL ZAKS: Well, I don't know yet. What I know is I've earned a bit of a rest and so I'm going to take that. And it's also, I've been living in a bit of tunnel vision so it's great to re-engage with the scientific world at large. The level of innovation happening in science today is just beautiful and gorgeous and all I want to do is step back and figure out how I re-engage with that yet again, and I look forward to that.

CRAIG THOMPSON: Well, Tal, thank you very much. For the sake of all of our future health, I wish you success at whatever you choose to do next. And with that, I'll turn it back over to John for closing.

CHAIRMAN JOHN C. WILLIAMS: Thanks, Craig, and thanks, Tal. It's been an incredibly informative 45 minutes. I'm sure everybody who has been watching has learned a lot, and I really appreciate you taking your time to share your insights with us.

With that, I'm going to turn to our program of future speakers. We've got a whole bunch of speakers lined up. We encourage you to attend and obviously invite guests as well. Tomorrow we have my colleague, Neel Kashkari, the President and CEO of the Minneapolis Fed. Then we have on April 12th, we have John Waldron, President and CEO of Goldman Sachs. On April 19th, we have Debra Lee, Co-Founder of the Monarchs Collective and former Chair and CEO of BET. On April 22nd, we have Paul Offit, Director of the Vaccine Education Center at Children's Hospital in Philadelphia. And then on April 28th, we've got Robert Swan, polar explorer, the first man to walk both poles. And then on April 29th, we have Ben Hecht, the President and CEO of Living Cities. And as we've been telling you with these events, we've not, not only do we have all the speakers we've announced for the next few weeks, but we have many more planned for the remainder of the year. If you're interested in joining the Club, please email the Club at the address on the screen.

And finally, I'd like to take a moment to recognize those of our 332 members of the Centennial Society joining us today as their contributions continue to be the financial backbone of support for the Club and help enable us to offer our wonderful, diverse programming both now and in the future. So thank you again. Please stay healthy and safe.