

THOMSON REUTERS STREETEVENTS

EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc Corporate Analyst Meeting

EVENT DATE/TIME: APRIL 14, 2020 / 12:00PM GMT



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

CORPORATE PARTICIPANTS

Juan Andres Moderna, Inc. - Chief Technical Operations & Quality Officer

Lavina Talukdar Moderna, Inc. - Head of IR

Stéphane Bancel Moderna, Inc. - CEO & Director

Stephen Hoge Moderna, Inc. - President

Tal Zaks Moderna, Inc. - Chief Medical Officer

CONFERENCE CALL PARTICIPANTS

Alec Warren Stranahan BofA Merrill Lynch, Research Division - Associate

Cory William Kasimov JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst

Edward Andrew Tenthoff Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Geoffrey Craig Porges SVB Leerink LLC, Research Division - Director of Therapeutics Research, MD & Senior Biotechnology Analyst

Hartaj Singh Oppenheimer & Co. Inc., Research Division - Research Analyst

Maxwell Nathan Skor Morgan Stanley, Research Division - Research Associate

Salveen Jaswal Richter Goldman Sachs Group Inc., Research Division - VP

Umer Raffat Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Yasmeen Rahimi Roth Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Co-Head of Biotechnology Research

Andrew Lo

Flor Munoz-Rivas

Kathryn Edwards

Mark Denison

Mark R. Denison

Paul Heath

PRESENTATION

Operator

Good morning, and welcome to Moderna's Virtual Vaccine Day. (Operator Instructions) Please be advised that this call is being recorded. At this time, I'd like to turn the call over to Lavina Talukdar, Head of Investor Relations at Moderna. Please proceed.

Lavina Talukdar - Moderna, Inc. - Head of IR

Thank you, operator, and good morning, everyone. I hope you are all healthy and safe. Thank you for joining Moderna's First Vaccine Day webcast.

During the presentations today, you will hear from members of Moderna's executive team and from key opinion leaders in the industry. You can access the press release and the slides accompanying each of the speakers' presentations by going to the Investors section of our website. Before we begin, I'd like to remind everyone that this presentation will include forward-looking statements. Please see Slide 2 of the presentation and our SEC filings for important risk factors that could cause our actual performance and results to differ materially from those expressed or implied in



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

these forward-looking statements. We undertake no obligation to update or revise the information provided during this presentation as a result of new information or future results or developments.

With that, I would like to hand it over to Stéphane Bancel, CEO of Moderna.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you, Lavina. Good morning, and good afternoon, everybody. I hope you and you loved ones are safe. Welcome to Moderna's First Vaccine Day. Thank you for joining us today.

Given 80% of vaccine worldwide sales are in big 4 pharmaceutical company, back in November, when we announced Vaccine Day, we thought it was important to provide our stakeholders an opportunity to appreciate 3 things about our vaccines.

First, that there are still an important number of innovative vaccines that need to be developed that the world needs. Second, the high probability of technical success of infectious disease vaccine caused positive Phase I data as they enter Phase II, which (inaudible) [is over for a particular] area. And third, the totality of Moderna vaccine platform clinical data and where we're excited about the opportunity to impact public health.

Obviously, a lot of things have changed since November. So let me turn to the agenda on Slide 3. After a quick introduction, I will turn over to Professor Andrew Lo from MIT, who we introduced at that time. Then Dr. Paul Hens is going to review traditional vaccines. Before Stephen Hoge is going to talk about what differentiates mRNA vaccines versus other technologies. Then we plan for a small coffee break before returning where Tal is going to review basically vaccines that we have against infections from mother to baby. i.e. CMV and Zika. And then we're going to review our vaccines against respiratory diseases, which, of course, is extremely important. So Tal will start, and then we'll be happy to welcome Dr. Munoz-Rivas from Baylor College of Medicine. And then we will go to Dr. Mark Denison from Vanderbilt University and then Tal and Juan will close that session.

Before my conclusion, we'll have Dr. Kathryn Edwards with an overview with us some overview on ACIP, which is an important framework in the vaccine world, as you all know. And of course, at the end, we'll be very happy to take Q&A.

So on Slide 4, as you know, we started the company on the central dogma of biology, believing that mRNA is a software of life and if we could find a way to create medicines out of mRNA, we could have a profound impact on patients.

On Slide 4, you see the 4 value drivers that have energized us since the very first days. An opportunity to create a lot of products that are first-in-class products because of their ability to do transmembrane protein, to do intracellular protein or to do combinations of protein. We believe the high probability of technical success of this modality because mRNA is an information molecule. And we use as raw material, either human DNA information or DNA or viruses -- sorry, DNA, RNA or viruses.

The third piece was, of course, speed and the ability, again, because of a platform because mRNA is an information molecule to move very quickly in the labs and to move very quickly into clinical research.

And fourth was the very interesting aspect of a technology that provide capital efficiency, which I'll come back in a few minutes.

And because of this opportunity on Slide 6, to create a new class of medicine, as many of you know, we have been and to this day, are very focused on managing the risk: technology risk, biology risk, execution risk and financing risk. And on Slide 7, you are all familiar with these metrics that we have been using to kind of guide our decision-making as we build the portfolio. Since the beginning, we thought that taking 1 drug to the clinic and hoping that we have figured out everything, was not very wise and was actually extremely risky and could actually jeopardize our mission to use this technology to help patients. And so we decided to try several technology in parallel into the clinic, which you see here on the X axis. And for each of our application and modalities, we decided to diversify our biology risk by going after several drugs in each application, so that we will not take all our risks on only 1 biology assumptions.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

On Slide 8, as you recall, we believe that 2019 is a very important inflection year in the company's history. Because as we said the strategy to lead the clinical data guide us from where the technology is working best, we have very critical clinical data in 2019. With CMV, we had 6 clinical data sets around our infectious disease vaccine, which gave us, of course, strong conviction that we believe the prophylactic vaccine modality has been de-risked. And at the same time, we shared new data on our systemic secreted and cell surface therapeutics were chikungunya antibody data in the fall.

So if you think about the company moving forward on Slide 9, this is how we think about the company, exactly in line with our strategy, which is because the clinical data have informed us that prophylactic vaccine and systemic secreted and cell surface therapeutics have been de-risked, we have named those 2 modalities core modalities, where according to our strategy, which were about years and years ago, we want now to double down and to enable many more important medicines to get to the clinic and hopefully, to get to the market to help people.

On the right side of the slide, the exploratory modality is a set of programs that are in the clinic for the personalized cancer vaccine, the KRAS cancer vaccine. We have 3 immuno-oncology assets in intratumoral immuno-oncology: the triplet, OX40L + IL23 + IL36y, OX40 and also IL-12, which is partnered with AstraZeneca. The VEGF program in Phase II. And for MMA and PA, we have 2 open INDs and 2 products that the FDA has fast tracked.

And so in the exploratory modality, we will continue to be disciplined to not add new programs until we learn from the clinic, are those modality working in such a case, we will move those product and those modality to core modalities. If they're not working, we will ask several questions. Is there a technology improvement that we've learned in the last few years that weren't trained again with an improved technology, or will we decide it is not a good use of our shareholder capital, and we will use that capital for product in core modalities.

I would like also to remind you, it is not on the slide, but on the far right of the slide, we still have modalities that we're exploring. One that is very public is the work we are doing with Vertex, where we are partnering with Vertex to explore and it is still in the labs, which is not -- it is not on this slide, to explore the ability to deliver into the line messenger RNA in this case to deliver CFTR, the protein needed for kids that have cystic fibroids.

So that's how we think about the company moving forward. Just different businesses with different risk profile and different investment thesis.

And on Slide 10, what you see is basically the illustration of what we said, which is we want now to expand our core modality by adding new development candidate. We believe the technology risk is similar to the ones we've already shared with you. We believe the platform and the manufacturing capabilities allow us to move very fast. And as you observed, in the first 2 more parts this year, we named 5 new development candidates, 3 new vaccines and 2 new product in systemic secreted and cell surface therapeutics modality in autoimmune disease space. So actually, we also announced in January, entering a new therapeutic area, which we believe is very important to continue to create value to help patient and to de-risk the company.

So today, on Slide 11 with Vaccine Day, we want to spend the rest of the morning with you to just focus on 1 modality because we think that modality has a lot to offer.

If I go to Slide 12, it's basically a copy and paste of our initial slide but just focus on vaccine. We believe mRNA has the potential to be a new class of vaccine. And if you look at the 4 value drivers, which you can see on Slide 13, I would like to spend the next few minutes reframing to you why we are so excited about the potential of our vaccine modality.

First, we believe it's a very large product opportunity. As some of you might know, the vaccine business around the world is around \$35 billion of annual sales and is growing at a very nice clip.

If you look at vaccine, and there's been some very interesting work published that shows that the return on each health care dollar invested in vaccine is one of the highest, if not the highest, in the health care system. As you can see, the numbers on this slide, the number of deaths that are prevented and the savings to society are just extremely large. And the return on every invested dollar in vaccine is very, very powerful.

If you look on Slide 16, we took the 2019 sales of the 4 large vaccine players trying to split their innovative vaccine in red and the established more legacy vaccines in gray. Those 4 players own more than 80% of the market for the vaccines.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

As we discussed in the past, on Slide 17, there are many features of the vaccine business that we like a lot. The first one is the ability to have blockbuster product potential. If you look at Pevnar, it is today Pfizer #1 product with more than \$6 billion of sales. If you look at Gardasil, the HPV vaccine of Merck, it is predicted in 2024 to be the #2 product of Merck behind KEYTRUDA. And if you look at, again, the 2024 production, Shingrix, the vaccine from GSK, is predicted to be the #2 product of GSK.

So as you can see, those products are very important for these large successful companies. We are pleased that it's exciting to us about vaccine is that if you have an innovative vaccine for high unmet medical need, we believe that those products can have a strong sales ramp. And I would like to point you to the GSK Shingrix vaccine, which in 2018, its first full year of sales was able to achieve sales in excess of \$1 billion in the first year of sales.

The other piece that we lack a lot about vaccine is the annuity-like long tail of these vaccines. There are many vaccines that have more than 25 years of sales. I just draw your attention to the dark blue on Slide 17 at the bottom, which is Pevnar. Pevnar was launched in 2000. Pevnar is still growing, and Pfizer anticipate for new product expansion to keep growing the Pevnar franchise.

The other piece too in term of margin, it is important to differentiate between [mE2] vaccines where the price is, of course, low compared to innovative vaccines. As we shared at R&D Day in September, we believe, for example that for innovative vaccine, like our CMV vaccine, we should be able to get to an EBIT margin of around 50%, 90% gross margin.

On Slide 18, the team has basically gone back over the last 40 years and looked at the new viruses that we have discovered by scientists and clinicians around the world. And it is quite remarkable, of course, enabled by new technology, including sequencing that more than 80 new viruses were discovered in just the last 40 years. That is an average, obviously, of 2 new virus discovered each year.

As you can see on the slide through a clip is that a lot of those virus, you know well, like the HIV virus, the HPV 16, which was the start of the creation of the product concept of Gardasil. We see a lot of viruses that you know, including, of course, the SARS CoV-2 in 2019, retrovirus is at -- you might not be as (inaudible). And again, it's just a representation of a vaccine.

If you go through a number click, what you see is a selected number of viruses that were discovered before 1980. I won't go through the list, you can have look yourself. But a lot of very important viruses that cause harm daily in our society. And if you go through a last click, what you see, is in green, the viruses for which there is a commercial vaccine today. Less than 4%, just a few vaccines from that long list last 40 years plus those selected viruses before 1980, as you can see in green, have a commercial vaccine on the market.

And as you can see, as you start to look at the red list, a lot of products that are on the Moderna pipeline, which I won't go through everything. And that's what really gets us excited. It's the ability that with this new tech player, this new mRNA platform, we have the potential to have a very large impact in public health.

Like we all know, vaccines are tremendous asset to clinicians. They allow to prevent disease. And we all know that prevention is more important and much better than curing the disease.

So let me now turn to Slide 22, where you will see the current development pipeline of Moderna with our wholly owned assets, but we have not included here the royalties that could potentially come from mRNA-1172, mRNA-1777, which are the IgG product that Merck has in development. So the royalty for those products are not included in those estimates.

And if you want to think about our development pipeline today, we basically are very excited to be working for pediatric setting as we described before of a potential product that we envision as being a combination of RSV and PIV3 and hMPV.

As you know, in the clinic, we have today hMPV, PIV3, mRNA- 1653, which is dosing in children right now in the Phase Ib. And we announced in February the pediatric RSV, mRNA-1345 for which our teams are working hard to get this vaccine in the clinic.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Our goal down the road is to potentially combine those 2 products, 1653 and 1345, so that we have 1 vaccine that could potentially protect children against those 3 viruses.

I want to remind you that there is no vaccine on the market against RSV, there is no vaccine on the market against hMPV, and there is no vaccine on the market against PIV3. So we believe this combination of vaccines could be very important to protect children from preliminary infection.

We've talked a lot over the last months around CMV, mRNA-1647, which we're extremely excited about for which we completed enrolling all the subjects in the Phase II and our teams are working toward potentially starting the Phase III next year in 2021.

We announced in February a new vaccine for EBV, which is the Epstein-Barr virus. This is a virus that creates -- that cause mononucleosis, mRNA-1189, same thing, there is no vaccine on the market to protect against EBV infection.

Tal will walk you through some of our Zika data. We're very happy to report today in our press release this morning some interim Phase I data for our first 2 dose, the 10 microgram and the 30 microgram, which Tal will describe to you in a while, mRNA-1893. Same thing, there is no Zika vaccine on the market. We believe Zika will eventually come back, and we believe the world needs an approved vaccine against Zika. To our knowledge, there are only 2 Zika vaccine in development pipelines by pharmaceutical and biotech companies around the world.

And of course, last but not least, the SARS-CoV-2 vaccine, mRNA-1273, which is dosing, as you all know, in Seattle to try to see if we could protect infection by the virus.

What we believe, as we look at the portfolio as an aggregate, is that the potential peak sales of the portfolio described on this slide could be from \$6.5 billion to \$12 billion of annual peak sales with this candidate, assuming they all reach the market. This, of course, does not include the potential vaccine that Stephen Hoge and his team are working on in the labs.

So if I turn to Slide 23, vaccine is a large opportunity. But when you look at the 80-plus viruses that do not have a vaccine today, we believe that our total addressable market for Moderna vaccine platform is potentially much larger than the market of pharmaceutical vaccines today.

On Slide 24 is probability of technical success. As we think about value of products, we always think about peak sales and think about probability of technical success.

One of the discussions we're going to have today in a few minutes when I turn to Professor Andrew Lo from MIT is the fact that I think is not always appreciated around the infectious disease vaccine probability of technical success.

In the past, all the studies that I had the opportunity to read around probability of technical success, including the category of infectious disease, and this included antibiotics which, of course, are treatment against bacteria infection, antiviral, treatment against viral infection and infectious disease vaccine. Those were all bundled together. But as you can appreciate, antibiotics and antiviral are most of the time small molecule products with very different safety profile than a platform-like vaccine.

And so Andrew is going to walk you through the data that he and his team were able to generate. What we believe it's very important to appreciate is that when a company has a positive Phase I data on the vaccine and decide to start a Phase II study, the probability from Phase II start to approval, as an industry, aggregate against all the products is 42%. And we think this is a very important driver for this franchise.

If I go to Slide 25, and we talked a lot about it, and I'm going to go pretty fast, that we think is a very important value driver is speed. Speed in the labs because given we have a platform, we can try many, many candidates in parallel in animal testing. And once we pick a development candidate we want to take to the clinic, we allow to try to go to the clinic very quickly because our engineers do not have to invent how to manufacture the product at clinical-grade scale. It's the same process using the same chemistry for the mRNA, the same chemistry for lipids, and this allows us to grow very fast. Most of you are very familiar with the speed at which our team was able to get mRNA-1273 into the clinic, which has Dr. Tony Fauci, our partner, the NIH, as described in the Wall Street Journal as being the world in the record. The team was able to go from the sequence and the product design lockdown on January 13 to dosing the first human in Seattle on March 16 in a little as 63 days.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

The team was able in 2 days from the sequence on Slide 26 published online by the Chinese to lock down the design of a vaccine, in 42 days variable to manufacture a vaccine to do all the quality testing and to ship the vaccine to the NIH and then there are 21 days for both the IND reviews, ethics committee reviews at the hospital, screening of healthy volunteers and start of the clinical trial.

As you can imagine, we are extremely proud of this time line because we believe every day matters to get a safe and efficacious vaccine into the market.

If I now turn to Slide 27, I'd like to spend a few minutes on the capital efficiency of our platform, which we think is really a game changer. The third dimension of this is around capital intensity. We believe because the manufacturing process to make the mRNA molecule is a cell-free manufacturing process that we can drive much lower CapEx versus recombinant protein because we do not have sales in our manufacturing process, we can concentrate our reaction, and we end up with much smaller reactors to be able to run our reactions. Because we have much smaller volume of reactors, we need much smaller equipment to purify the product before formulation. And so this, we believe, drives a lot of value, lower CapEx is, of course, a good thing, drives lower depreciation in the product cost of good, drive lower investment and use of cash from the business.

The second dimension is the CapEx leverage across the value chain as you develop new products. Let's take 2 easy example. When we decided in January to go after SARS CoV-2, we did not have to buy new machines. One team in our manufacturing plant was able to leverage existing CapEx and to basically, in a matter of days, to run the manufacturing process in existing equipment. We didn't need to buy new machines to wait for them to qualify them and to spend our capital against those machines. Same thing with the EBV vaccine. We [invent] the EBV vaccine in the clinic using existing capital equipment that we have already in our facility.

The last I mentioned around the platform that we have around our vaccine is very important from a value maximization. It's around maximizing sales at launch.

As many of you have observed over the years, regularly, pharmaceutical company reports that they cannot meet sales of new product launch. And the reason is pretty simple. Because they have a dedicated manufacturing plant, which we had to build during the Phase III studies, they have to get the demand that they will get if a product got approved. They have to guess the labor they were going to get from the regulatory agencies as the clinical data from a Phase III was going to be unbilled.

It is not easy. And you have to basically decide to spend hundreds of millions of dollars in capital equipment for a product that is still in Phase III that might fail the Phase III and never launch.

And so for having been through those discussion early in my career at Eli Lilly, those are very complicated discussions where you face a lot of over capital allocation of that capital in the business and you have to decide the size of the plant you're going to build.

As has been reported recently, for example, by GSK on Shingrix, they cannot meet sales despite the \$1 billion of first day of launch, they could not meet sales, they could not lot in every market because they could not supply the markets.

And as you can appreciate, if those products have a 90% gross margin, the incremental sales is actually incremental EBIT margin. And so the chance we have with mRNA is we have a platform with the same equipment to make CMV, or EBV or mRNA-1273. And so we are managing the portfolio of products. And the more products we have in the portfolio, the more we have margin for error. And this is not only across vaccine, it is also across therapeutics. We use the same manufacturing process are extremely similar between the MMA drugs or our oncology triplet or mRNA-1273 against SARS CoV-2.

On Slide 28, we have a pictogram. Just to give you a sense on the left of the size of the standard biotech reactor in a vaccine company. And on the right, you have a size of reactors, the little one is a clinical manufacturing for clinical studies. And the one on the right is the "large reactor" for commercial manufacturing.

So on Slide 29, it just gives you a sense on the summary of why we are very excited about Moderna's vaccine platform, a very large product opportunity. We believe for many years to come, we have new vaccines to go invest in our labs and to take to the clinic to potentially help protect



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

people against infection. We believe the probability of technical success of those vaccines is much higher than what you see across other therapeutic area. The speed that we have demonstrated will continue to create value. And the capital efficiency of our business is quite remarkable compared to other industries.

So with this introduction, I would like to now turn to Professor Andrew Lo on Slide 30. So Andrew is the Charles and Susan Harris Professor, the Professor of Finance, the Director of the Laboratory for Financial Engineering at the MIT Sloan School of Management and the Principal Investigator at the MIT Computer Science and Artificial Intelligence Lab.

Andrew received his Ph. D. in economics from Harvard University. I had a chance over many years to get to know Andrew better by reading his publication and by reading one of his book, Adaptive Markets.

I'm really happy and pleased to have Andrew join us today so that he can share with you his work around infectious disease vaccine, probability of technical success. Andrew, over to you.

Andrew Lo

Great. Thank you very much, Stéphane. And I want to begin by thanking Stéphane Bancel and Moderna for organizing this Vaccine Day and for inviting me to participate and to thank all of you for joining online.

As a financial economist, it's a particular pleasure and honor for me to be part of this gathering because up until relatively recently, I have had no interest or work in health care, and became interested in the field, mainly because of personal reasons, friends and family dealing with cancer and other challenges. And so what I want to talk to you about today is some of the work that I've been doing with my colleagues on estimating the probability of success in clinical trials for vaccines and other anti-infectives.

Let me begin with the next slide, which is an observation that I suspect most of you on the call know better than I do. And that is that over the last few years, it's become clear that biomedicine is at an inflection point. There are all sorts of incredible breakthroughs that have occurred over the last few years. And my colleagues, Susan Hockfield, Tyler Jacks and Phil Sharp published a report a few years ago, titled the Convergence of the Life Sciences, Physical Sciences and Engineering. And this convergence is often characterized by what's known as the "omics" revolution, tremendous advances in genomics, epigenomics, transcriptomics and so on.

But the 1 omics that hasn't had nearly as much innovation, is economics, namely the business approaches to commercializing all of these tremendous breakthroughs. And on the next slide, I will show exactly how, from a financial economics point of view, we think about these kinds of issues.

So that slide has what I consider to be the single equation that summarizes the challenges of drug development and the health care financial issues at the heart of it.

And on that Slide 33, it's really the expected value of the net present value of future cash flows that investors look for.

So what is that expected value? Well, it's simply the present value of all future revenues of any particular product, assuming that you're successful, multiplied by that probability of success minus costs.

So in this equation, from the economic point of view, it's actually relatively straightforward to understand what all of the variables are, except for one, and that is the probability of success.

So one of the things that I started out trying to understand at the very beginning of this process is how do we get our arms around this PoS?

And on the next slide, I illustrate the fact that from the historical perspective, there have been several different ways of estimating the probability of success. Probably the most well-known of these is the work that Joe DiMasi and his colleagues at the Tufts Center for the Study of Drug Development has done. In one of their classic papers in 2010, they estimate the probability of success of all drugs across all fields at about 16%.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

However, in 2016, the industry organization, BIO, published a separate paper that said, no, actually, that number is 9.6%. So confronted with this difference in these estimates, my students and I decided that we wanted to estimate our own numbers based upon as large a data set as we can find.

And so on the next slide, we show that using data from a vendor called Informa, we actually were able to come up with our own estimates that, in some cases, were quite different from what we were reading in the literature.

So the Informa data is much, much larger than any other data set that we've ever seen. In 2016, we had data going from 2000 to 2015, and that data set had over 15,000 drugs across a 15-year time span, nearly 6,000 sponsors and 175,000 phase transition events, which allowed us to estimate the probability of success of a variety of different therapeutic areas with a great deal more precision.

Now this approach is not a criticism of the work that has gone on before. For example, the main difference between our study and some of the prior studies is the fact that we include many more biotech companies and smaller specialty pharma companies as well as academic medical centers and universities.

That's not meant to be a criticism of the earlier studies because went back in 1976 when Tufts started doing these analyses. At that time, most drugs were developed by the big pharma companies. So it's not surprising that their focus was on big pharma at the time. In fact, in 1976, the biotech industry didn't exist. In fact, most people put 1976 as the year that the biotech industry began with Genentech. But certainly, there was no data on any kind of biotech drugs.

But I want to turn to the next slide because I think you'll see something rather surprising, and it really motivates why we decided to include a much larger sample with smaller companies as well as academia.

On the next slide, you'll see that if you look at the top 30 drugs by worldwide sales and compare them in 2000 to 2015, you'll see something rather surprising.

On the left is the list of the top 30 best-selling drugs in the year 2000. And highlighted in blue are those drugs that came out of universities in one form or another. And you can see that of the top 30, only 5 came out of universities in 2000 and none of the top 5 drugs had anything to do with universities.

Now fast forward 1.5 decade, 2015. And in that year, 13 out of the top 30 best-selling drugs came out of universities and 4 out of the top 5 were related to universities.

So this is part of that inflection point I was referring to. And for this reason, we felt that it was important to include smaller biotech and specialty pharma companies because more and more now, the innovation is happening at these smaller companies.

So on the next slide, I'll show you the results that we came up with using this larger data set and in the paper that we published just last year in biostatistics. So what we estimate in that table on the right is the probability of success across a variety of different indications. So for example, if you take a look at the very top row of the table on the right, you'll see that this is the probability of success from Phase II all the way through approval. And for oncology, in that first row, you're getting only a 6.7% probability of success.

If you now go below to the row with vaccines, you get the number, 42.1%.

So if you go to the next couple of slides, we can just skip over because of the animations. You can see that the probabilities are actually much, much higher for vaccines than for any other indication out there.

That was really surprising from my perspective because as Stéphane mentioned, over the last few years, fewer and fewer companies are taking this on. They're taking on the area of vaccines, and there are only 4 big pharma companies that are doing it. So I'll come back to that in a few minutes.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

But more recently, if you take a look at our website, projectalpha.mit.edu, we actually provide an updated estimate of these probabilities because of the data changing over time. And you can see that the bar that's highlighted for vaccines using data up to 2019 fourth quarter, the probability of success has now gone up to 45.8%.

So if you turn now to the next slide, I'm going to just mention some more current research that we've been focusing on. And that current research is using the data to actually parse through the different areas of vaccines versus other anti-infectives. This is a paper that we posted on MIT archive. It's not peer-reviewed yet, it's still a preprint, but it's under review. So I welcome comments, and you can download it from MIT archive. We just posted it today, in fact.

And what we see from the various different areas that there are actually quite a bit of differences in the probability of success across different types of diseases. And one of the interesting insights that has come from this analysis is that the probability of success for vaccines is, once again, quite a bit higher than for antibiotics, another important challenge that needs to be addressed.

So our hope is that by producing more accurate measures of probability of technical success across these different areas, we can actually provide investors with a clearer guide to the risks and rewards that are involved in this important area.

On the next slide, we just have a graphic that illustrates our more ambitious goal of not just producing historical estimates or probability of success, but rather to focus on forward-looking measures of probabilities of success. And we published a paper last year as well, where we used that data set that includes not just historical success and failures, but also various different characteristics of clinical trials of the particular drug involved and the trial design to forecast the probability of success.

So on the next slide, we have an abstract of the paper that we published last year in the Harvard Data Science Review applying machine learning techniques with statistical imputation to predicting drug approvals.

And on the next slide, we illustrate the application of machine learning using the -- just listing the top and bottom 10 forecasts probability of technical success across the various different vaccines that's in our dataset.

This was done as of January of 2020. So we don't have the [material] clinical trial in here, but there are many others. And you can see from the machine learning forecasts that there are a number of vaccines that have much higher probability of technical success than just the 42% or 45% averages that we were getting. And there are also those that have much less because they're focusing on much more challenging diseases. And the hope is that using these models, we can actually help improve the odds of these important clinical trials and then help investors make better decisions.

So on the next slide, I want to just start wrapping up by exploring what next steps might be using these various different techniques.

Imagine if we had detailed chemical and biological properties of the various different drug candidates that are in the pipeline, imagine if we were able to make use of PubMed citations, had access to electronic medical records, and imagine if there were new business and pricing models for vaccines, and better and faster ways of making them. And finally, imagine if government engagement were focused squarely on applying various different policies to speeding the development of these vaccines.

This last point is probably one of the most important because, as I mentioned at the outset, the probability of success of vaccines is higher than many other areas and that the number of companies have decided to leave the space and it's because from the economic perspective, it is often challenging to be able to generate profits for investors. However, that is likely to change, particularly given now with COVID-19, we now have the attention, I think, of governments around the world. And the hope is that over the course of the next few years, we're going to see much more progress.

So let me wrap up on the next slide by pointing out that we often like to think about a waging war on disease. We had a war on cancer since 1971, and people have talked about waging a war on COVID-19. Now I'm no medical expert, so I can't tell you whether we're winning or losing the war



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

on cancer and other diseases, but as an economist, I can tell you that war is probably the wrong metaphor because war is based upon fear and hatred, and those are not sustainable states that humans can live in.

But on the next slide, you'll see the point that I want to make, which is that while fear and hatred are not sustainable, greed is a very sustainable state. And if we can get investors to take an interest in this important and underserved area, we can actually make much more progress and finance is really not -- it doesn't have to be a zero-sum game, we can actually do well by doing good if we use the proper structures to finance these investments.

So I want to, again, thank Stéphane Bancel and Moderna for hosting this event and allowing me to participate. And on behalf of everyone around the world, I want to thank Moderna for mRNA-1273 and of all the dedicated people that have been pulling all nighters for the last several months to be able to get this into the clinic and hopefully, into patients in the near future. And thank you all for participating, and I wish you be safe and healthy. Thank you.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Dr. Lo. This is Tal Zaks. I'm the Chief Medical Officer here at Moderna. Really appreciate this course.

It's my pleasure now to introduce Professor Heath for the next segment. Professor Heath is a pediatric infectious disease specialist at the University of London, where he leads the Pediatric Infectious Disease Research Group and serves as the Director of the Vaccine Institute.

Dr. Heath has over 240 publications in vaccinology with a strong focus on the epidemiology of vaccine, preventable diseases and vaccine clinical trials.

In addition to the academic contributions, Dr. Heath sits on the National U.K. Vaccine's Guidance Committee, the Global Immunization Safety Committee and is the Chair of the Research Committee of the EU Society of Pediatric Infectious Diseases and a member of the WHO technical working group for surveillance of infectious diseases.

Dr. Heath, due to conflict, had to prerecord his talk. And so we will now hear it.

Paul Heath

Well, hello, everyone. It's a great privilege to be speaking with you today from across the pond. It would be great to be there in person, of course. And I look forward to hearing the rest of today's presentation because it looks like a great day.

So thank you for the invitation to speak. And I was asked to provide an overview of immunization. Next slide. So let me do that by beginning with a definition. So when we're talking about immunization, we're talking about the process whereby a person is made immune or resistant to an infectious disease. When we're talking about vaccination, that's the process of administering our vaccine to induce immunization. So it's important to get the global perspective here. Over 100 million children are vaccinated every year before their first birthday. Vaccination is estimated to save up to 3 million children each year. But almost 20% of the children born each year do not complete their routine vaccines. And this means that 1.5 million children are still dying every year from diseases that could have been prevented by vaccinations, just 1 child every 20 seconds. So it's vitally important we develop new vaccines, but we need to make sure that any vaccine that we develop is delivered to those children that need them.

Next slide. So I need to remind you about some aspects of the immune system but not talking specifically about vaccination. And we can broadly divide the immune system into the nonspecific part of the immune system and this specific part of the immune system. Here, I'm referring to antigens, an antigen is a substance that causes the body to make an immune response against that substance. So that substance might be a virus or a bit of a virus, a bacteria or a bit of a virus -- a bit of a bacteria, for example. So we have the nonspecific part of the immune system. And the specific part of the immune system.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

The non antigen-specific part of the immune system is a less sophisticated, more primitive, more basic part of the immune system and includes such things as our skin and the mucosal surfaces. The lining of our gut and our respiratory tract. And these present barriers to infections.

We also have in our blood stream cells such as white cells, such as neutrophils, proteins such as complement, which are also important in dealing with infections that they encounter. And these are any types of infections, and there's no memory that is each time they encounter them they'll respond to them in the same way.

Next slide. In contrast, the non-antigen specific part of the immune system is more sophisticated. Here, the mechanisms are distinguished by their ability to respond to specific antigens. So specifically to tetanus or specifically to COVID-19, SARS coronavirus 2, for example.

And by doing it specifically, the response is more focused, more vigorous and hopefully more protective. And part of this is the concept of immune memory. So the antigen-specific part of our immune system is characterized by its ability to induce immune memory, the concept being, of course, that if an antigen, be it a virus or a bacteria, is encountered once, it's likely to be encountered again in the future. So by recognizing that and being better prepared for the next encounter, the greater the chances that protection, complete protection will occur.

When we're talking about the antigen-specific part of the immune system, we are speaking about T cells, T lymphocytes, which are broadly responsible for cellular immune responses. And B lymphocytes, which produce antibodies. And the antigen-specific part of the immune system, this concept of immune memory results because of previous exposure through natural infection or previous exposure through vaccination because a concept of vaccination is to induce immune memory.

On the next slide, you can see a cartoon of how an antigen, a foreign antigen, an intruder, encounters our immune system, beginning first with the nonspecific defenses, the nonspecific part of our immune system, such as the skin barrier, such as the neutrophils in the blood stream. And then the specific defenses produced by the B cells and the T cells.

So moving down the left-hand side of the slide, you can see, first of all, the B cells. The B cells have on their surface antibodies. And those antibodies, the Y-shaped figures, are -- recognize specific antigens. So there are antibodies against tetanus, there antibodies against diphtheria and so on. And those B cells are coated with the specific antibodies. And by recognizing their specific antigen, they then proliferate and produce what are called plasma cells. And plasma cells produce more and more antibody, so there's more antibody floating around to encounter and engage with the antigens. They also induce the memory B cells, which then remain relatively dormant, but able to start producing antibody again much more quickly and more specifically, the next time that the antigen is encountered.

Down the middle of the slide, in orange, is the cellular immune response. So here, we have the intruder being engaged by a macrophage, by an antigen-presenting cell, which are found, for example, in the skin. They then present the antigen in such a way that T cells can recognize them. And we have the helper T cells, we have the cytotoxic T cells. And both of these can then generate memory cells, which in the same way as the memory B cells will remain dormant until the next time the antigen is encountered. The cytotoxic T cells will also attack the bacteria or the virus, doing so through the production, amongst other things, of cytokines: proteins, which can attack, damage and neutralize the relevant antigen. So this cartoon describes both arms of the immune system, the antibody or humoral immune system in green, the cellular immune system in orange.

Next slide. So when thinking about immunization, the process whereby a person is made immune to an infectious disease, we need to distinguish between passive immunization and active immunization. Passive immunization is where antibody is transferred to a susceptible individual. The best example of natural passive immunity is the protection in a baby that occurs because of the antibody passed from their mother across the placenta to them. So the mother's antibodies against tetanus, pertussis, influenza, measles and so on, pass across the placenta to the infant and then into the infant's bloodstream and protect that infant for the first few months of life against those particular infections. So they're passively immunized against those infections.

In practice, passive immunization will often be used to protect individuals who are susceptible to an infection, one that they have just encountered, for example, and one that they have no antibodies against. And here, we can give them antibodies against that particular infection. For example, chickenpox antibodies, so varicella zoster antibodies. Here, a good example would be a child who is being treated for cancer who encounters another child with chickenpox, which is very contagious. That child with cancer has a high risk of severe chickenpox. If we recognize that encounter,



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

we can give them antibody against chickenpox. We can passively immunize them, and that will protect them against that particular encounter. It won't be long lasting. It will disappear, and they will be susceptible again, but they will have been protected at the time. So the aim of passive immunization is to provide protection after exposure in those who don't have any antibody because they didn't respond to a vaccine or they were not able to get a vaccine and who are at high risk of disease from that particular infection.

In contrast, active immunization is vaccination. So the next slide. This shows you the different types of vaccines that are available. So live attenuated vaccines, and examples of that are the oral polio vaccine; the measles, mumps and rubella vaccine; rotavirus vaccines; TB, the BCG vaccine. Inactivated or killed vaccines. Examples include the inactivated polio vaccine, IPV; and the whole cell pertussis vaccine. Subunit vaccines, which are purified antigens taken from a pathogen of interest and then administered as a vaccine. So examples include the acellular pertussis vaccine, Haemophilus influenzae type b conjugate vaccine, pneumococcal conjugate vaccine. Toxoid vaccines are inactivated toxin-based vaccines. And the best examples of that are tetanus and diphtheria. And then we have the newer vaccine technology. So nucleic acid vaccines, DNA vaccines, and messenger RNA vaccines. And then recombinant vector vaccines, which are our newer platforms for administering the genes from pathogens, genes that are important in expressing a particular protein that is necessary to immunize against that pathogen. Those genes are inserted into a different vaccine or a different virus, for example, a weakened virus, which then expresses the protein when it's administered as a vaccine.

So to the next slide. The live attenuated vaccines. Well, these are attenuated or weakened strains of the relevant pathogen. So best examples are with viruses. So the measles, mumps, rubella live attenuated vaccines, which are weakened forms of those viruses. They're weakened so that they are not as virulent. They're unlikely to cause the disease in the host, in the vaccinee, assuming that vaccinee is a healthy immunocompetent individual. They act like a natural infection. And for that reason, they are the closest to actual infection and therefore elicit good, strong and long-lasting immune responses.

Next slide. The advantages, therefore, of the live attenuated vaccines is that they replicate in the host. And through that replication, they're presenting multiple antigens from the virus at its different stages of development, its life cycle in their native conformations and that induces immune responses to those different antigens and a more complete response. A single dose often is sufficient to induce long-lasting immunity. And that immunity is both in terms of antibody production, but also cellular immune responses and also mucosal responses, which can be particularly important for infections that affect the gastrointestinal tract or the respiratory tract, where local responses on the surface, such as IgA responses, are important.

The disadvantages in red of the live attenuated vaccine technology is that being live, they often require complex containment and biosafety measures, there is the potential for them to revert to no longer be weakened forms of the virus or the bacteria, but to be the full virulent wild strain, and that can happen also. Though they're attenuated, they are attenuated, really, in the context of an immunocompetent host or vaccinee. So if that is an immunosuppressed individual, they may not be sufficiently weakened. They may cause disease. So they're contraindicated in immunosuppressed patients. There are issues about stability and there are potential issues about contamination.

Next slide. Inactivated or killed vaccines are suspensions of the whole intact killed organism, are very primitive, but often effective, albeit reactogenic way of vaccinating against the disease, the whole cell pertussis vaccine being a suitable example.

The subunit or purified antigens is where 1 or a few components of the organism that are particularly important for inducing immunity are extracted from that organism and they are then the basis for the vaccine, such as with the acellular pertussis vaccine, where up to 5 different key purified antigens are extracted from the pertussis organism and administered as the vaccine.

And then the toxoid vaccines, which are based on the toxin produced by the bacteria, tetanus and diphtheria, for example, and those toxins that cause the disease that we see with tetanus and diphtheria and the toxoid is an inactivated toxin, and that's the basis of the vaccine.

Next slide. So non-live vaccines can't cause disease, and they're often safer and more stable than live vaccines, although often associated with more local reactions, that is, at the time of vaccination, with redness and swelling and tenderness at the site, for example, than are the live vaccines. But the responses are often poorer as compared with live vaccines. They may not be long lived. And often an adjuvant is required to boost the immune response, an adjuvant being something like alum or aluminum hydroxide, which in and of itself, induces immune response and is required to support and improve the immune response to the non-live vaccine antigen itself. So often several doses are required to evoke a sufficient immune



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

response. In an older child, 3 doses of whooping cough vaccine will be required to induce immunity, whereas perhaps 1 dose of a live vaccine will be sufficient to induce immunity, for example.

Next slide. A particular example of -- a particular, more sophisticated and recent example of a subunit vaccine is a conjugate vaccine. And here, certain pathogens, certain bacteria such as *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Streptococcus pneumoniae*, which are important causes of meningitis in children, are characterized by an outer coating of the bacteria with sugar or polysaccharide. Now polysaccharide is not efficiently processed by the immune system, particularly the infant's immune system, which doesn't recognize it as an antigen. So it doesn't produce an immune response to it. This is part of the reason why these diseases are diseases of young children. But for that reason, the polysaccharide isn't a suitable vaccine by itself because it doesn't produce an immune response. However, when it is conjugated or joined to a protein, and that's a common protein such as diphtheria or tetanus, for example, then because proteins are recognized by the immune system of young infants, they are immunogenic. Then the immune system is, if you like, tricked into generating an antibody response, both against the protein and the polysaccharide.

So you can see in the cartoon there, the polysaccharide coating taken from the bacteria and joined to the protein to produce the vaccine, and this has led then to very successful vaccines against these meningitis bacteria that are now given to young infants and successfully prevent them.

Next slide. Moving to the nucleic acid vaccines, this new vaccine technology. The concept here is that actually the antigens are expressed naturally because they are expressed by the cells themselves. So here, in the case of DNA vaccines, DNA is inserted across the cell membrane into the cytoplasm of the cell and then into the nucleus. It's then transcribed, that DNA code is transcribed into messenger RNA, which is then in the cytoplasm and then in structures called ribosomes, that is translated into a protein and, here into the protein antigen of interest, the protein is then expressed on the cell, recognized by the immune system and an immune response to that protein, which is derived from the DNA code that has been administered in the vaccine, then produces a successful immune response.

There are those 3 cell membranes that the DNA vaccines need to encounter and go through. And to get this response requires sometimes large doses and special delivery devices. And then there's also the theoretical concern with DNA vaccines about the fact that being DNA, they may integrate with the DNA, the human host DNA with unknown consequences. That's a theoretical concern.

On the next slide, if we move to the mRNA, messenger RNA vaccines, it's a similar concept because it's natural antigen expression. But here, the RNA is administered. It therefore doesn't need to go into the cell nucleus. It remains in the cytoplasm. It's translated by the ribosomes into proteins, which are then presented and immune response to the relevant proteins are [infused]. It requires smaller doses than the DNA vaccines and doesn't require a special delivery device. So these are the 2 examples of nucleic acid vaccines, which are, of course, the most recent and sophisticated vaccine technology.

On the next slide, there's a comparison between the nucleic acid vaccine approach and that of traditional vaccines, comparing them in terms of development, in terms of facility scalability, in terms of proposed potential costs of the development phases, stockpiling and potency. And I'll just point out that in terms of potency, traditional subunit vaccines generally produce antibodies. It's a humoral antibody response. And sometimes, and indeed often, adjuvants are required as well as the antigen. Whereas with the nucleic acid vaccines, it's possible that both a humoral and T-cell response is developed. Important, particularly when thinking about virus vaccines, such as against SARS Coronavirus-2, the cause of COVID-19, and adjuvants are not usually required. So there's this comparison between the newer and the older methods.

On the next slide, the routes of administration of vaccine is shown: oral, intramuscular, subcutaneous and intradermal, and the little picture in the middle demonstrates the different depths of needle insertion required, and the immune responses can be different according to the depth of insertion.

Okay. To the next slide. So having spoken about the different types of vaccines, the principles of vaccination, obviously, to get a vaccine from concept through to implementation can be and often is a very lengthy process. And that's for a number of good reasons. Because safety is so important, and that can't be rushed. But also, I think it's true to say that, that also is a reflection of the technology that has been used up until now and with some newer technologies, the process may not need to be quite so lengthy. It can be much more controlled and fine-tuned and focused, and therefore, shorter.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

But nonetheless, the process remains -- the overall process remains the same with the first steps around the laboratory and animal studies; the exploratory stage, identifying the vaccine candidates; and then the preclinical stage where they're tested in tissue or cell culture systems and then often in animals. Animal testing is often a necessary prerequisite before clinical studies begin. That will depend largely, of course, on the infection and whether there are suitable animals that can reflect what will or what may happen in the human. And for some pathogens, that is true. And for some pathogens, there is no suitable animal model and therefore, potentially human challenge studies or human studies might need to begin earlier. The clinical studies then are divided into 4 phases. Before they begin, of course, regulatory and ethical approval is necessary. And then they proceed through these 4 stages of evaluation.

Next slide. Phase I studies take place in healthy adult volunteers, often numbers of around 20 or 30, so relatively small numbers of fit, healthy adults. And the concept of the Phase I study is to assess safety and also to obtain a limited amount of immunogenicity, immune response data as well.

The Phase II studies come next. These tend to be larger. And at some point, will also include the target age group for the vaccine. So if ultimately, a vaccine is being developed against meningitis that only occurs in young infants, then young infants will need to be involved in Phase II studies at some point. The numbers are larger, and there will be a better assessment of the common reactions that might occur with the vaccine in the target age group, and there will also be the ability to generate more immunogenicity data, more immune response data.

In Phase II studies, there may also be dose responses that are tested. So comparing smaller with larger doses in terms of the side effects, in terms of the immune responses. Often Phase II studies will compare the study vaccine with another vaccine or with a placebo, which could be a saline saltwater placebo. And it's important to think about the blinding of vaccine recipients and indeed investigators in these studies so that the reported results are unbiased by knowledge of which vaccine the individual got.

So in children, we tend to compare a new vaccine, study the new study vaccine, a vaccine that we're using already in that age group, one for which there is plenty of safety and efficacy information so that the children are getting a useful vaccine as a control vaccine. Sometimes in adult studies, it's more appropriate and indeed, ethically acceptable to use a saline placebo as the comparative vaccine or comparative arm.

Next slide. Traditionally then, vaccines will move into the Phase III study. And the Phase III study is where the subjects, the volunteers are from the target population of interest for that vaccine, be it adults, be it children, be it adults with cancer, be it children with sickle cell disease, whatever the population that is being targeted with this new vaccine. And the numbers will be much larger because the numbers are now designed to reflect the incidence of the disease, how common or rare it is, so that the vaccine can be tested and shown to reduce the disease incidence in the vaccinated group. So a comparison will be made about the disease in those who receive the vaccine with those that don't receive the vaccine, and out of that will be generated the assessment of efficacy, how effective the vaccine is. So for a disease that's very rare, a large number of subjects, thousands of subjects will be required to demonstrate the benefit and the safety of the vaccine. For a disease that's much more common, a relatively fewer number will be required to be able to demonstrate with statistical confidence that it is effective and safe. Phase III studies in which efficacy with clinical end points, that is the ability to show that it protects against the disease in question, are typically required to get a vaccine licensed.

Next slide. The Phase IV study, also called the post licensure study is the next phase. Studies of new vaccines do not stop at the point of licensure for a number of reasons, one of which is that the number of subjects, even in large Phase I, II, large Phase III studies, may still be too small to detect rare but important events that could occur with that vaccine. So for example, with the rotavirus vaccines, studies of 70,000 were required to demonstrate whether or not a very rare but specific side effect called intussusception occurred as a result of vaccination.

So once a vaccine is in use, once it is licensed and implemented, ongoing studies of its effectiveness and safety are required to detect those rare adverse events. And because the population now is likely to be potentially very different, the population that was tested in the Phase III trial and also because the vaccines might now vary a bit because they're being stored differently, prepared differently, the people will certainly be different in amongst the group that now receive post-implementation will be individuals who've got slightly weaker immune system or slightly different underlying health conditions. So the post licensure or Phase IV studies are important for assessing effectiveness of the vaccine in the field as well as vaccine safety in the field.

Next slide. To monitor the effectiveness of vaccine once implemented, it's important that surveillance for disease incidence occurs, that there is monitoring of vaccine coverage and that those who go on and develop disease despite vaccination are identified and investigated. No vaccines'



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

100% effectiveness and the effectiveness of all of these vaccines will vary and it is often that the vaccine effectiveness of Phase IV studies that identify that actually more than 1 dose is required or booster doses are required. For example, the second booster doses of MMR and varicella zoster vaccine, where the need for them was identified by the fact that the disease became more common again in those who had just received 1 dose. So that's an example of how these post licensure studies can identify the need to modify vaccine schedules, for example.

Next slide. Now I mentioned that Phase III trials, trials in which the efficacy of the vaccine against clinical end points, are often needed to get a vaccine licensed, and that is true. There is a potential alternative pathway to get a vaccine licensed, however, and that's around the concept of serological correlative protection.

Now the ability to assess the protective efficacy of a vaccine by measuring the proportion of vaccinees who generate a particular immune response without having to measure clinical outcomes has significant advantages, advantages in terms of vaccine development, in licensure and monitoring because in general terms, it will require a much smaller number of individuals to be assessed for their immune response than it will be for -- to be assessed for the clinical end point, the ability of the vaccine to protect them.

In the figure, which is taken from a World Health Organization document on serological correlates of protection, you can see a simple illustration of the induction of protective immunity via vaccine. So we have the vaccine. We then have an immune marker, IM-1 and another one, IM-2; and we have protection and protection implies that immunity, an immunological mechanism, has been able to prevent or reduce infection in the vaccinee. Now that immune mechanism, that immunological mechanism, may be antibody, it may be a cellular immune response. So IM-1 and IM-2 are two sorts of immune markers that are involved in or influenced by the relationship between vaccination and protection. And the question is whether IM-1 and/or IM-2 can be used, therefore, to infer protection rather than doing a large trial where clinical end points are measured.

Next slide. IM-1 and IM-2 are therefore called correlative protection, as they are statistically associated with vaccine-induced protection. Now IM-1, from that figure, is on the direct pathway between vaccine and protection. And it, therefore, is involved in the actual mechanism of protection, immunological mechanism of protection. It can be called a surrogate of protection. IM-2 is not on the pathway, is related to IM-1 and also changes in response to vaccination and protection, is called a correlate of protection.

Next slide. So the figure 8 there, again, from the same WHO document, shows simplest possible relationship between vaccine, the substitute end point, the surrogate or the correlate of protection and the clinical end point. And there are a variety of approaches that can be used to identify, confirm and evaluate these immune markers as indicators of vaccine-induced protection.

So the classic way will be the randomized controlled trial with clinical end points, a sort of Phase III trial I described earlier, but also in which the vaccinees also have blood tests in which the immune marker is measured. And then the relationship between the vaccination, the development of the immune marker and the development of protection can all be related to each other to identify that the immune marker actually can be used as a correlate of protection, reflects the protection that occurs.

Immunogenicity studies in which these immune markets are measured will be the first part of this, between vaccine and immune marker. Passive immunization studies in which a certain amount of immunity antibody is administered to a susceptible individual and then that could be related to their protection against disease and the relationship between the 2 can be assessed. Challenge studies, where an individual who is susceptible, has a certain amount of immunity which can be measured, they're then challenged with the infection in question and the relationship between the amount of immunity that they have and their likelihood or not of developing disease can be related to generate the corollate of protection. And then cohort studies and natural history studies where individuals are followed and then whether or not they go on and develop disease is related to how much immunity they had in blood tests that were taken prior to their developing disease.

Next slide. Now there are various ways to relate the immune markers to vaccine protection. A simple approach is the sort of a dichotomous variable. You're either protected a threshold level above which subjects are assumed to be protected can be generated and then below that, they're not protected. The simplest way to estimate a threshold level is to relate their pre-exposure level to their likelihood of going on and developing disease.

An example of that is a study in which university students coincidentally had blood samples taken for something else. And then, in fact, there was a measles outbreak. And then the investigators were able to relate back those who developed measles and those who did not to the antibody



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

levels against measles that were in their blood before they developed measles. And out of that, they were able to generate a surrogate level, immune marker level, of protection against measles, which was a PRN, which is plaque reduction neutralization titre, the amount of the antibody above 120. If it was above 120, they didn't develop measles. If it was below 120, they were more likely to develop measles. So that's an example of how they're moving forward. That level can be used in other studies without having to do the full study in which they're followed through to develop to their development of disease and then smaller numbers are required.

Next slide. So the type of immune markers that are preferred are those that somehow closely relate to the function of the antibody. So it's possible to measure total antibody levels using something like an ELISA. The problem is that some of that antibody may be functional, may be active against the pathogen and some may be inactive.

Functional assays measure -- just measure the antibody that works against the antigen in question. And by doing functional assays, it provides biological plausibility that the level that's being measured will associate much, much closer with clinical protection. And it increases the confidence in the measures, the vaccine protection measures estimated using that as a substitute end point.

So what sort of functional antibodies can be done? Well, in terms of bacteria, a critical function of antibodies to opsonize, to encoat and kill the bacteria. In the case of viruses, neutralization of the virus. And these can be measured using functional antibody assays. And then the results of that are -- can be then reinterpreted as correlative protection.

So virus neutralization, it describes the -- which is an antibody response crucial for preventing many viral infections. Antibodies can be produced against many antigens on multiple virus proteins. And some of these antibodies can block virus infection by a process called neutralization, and that may happen in a number of ways. The antibody interfering with the virus binding to the receptor, blocking uptake into cells, preventing uncoating of the virus, causing the virus to aggregate together and, therefore, not be able to engage with the cells. So virus neutralization is the -- and neutralization assays or functional assays, which provide an assessment of the protection against the virus in question.

So serological correlates of protection are important, and we are thinking about them for a number of different vaccine candidates as a way that these vaccines might get licensed without needing to do Phase III, large Phase III efficacy trials. But also not just to prevent that, just to avoid having Phase III trials. The knowledge of serological correlates of protection allows comparisons to be made between the vaccines as they work in different populations or in different age groups or different batches of vaccine and so on. So it provides a lot more ability to extrapolate the results in different situations.

And then the final slide. And I think I would like to finish with this very positive statement about immunization, which I'm sure I don't need to tell this audience about. I hope I've provided an overview of some aspects of immunization, and the hope that it's -- it will set the scene for the other presentations that you have today.

So let me just finish by saying with the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction worldwide as immunization.

I thank you for your attention.

Stephen Hoge - Moderna, Inc. - President

So this is Stephen Hoge, I'm the President of Moderna. I just want to start by thanking Dr. Heath for that really wonderful overview of vaccination and immunization. What I'd like to do for the next roughly 20 minutes, prior to our coffee break, is provide a little bit of an introduction to our mRNA vaccines platform, with a focus on really what makes it different, why is it so novel and perhaps different from all the things that have come before that Dr. Heath gave us such a great overview of.

So starting on Slide 82, just returning to the 4 sort of upfront concepts that Stéphane (inaudible) out there as we moved into mRNA medicines as a company about a decade ago. There were 4 big thematic things that we talked about: a large product opportunity; a higher probability of success; accelerated time lines; and the opportunity for greater efficiency versus recombinant technology approaches, and all 4 operate on vaccines.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

If we jump to Slide 83, what I'd like to do is just briefly go through some examples of how our platform technology approach and some of the data we've generated demonstrates the differentiation across all 4 of those aspects. So first, starting on the concept of large product opportunity. There are really 2 features that we talk about most often when it comes to our mRNA vaccine platform and how it is quite different from things that have come before. The first is the ability to do highly complex antigens, and I'll speak to that in a minute, and the second is the ability to do combination vaccines in a very novel way.

So on Slide 84, on the concept of complex antigens. I just wanted to highlight 2 examples of highly complicated multi-protein antigens that we have in our development pipeline, both are actually familiar to many of you. On the left-hand side, we're talking about our cytomegalovirus vaccine, or CMV vaccine, mRNA-1647, which, as you know, includes 6 messenger RNAs in it. Five of those messenger RNAs encode for a single antigen, something called the pentamer, which is actually illustrated in the inset. The pentamer is a protein complex, which is essential for the virus to get into epithelial cells, your primary barrier tissues. And the pentamer is made up of 5 different proteins: gH, gL, UL130, UL131 and UL128, as you can see labeled there. As you appreciate from the structure in the cartoon, these proteins have to fold together to make a functional antigen, both for vaccination as well as functional protein for the virus to get into cells. And making that through traditional recombinant protein technologies has, to date, been impossible.

There is also another protein, another glycoprotein that's important for CMV infection, which is glycoprotein B or gB, which is important for both fibroblast and epithelial cells. And as you can appreciate, that is a transmembrane protein, one that sticks in the lipid bilayer of the cell and the virus that helps facilitate its infection. All 6 messenger RNAs are in our CMV vaccine, something that traditional biotechnology approaches with recombinant proteins or sub-unit vaccines would have been very, very difficult. That's not the only example of a complex antigen though in our pipeline. The Epstein-Barr virus vaccine illustrated on the right, or mRNA-1189 that we announced earlier this year, includes 5 messenger RNAs, and makes a very different but complex set of transmembrane antigens as well. This includes an antigen that's important for B cells, as you can see in the inset, gp350, which, just like in the CMV case, is very important for how EBV variants or variances infect the B cells. There's also a complex trimeric and tetrameric complex made up of another gH, gL and gp42 glycoprotein, which, again, need to come together in a very complicated 3-protein antigen, both for the virus to function and for a good antigen to do vaccination.

Lastly, there is also a gB protein in this EBV virus, which is important for epithelial cell as well as B cell transfection. Putting all 5 of those together with recombinant protein technologies would have been incredibly difficult. In fact, the prior approaches to vaccination in EBV only functioned with the gp350 antigen alone, just that 1 single protein because the complexity of making the gH, gL and gp42 trimer would have been a bit too much.

So our platform allows us to do this with remarkable facility because all we have to do is put an additional mRNA for each of these proteins in these complex antigens. All of those messenger RNAs go with the vaccine into the cells. And as you can see in the cartoon on the bottom, they assemble all of the protein complexes in exactly the way the virus would try to assemble those complexes, for placement on the cell if the virus was starting to replicate for viral replication. That ability to make those complex antigens, I think, is truly differentiated.

On Slide 85, it's not the only differentiating feature. We also have the ability to do combination vaccines, and I'll let Tal and others speak more to this as an example later. But as we've announced, we are actually developing a respiratory combination vaccine against 3 of the leading causes of medically attended respiratory disease in young children, that is a vaccine against RSV, mRNA-1345. And our combination vaccine, mRNA-1653, which is against human metapneumovirus, or hMPV, and parainfluenza virus 3, or PIV3. Those 3 different respiratory viruses cause a relatively similar syndrome in children and account for almost 3 million visits every year to doctors offices and hospitals in the United States alone. The ability to combine them in a single vaccine is one of the major advantages of our mRNA technology platform, again, because we just bring additional messenger RNAs into that same vaccine.

So moving on to Slide 86. I'd like to talk to a couple of examples of how we see higher probability of technical success, and specifically, talk about our vaccines' mechanism of action and how important it is for T cell responses, something that Dr. Heath just touched on from a balanced immune perspective.

So first on 87, just repricing some of the things that Dr. Heath just covered in terms of how vaccines work. I wanted to talk about our vaccine platforms' mechanism of action. So if you inject in the muscle, in this case, a shoulder muscle in human with our vaccines, what will happen is the



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

vaccine will drain into the lymph nodes and find its way into antigen-presenting cells, as you can see. There, the messenger RNA will be unwrapped by the antigen-presenting cell, and that cell will go off and make the protein encoded. In this case, we're illustrating with a blue viral protein that's analogous to any of the glycoproteins that I was describing before. That will then get presented by that cell in the immune environment of the lymph node to a range of different other lymphocytes through a whole bevy of different receptors. First, it will get presented to B cells, as exemplified by that middle panel on the right, right on the surface of the antigen-presenting cell or through secretion in some cases. That will have a chance to activate T cells. It will also get presented through different antigen-presenting molecules called MHC class I and MHC class II, which will present, respectively, to CD8 T cells and CD4 T helper cells. So the antigen-presenting cell that has made this antigen, in our case, will go and present to both arms of the immune system, both B cells and T cells.

If you move forward to Slide 88. What then happens is activation of the immune response. And so when T cells see their cognate antigen, you'll get activated CD4 T cells in this example, and those CD4 T cells will go off in search of other cells to interact with. And specifically, they'll go look for activated B cells because, in fact, it is the interaction between those CD4 positive T cells and B cells that primarily drives the mutual reinforcement of that immune response. That happens through an immune synapse where the activated B cells will be presenting on MHC class II, the same sorts of antigens to that T cell, but the T cell will learn from the activation state of the B cell and lock in its responses. That CD4 positive T cell will also go off in secrete cytokines, including cytokines like TNF-alpha and interferon gamma, the so-called Th1 cytokines, which will drive other forms of activation, both of the antigen-presenting cells, but also CD8 positive T cells and immune responses.

What then happens on Slide 89 is the adaptive immune response, including the memory response that provides protection to that virus. And 2 different forms of that, starting on the bottom, obviously, you have cell-mediated immunity, [CD8] (inaudible) positive T cell-mediated immunity, where cells can go off and identify infected cells, for instance in barrier tissues, that have been infected by a virus and act against those cells both to suppress replication of virus and actually clear those damaged cells. But the highest form of immunity is actually sterilizing immunity, generally produced by secreted antibodies. And those activated B cells, after they have gotten a reinforcing signal from CD4 positive T cells, and really only after that, will they go off and differentiate into plasma cells, establishing very high levels of neutralizing antibody titers that actually can prevent the virus from ever productively being able to infect other cells.

What's really important to recognize about our platform technology is because we enter through the immune system in a way that's analogous to a virus and ultimately, are presented both to B cell and T cell arms of the immune system by antigen-presenting cells, which allows a balanced immune response where T cells and B cells can collaborate, can reinforce each other. What we see is a very balanced humoral or antibody as well as cell-mediated immune response in our vaccines.

I'd like to present a couple of examples of that, and starting on Slide 90. And so the first thing I'd say is that we have actually presented previously, evidence of T cell responses after vaccination in a range of preclinical models as well as in humans. In fact, we've reported T cell responses in our RSV vaccine in collaboration with Merck in humans. And we've actually most significantly characterized those T cell immune responses, CD8 responses in particular, in our personalized cancer vaccine study, both ourselves and the National Cancer Institute with the Rosenberg lab. Those have been presented previously. So we've demonstrated the ability to generate those sorts of productive immune responses to antigens through vaccination in humans.

Now focusing here on our examples in our infectious disease vaccines, which is the subject of today's presentation, our mRNA vaccines have been also shown to generate productive Th1-type immune responses to CMV, and that's measured in a number of different ways. But for instance, on the panel on the right, we're looking at CD4 positive, interferon gamma positive and TNF-alpha positive cells on the top 2 panels. In this case, looking at the percentage of those cells in rodents, in a publication for the reference below, that were generated following vaccination. And in the bottom 2 panels, you can see the CD8 fractions or the cell-mediated immunity associated with CD8 T cell [killing] in interferon gamma on the left and TNF-alpha on the right. So substantial CD4 and CD8 responses generated in rodents.

If you jump to Slide 91, just to show that, that has translated in our experience into humans, I'm showing here an exploratory analysis of T cell responses that we had done as a part of our Phase I study for mRNA-1647. So mRNA-1647 is our CMV vaccine, and while this is just an exploratory analysis because we believe that the primary protection of interest for us in CMV is neutralizing antibodies, it does show exactly that same sort of balanced response that we're expecting between T cells and humoral immunity. So the plot on the left, again, looking at very low end, I'll remind you, is 30 micrograms in red, 90 micrograms in blue and 180 micrograms in yellow. And what you're looking at is the number of interferon gamma



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

T cells measured against the gB, the glycoprotein B antigen in these subjects. What we saw was all subjects that we evaluated, so T cell responses that were primed and boosted, so these were subjects that were negative for these T cells in their blood prior to priming and boosting, and all subjects have seen that response by day 63. We then followed up a month later with our primary focus, which was on neutralizing antibody responses. And again, we look at fibroblast assay because that is the same sorts of antigen, gB predominantly, that we think is relevant. And there, what we saw was neutralizing antibody responses, as we've reported previously across those dose levels. In this case, we're just showing the neutralizing antibody responses for the subjects that were in their respective groups here. And what you can appreciate, I hope, is that we saw a very broad and a very substantial high neutralizing titers, geometric mean titers, across all the vaccination groups.

Taking a step back, this shows exactly what you'd expect. We're getting high neutralizing titers from B cells secreting high amounts of antibody, which can only really happen if there's a productive T cell component, particularly at (inaudible) T cell component CD4 positive component, in the memory space in these lymph nodes. And if you go and measure the blood of these same patients just after boosting, what you will find is recirculation of exactly that T cell component, so expansion presence in the blood of those CD3 positive interferon gamma positive cell. The immunology is exactly as expected.

So Slide 92, just moving on from higher probability success to accelerate research and development time lines. We do believe that the platform is starting to show evidence for its ability to move quickly to clinical studies as well as to market and that we are showing the ability of our platform and, particularly our manufacturing processes, to allow for fast scale up.

Slide 93, this has been covered in detail by Stéphane, but just briefly to reprise. Our SARS CoV-2 vaccine, mRNA-1273, which was the subject of much work in discussion in Q1 of this year, demonstrate the kinds of speed that we believe the platform provides, from first selection of a sequence by our scientists and our collaborators at the NIAID on January 13 to production of a clinical batch on February 7, took just 25 days. That had been released by February 24, and by March 4 was associated with an open IND that the NIH themselves had filed. And within 63 days, as you can see on the chart, and as what we've talked about before, the first participant in that Phase I study had been dosed. Perhaps highest import, when we're talking about the flexibility and speed of the platform, is back to that January 13 to February 7 time horizon. That was 25 days from selection of sequence to manufacturing and filling of that batch. So clearly, we think the platform has demonstrated remarkable abilities to move quickly when necessary.

We also, on Slide 94, think that the platform has demonstrated an incredibly high degree of flexibility across a range of programs. I'm just highlighting 4 programs here that we've talked about: CMV; hMPV/PIV3, that is our respiratory vaccine for children; EBV and the COVID-19 program. In all cases, we're using the same lipid nanoparticle formulation, we're using the same mRNA nucleotides and components, we joke it's the same 4 ingredients, and the mRNA and LNP manufacturing processes are highly analogous across all of them. In fact, we can use same equipment and capital equipment and much the same processes all the way through. It has allowed us to move in parallel across all of these programs and many others, as you know, with an incredible degree of flexibility, and it also allows us with confidence to scale up within programs and across programs when it's necessary from a manufacturing perspective. This uniform (inaudible) process and what it affords us, will be subject of much discussion, I believe, when Juan speaks later in the context of some of our company.

So lastly, on Slide 95. I just wanted to cover briefly the greater capital efficiency that we see over time versus recombinant protein technology. And again, here, I will allow Juan Andres, our Chief Technical Operations and Quality Officer to go into more detail here, but we do see single dedicated capital expenditures, for instance, like our manufacturing site, have allowed us to advance a very large number of programs in parallel. We think that will translate into lower capital intensity and higher capital efficiency over time. We've also shown, as I hope I've just demonstrated, a high degree of flexibility in that manufacturing process to move from very small scales to very large scales without substantial retooling.

So overall, we are quite pleased with our vaccine platform and the progress to date. We have a long way to go, of course, but we think we have demonstrated progress against all of the 4 key dimensions, as Stéphane described upfront. An ability to do complex antigens in combination vaccines, a unique mechanism of action, which provides a balanced humoral and cell-mediated response, showing a good balance of CD4 and CD8 responses within the cell mediated. We've demonstrated time to market and time to study clinical studies that we think is differentiating for our platform and a high degree of flexibility and capital efficiency to move a large number of programs forward in parallel.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Now with that, on Slide 96, we're ready for our coffee break. We will resume at 10:00 a.m. with the presentations of some of our clinical programs, starting off with Dr. Tal Zaks, our Chief Medical Officer. Thank you very much. Speak to you soon.

(Break)

Operator

Welcome back to the Moderna's Virtual Vaccine Day. At this time, I'd like to turn the call over to Tal Zaks, Chief Medical Officer at Moderna. Please proceed.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you so much, and welcome back, everybody. This is Tal Zaks, Chief Medical Officer. I'm going to start this section by looking at our portfolio as it relates to the vaccines we have against infections that are transmitted from mothers to baby, and this is a little bit of news of the day in terms of our activity with Zika.

So on the next slide, just as a reminder where this sits in our portfolio, you can see grayed out the rest of our vaccines portfolio, and I'll be starting with Zika, and then we'll go on to some of the rest.

On Slide 99, you have a sense of our history with this vaccine. And as some of you may recall, we started that when there was a sense of an imminent pandemic threat in the United States towards the end of 2016, and we quickly entered the clinic with what was then thought to be the latest viral isolate and started a great collaboration with BARDA who came to the table to fund this program all the way through licensure. And over the next year or so, we've learned 2 things: one was that the first vaccine we had developed that listed doses up to 100 microgram wasn't showing the sufficient immunogenicity. And at the same time, the team, in collaboration with Mike Diamond's lab, was actually studying the potential to improve the initial vaccine based on both the leader sequence that we had and a better understanding of the sequence of the isolates that were being characterized. And so as we were dose escalating in the clinic, we actually came up with a sequence that, at least preclinically, was at least 20x more potent in the nonhuman primate model than our first candidate. And so with that, in collaboration with BARDA, we took the second vaccine into the clinic, and we started this study that is leading to the results today. This is mRNA-1893, and it's our second-generation vaccine candidate. Now these results, as I'll show you in a minute, are positive already at the dose starting at 10 micrograms.

As a background for what Zika is, this is a mosquito-borne, an arbovirus, and it's a member of the Flaviviridae. It actually was cloned back in the late '40s, and so this is not one of those [80] events that Stéphane alluded to earlier in the talk. Initially it was thought to be restricted to Africa and then more recently, in the past decade or so, its made its way out through Southeast Asia and hopped over to Latin America and then Central America, such that in the 2015, 2016 time frame, we became aware of it in our continent.

In terms of the disease that Zika causes, as a reminder, and this is on Slide 101, there are 2 really important characteristics here. One is that this virus has a relatively high clinical attack rate, meaning that most people who get infected become symptomatic, which is not a common feature of Flaviviridae, although these days with coronavirus, everybody is highly attuned to the importance of the relationship between how many are asymptomatic and how many are symptomatics. So in the case of Zika, the majority is symptomatic. The symptoms, by and large, are transient, although they can be severely debilitating in terms of the joint pain that is then associated with fever, rash and headaches. Of course, the adverse event that caught the world's attention is the microcephaly and other neurological birth defects that are associated with transmission in utero. And so that led to attempts to develop a vaccine, including ours. To date, this remains an unmet need, there is no approved Zika vaccine, although the sense of the pandemic threat in the United States has receded somewhat in the last few years. There clearly isn't an anticipation that in the future there is a significant likelihood that this will resurge, and it continues to circulate endemically in the regions that I described previously.

So what is our vaccine candidate on Slide 102? Well, this is really a single mRNA, but it encodes a complex protein, it actually encodes for the viral structural protein. And while this looks simple on a cartoon, this is actually from a molecular biology standpoint, one of the more complicated vaccines that we've attempted to do using our technology because in order to immunize, what needs to happen here is that this precursor



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

membrane, the prM, has to get cleaved from E, which is the envelope protein. Both have to be transported and then both have to reassort themselves on the membrane so that they can bud as viral-like particles, and these particles have heterodimers of this prM, the memory protein together with the envelope protein, and it is that ordinary structure that actually presents the right immune epitopes to the immune system. And so if you think what needs to happen to have a productive vaccine here, this is not sufficient to just express a cell membrane protein, you actually need a viral-like particle to be able to form.

On Slide 103 is sort of a capture of the difference between that first attempt we had, which was based on the Micronesian (inaudible) 2007 sequence and an IgE leader peptide that is required to lead the sequence of this complex polyprotein through its processing in the cell. And what is our current vaccine, mRNA-1893, this was based now on the Rio strain that was characterized. There are 5-point mutations that really don't have to do with the epithet that's being presented but have to do more with the efficiencies of processing as we understand it. And now we connected it to the Japanese encephalitis virus signal peptide and had shown in the paper I mentioned previously that actually, this is potent and comparative experiments that we had done in collaboration with BARDA, as mentioned, much more potent than that first one.

And so that led us to this clinical trial, which is on Slide 104. What we did here was to take (inaudible) 30 subjects per dose, most of them are seronegative, but we put a few seropositive, just to ascertain the safety and tolerability as well as the ability to boost further seropositive, and we took it through 4 putative dose levels against the first one, all the way up to 100 was still not immunogenic. And so here, we wanted to make sure that we take it all the way up to 250, but we started at 10 microgram. And the endpoints here are beyond safety and tolerability. The secondary endpoints are our ability to show the neutralizing titers, and these are going to be measured sort of by 2 end points, one is the plaque reduction neutralization test and the other one is a microneutralization assay. There is a slight difference between these 2. Think about it as the plaque neutralization, actually, you are measuring the ability of the blood when diluted to prevent the virus from causing plaques. Now plaques happen in a cell culture when the virus jumps from cell to cell, and so it really demonstrates the ability of the blood to inhibit the cell's ability to fully go through its maturation and infect other cells. But it's a complicated assay that takes several days to read out, and so people have developed over the years a much simpler assay that tends to be more sensitive, which is the microneutralization. This is actually done on an individual cell level, so you can use things like facts analysis to do this in a relatively high throughput. But the gold standard in the field is still considered this plaque reduction neutralization titer 50 just means that at that titer you have 50% inhibition of the plaques that will be formed. And so these were the end points on this trial.

On Slide 105, you see the schema here. This is a prime boost, like most of our vaccines where we're going after naive populations, we believe the boost is necessary. That's true, I think, in immunology as a whole. The study completed dosing recently, and what we're showing you are the first interim analysis from just those level 10 and 30, so the first 2 cohorts. We have 2 more cohorts to go and complete follow-up and analyze the data.

So on Slide 106, let's talk about the safety data. Not really much to write home about here. The expected adverse events that are either local, in this case, really just pain up to 50% of participants, but mostly grade 1s, a little bit of grade 2s. We actually started out grade 3 adverse events so far. In terms of systemic flu-like symptoms that we look for, you see a little bit of fatigue, myalgia, et cetera. Again, all of these were mild or at most, moderate. There were no grade 3 events. There were no serious adverse events that were related and nothing really otherwise worth mentioning here.

Let's talk about the data. So this is Slide 107, and we were really happy to see that, already at 10 micrograms with this vaccine, we are getting good immunization. In fact, if you look post dose 1, you don't really start to see much with the PRNT50, but clearly, after the boost, you know are starting to see nice rises in titers. We can talk about the seroconversion rate just to give you a sense of not just looking at the mean titers, but how many of the vaccinated individuals actually saw a boost, and the answer here is practically everybody. You can look at the microneutralization titers. Again, it's a different assay, so the numbers appear higher, and this is a more sensitive assay so it's not a surprise that here you're actually starting to pick up immunogenicity even after just the prime dose. But clearly, the boost is giving us a very significant 1.5 logs above what you saw just following the initial prime. And again, if you ask, okay, what percent of the population here is seroconverted, the answer is practically everybody. Now this is in the seronegative population, so this is the majority of the population.

On the next slide, we look at the data in those few subjects who are seropositive to begin with. So seropositive here is not seropositive for Zika, it is seropositive for related flavivirus and this is Japanese encephalitis or dengue and this is all -- most of these, we believe, are dengue, but it's hard to say without actually going and running neutralization assays on their blood. And because of the relatedness of these viruses, it's important to



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

be able to demonstrate lack of interference and the ability to still specifically boost Zika responses in flavi seropositive participants. So please don't confuse this with the story of CMV, where seropositivities is true CMV positivities. These really should be thought of as related flavi viral positive participants at baseline. And what you can see here is, because of some level of cross reactivity, there is a sense that the baseline may be higher. This may [help continue to] participant getting injected during the trial until we have the full (inaudible) to discern. But if you look at the totality of the data here, clearly, even in the seropositives, we're seeing a very nice boost that we can discern, and you can see that both with the PRNT50 numbers as well as the geometric mean titers, they go up. These are fairly small numbers. This was done mainly just to take sort of a first glimpse, a first look. So I wouldn't put too much emphasis on the absolute numbers here. These are 4 to 5 participants per group.

On Slide 109, you can sort of see this depicted graphically. I think the arrow bars are wide on the red at baseline. That likely reflects somebody who got infected in between screening and actually showing up for their first visit, but then you can see very nicely the titers go up over time and demonstrating the benefit of the prime and boost.

On Slide 110, you also see the graphical depiction now of the populations carved out between the seronegatives and the seropositives. And again, the wide arrow bars on the right are simply reflective of the fact that these are very, very small numbers and a few participants, and I expect in the future once the trial is fully unblinded -- when you show data for 4 or 5 subjects, will simply show the individual curve, so that people can get a better sense. Overall, I think the story here is clear. This vaccine works. It works as little as 10 microgram. You start to see a hint of activity at the 30 microgram. If you look at the left, even after just the prime, there appears to be higher titers at the higher dose of 30, but of course, claiming the full dose response and understanding that will require us to look at the totality of the data. These curves will either continue to get better or it will become apparent that we were close to maxing out even at a very low level. I think that's hard to predict. The bottom line for me is that we've clearly now demonstrated that this vaccine works with a dose as low as 10 micrograms.

On the next slide, on Slide 111, the same view now looked at the more sensitive assays of microneutralization, which is starting to pick up that difference between 10 and 30, just following the prime. So in summary, what have we seen both 10 and 30 microgram dose levels and use of strong neutralization, Zika-specific antibody response, it appears that the 30 can seroconvert the seronegatives even after a single vaccine administration, and both of these assays are correlating with the same overall picture. The safety profile has been one that is so far very well tolerated, with no related serious adverse events, in fact, not even grade 3 expected related adverse events of either local (inaudible) or systemic flu-like symptoms.

If you step back now on Slide 113 and view this sort of in terms of the totality. We've clearly demonstrated, I think, with this program, the flexibility of our platform and the ability to improve when an improvement is needed and when we understand the molecular basis of the sequence. This allows us to use the same manufacturing facility in process. BARDA have been terrific partners throughout. They understood what we were trying to achieve and they remain committed, believing that we still need a vaccine in the United States. We believe that whether this pandemic returns or not, this represents a significant financial product opportunity because it is circulating endemically in so many places in the world, and the risk to women who have not been infected during pregnancy is very significant. And I think, finally, if you kind of step back and look at our scorecard, this is the eighth virus out of eight for which we've been able to demonstrate immunogenicity in Phase I clinical trials with, I think, a well-understood safety profile.

Now in terms of what's next for Zika. Just the high level story here is that without a pandemic circulating where one can design a clinical trial, it's pretty clear that approval will require one of those alternative pathways that Dr. Heath spoke about. And we've been working together closely with BARDA and other collaborators to develop a surrogate of protection. I've shown you both PRNT50, plaque reduction neutralizing titers, as well as microneutralizing titers, either of these could potentially serve as true surrogates because we believe they are mechanistically linked to the ability to prevent disease. We now have a pathway of correlating both these antibodies and the levels with the ability to prevent disease. Doses as low as 2 microgram in nonhuman primates were completely protective, and so there's work ahead of us to run a larger Phase II trial that will enable us to confirm with larger numbers the safety profile in both flavi seropositives and flavi seronegatives, and also affirm the neutralizing titers and be able to correlate them back as surrogates of protection with the nonclinical models. That is what I anticipate today to be the pathway to licensure for this vaccine, and I expect that as soon as we're sort of back to a normal operating environment that this trial will kick off. And from there, it should be, I think, a relatively straight pathway to eventual licensure here.

Let me now turn the attention over to cytomegalovirus. This is Slide 114. As a reminder, the -- we're all living in a world of coronavirus, but this continues to be a huge, huge unmet need. During the time that I'm talking today, 2 to 3 babies will be born infected with cytomegalovirus just in



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

the United States. In the 4 hours of this presentation, there will have been 2 babies that will have been born and will suffer neurological sequela for the rest of their lives. The numbers here are, as you will hear, quite significant. The unmet need here, obviously, is a spectrum. Some children are asymptomatic, but there is a proportion that is symptomatic and the symptoms vary in severity, starting from relatively mild hearing deficits, all the way through microcephaly and in the case of severe illness, even perinatal death. There is no approved CMV vaccine on the market. What we are trying to do here, on the next slide, as a reminder, Stephen spoke to some of this, but our antigens are actually -- there's 2 antigens. There's the pentameric complex, which requires 5 separate proteins to come together, and so we have 5 different mRNAs that go into the vaccine. And we also put in that monomeric gB, which, on its own, creates another antigen. And what we've learned in the field is that the pentameric complex is likely the hook the virus uses to attach itself to epithelial cells, whereas the gB is likely required a fibroblast.

The design of the trial, on Slide 117, is a prime boost and then a third -- or a second boost, a third vaccination at 6 months. And so we had disclosed the initial 3-month interim data back in September, and earlier this year, we followed up with a 7-month interim analysis.

As a reminder of what these assays are doing on Slide 118, you take blood from somebody who's been vaccinated, you serially dilute it, so you first dilute it twofold, fourfold, 16-fold, et cetera, and you check at which dilution is the blood actually able to prevent the virus when put on cells from actually infecting those cells and killing them. And so that 50% mark is what we look for in terms of neutralizing antibodies, and that's how we define the titers.

Now on Slide 119. As a reminder, CMV, as a way to understand vaccination, is fairly straightforward because we have the people who have already been infected and are walking around, those are the seropositives. And so that gives us a baseline of the level at which we're shooting for because we know that those seropositive people are relatively protected. And what is shown on Slide 119 is sort of a recap of the data. We can boost the people who are seronegatives to titers, far and above. In fact, about a log above those of seropositives, those people who are walking every day of the week with active -- their immune system actively fighting a latent vaccine with antibodies. And yet if you focus the immune system's recognition on just the pentameric and the gB here, you can prevent, you can induce neutralizing titers that are higher, that supersede what natural immunity is able to come up with when it sees the virus. In the case of the fibroblast as well here, you see the ability to induce. You not just get close to the level of where seropositives live, which would have given you a ratio of 1 at the bottom most row, you actually exceed that to 1.3, 1.4. Again, even with this assay, we supersede the ability of natural infection.

On the next slide are the data for the seropositive. So these are people who are already immune and they're already recognizing the virus. And yet, if we come in and now boost their immune system with the recognition for these 2 antigens, what you can see here is that we achieved a further induction of the ability of their immune system to recognize both the epithelial cells and neutralized epithelial cells as well as the fibroblast. And here, we can get north of 20-fold in terms of what the vaccine is able to induce compared to their baseline. And even against the fibroblast here, we're able to further boost this significantly.

In terms of the safety profile, I think the salient point here is as we dose up between 30, 180, and then we added 300 micrograms just to make sure we weren't missing the top dose as we were dose escalating, it appears that the 300 microgram causes a little bit more, both local adverse events and some systemic flu-like symptoms. As you can see here, the overall numbers in black, the grade 3s in red, we still did not really see anything beyond that, so this speaks to tolerability. It does not really speak to safety concerns per se. We did not see any vaccine-related serious adverse events, nor did we see any Grade 4 adverse events.

If you look at what happened after the third dose of vaccination, that's on Slide 122. Again, nothing here that hasn't been seen before, and so we believe at the end of the day, that probably an optimal dose is going to be somewhere in the range that we've tested here. The Phase II is ongoing. It's completely enrolled, and it's testing a similar dose range roughly to the one that's been done here, narrowing down a little bit on the range to enable us to pick the right dose for Phase III.

Slide 123 just shows you how immunity looks over time. And I think the relevant point here is to see that the prime boost not only gets us to the level far above those where seropositives live, but they also then have a very nice plateau. So you can see how after the prime boost at the 6 months, the top 2 doses are still above the seropositives. You give them another boost and then at least the initial data we have for the first subjects that were dosed earlier in the trial, you can see those levels up that a year are still higher than the baseline. Even the lowest dose here is still maintaining



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

the level of the baseline seropositives, which is expected to correlate with protection. And if you look, those deltas may appear small, but this is a logarithmic scale. So it is significant.

A similar look on Slide 124 on the seropositives initially, and you can see the same thing here. There is actually no further decline in between the prime and the second -- and the boost and the further boost, which is quite interesting if you think about it. So you are boosting people to above the levels at which their immune system lives anyway, and you actually now don't see decline. And it may be that we've kind of reset their immune system ability to recognize this virus at a level that it's been reset before, and that's why they'll continue to live at that level. I say this is because demonstrating benefit in seropositives is going to be hard. There still is congenital infections happening in seropositives. In fact, worldwide because of epidemiology and math, most of the cases of congenital disease happened in seropositives because seropositives are much more prevalent in developing world versus places like the U.S. and Europe. And while the FDA does not expect us to demonstrate clinical benefit in seropositives, I think the ability to show this boosting lends itself to the scientifically plausible path that there could be benefit in seropositives as well by preventing whatever risk remains, and so we will keep looking at this pace and intend our vaccine ultimately to be used in both seropositives and seronegatives.

So on Slide 125 is the interim analysis. I won't repeat these data except to say that we can clearly get seronegatives above the level of seropositives. We can get the seropositives to boost further than what natural infection would ever get them to, and the early evidence shows that our effect is durable at least out to 12 months. In terms of what's next step for CMV for us, the Phase II dose confirmation study is fully enrolled. Not everybody has received the second and third dose. And clearly, we are dealing with an environment out there right now, given corona that makes it problematic. Some sites are shutting down.

We believe, to date, that we should be able, even with some missing data, to analyze this trial and maintain the scientific integrity and understanding of how the dose response curve behaves and be able to pick a dose. But clearly, this is a fluid situation, and we'll update the community as our understanding of data and time evolve.

We know from FDA that prevention of primary infection is going to be an acceptable endpoint. Of course, once we have the Phase II data, we will go and have a formal discussion with the agency on what the Phase III should look like. We also need to have those regulatory discussions beyond the U.S. That being said, we're well on our way with that understanding to preparing for the pivotal trial, which we still believe should happen next year or should start next year.

With that, let me move on and talk about what that endpoint is going to look like in the Phase III. So this trial is meant to show prevention of infection and here, it -- actually having a vaccine that just has some components, but not all of the virus make our life easier in terms of an endpoint because what we're able to do by measuring antibodies, or the ability of the blood to recognize those antigens on the left bottom that are not in the vaccine, we can distinguish somebody who's actually started seronegative, but then got infected.

Our vaccine will not induce immunity towards those antigens. So while you may not be able to distinguish it by neutralizing assay against the entire vaccine, by measuring antibodies that are specific to the different components, we will be able to distinguish immunity from the vaccine from immunity that is indicative of infection. And so developing these assays, we're on our way to establishing what would be the primary endpoint here in the trial.

With that, let me now close on CMV. This is a significant opportunity. I think we have shared this in the past. This is not just our judgment, this is, I think, the world of CMV. There are others who are trying to develop vaccines. And I think this is sort of a consensus view, if you will, but this is a significant market size, likely north of \$3 billion in terms of peak year sales. And some of the assumptions are listed there.

From my parochial perspective, I think having the gB antigen alone already having shown a 50% vaccine efficacy based on Sanofi's trial in the past, I think, sets us very well for a high probability of success once we do the Phase III. And this is one where we wholly own the rights to it.

So in summary, CMV, the Phase III preparations are underway. We're going to be leveraging the ability of this platform to scale and manufacturing. We've mentioned the probability of success here, and it is a very significant multibillion-dollar commercial opportunity.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

I'm going to now switch gears, and talk a little bit about respiratory diseases. And I'm really just going to highlight where we are, before I introduce Dr. Munoz, on Slide 132, is our approach against HPV and PIV3, human metapneumovirus and parainfluenza type 3. I won't go through the disease, Dr. Munoz will do a much better job of that than me.

The salient point for me as a clinician is really the fact that the disease of hMPV and PIV3 in the infant and pediatric population are indistinguishable. In fact, when I went to medical school 30 years ago, we didn't know about these. They hadn't been yet described, and yet this was part of sort of the -- what you would see in pediatrics of very young children presenting with viral pneumonias.

We had described, and this is on Page 133, the ability of our vaccine to boost the serum neutralizing titers. And in fact, when we combine here, these are the fusion proteins of both hMPV and PIV3, we are able to independently boost the immune recognition and neutralizing titers against both of these.

The second boost didn't really do much. There wasn't much of a dose response here. It appears we had peaked here as well quite early at the 25-microgram dose. And this is indicative of the type of immune response you get when you go into pre-immune people. So recall this was done in adults. All of us have been exposed to these viruses, and so we're walking around and the vaccine can only boost us. The target population is going to be infants who have never been -- have never seen this virus, and so they will be seronegative towards these vaccines. So we will need to define the right dose in those infants once we get there.

The safety and tolerability were similar to everything else I've described for our platform to date. There was nothing surprising here. You see the expected local reactogenicity and systemic flu-like symptoms. And I've described the immunogenicity here.

On Slide 135, speaks to the potential of combining this with RSV. So one of the things that was very appealing to us, even though it's not necessarily an obvious regulatory pathway, is to say, well, if it's the same disease caused by either hMPV or PIV3, then you should be able to come up with a Phase III trial. Eventually when you get there, that combines the single clinical endpoint, whether it's caused by virus A or virus B, if your vaccine is against both viruses. And in fact, we have discussed with, at least, FDA, a very novel statistical manner in which to envision this combination trial when we get there.

Now RSV is, obviously, a more prevalent disease, albeit with a slightly different epidemiology, as Dr. Munoz will describe. Now that being said, if we can develop RSV to the same level and the same degree of immunogenicity, then, on Slide 136, the logical conclusion is, well, why don't you have a vaccine that just combines the pre-fusion protein of all of these 3? And indeed, that's where I expect and hope we will eventually end up in terms of full development. So I anticipate that both of these programs, once they are taken through their sort of Phase IIs, we'll end up in a combination product that should prevent the same type of illness, whether it's caused by RSV, hMPV or PIV3.

And so with that, let me conclude my section here, and it's a real pleasure to introduce Flor Munoz. Dr. Munoz, is an associate professor of pediatrics and infectious disease at the Baylor College of Medicine, and is the Director of Transplant Infectious Disease at the Texas Children's Hospital in Houston. Her academic expertise is in vaccine development, and she's focused on pediatric respiratory vaccines and maternal immunization.

In addition to her academic contributions in the field of vaccine development, Dr. Munoz serves as a member of the American Academy of Pediatrics Committee on Infectious Diseases, the CDC's Advisory Committee on Immunization Practices, or ACIP, and the American College of Obstetrics and Gynecology Immunization Expert Work Group. On top of that, we're super happy to have Dr. Munoz familiar with our programs, as she has been supporting us as looking over our shoulders in terms of our safety advisory committee.

So with that, Dr. Munoz, the floor is yours.

Flor Munoz-Rivas

Thank you very much, Dr. Zaks. I hope that you can (inaudible) discuss with you today the topic of RSV, hMPV and parainfluenza and focusing on the need for pediatric respiratory virus vaccine.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

In the next slide, I just have put a few of my disclosures regarding research. And I would like to just go ahead and jump into Slide #140, which is going to be the initial description of the viruses.

So we have here 3 different viruses that belong to the same family. They are paramyx severity and pneumoviruses. Specifically, RSV is classified as a pneumovirus. But I wanted to start by just showing you these pictures because you'll see how they have similarities and how they have commonalities here. They're all enveloped single stranded RNA viruses. They have a similar confirmation. They have this envelope or lipid layer that is forming the capsule of the virus, that is lined internally by the matrix protein. That's the same structure for all of them.

They also have a fusion protein that sticks out of this capsule. And you see how this fusion protein is constant in all 3. That is an important piece as we have heard, because it's what allows these viruses to enter the cells that they infect.

And RSV and hMPV also contain an attachment, or G protein, it's been called. The fusion protein is really the main target of our immune system's response to these viruses, and you'll see how that is, again, one of the targets of vaccine.

The parainfluenza virus instead of a G protein has what we call a Hemagglutinin-neuraminidase type protein that it also serves a similar function. What you see here as well is that they all have different internal proteins. And importantly, I wanted to point out the fact that the fusion protein is actually conserved, and again, a target of a vaccine development.

In the next slide, we will start talking specifically about RSV, respiratory syncytial virus. So this is a virus that we know of for a very long time. It was first described in the late 1950s as the chimpanzee coryza agent, and it is the main cause of upper and lower respiratory track illness in infants and young children. It is actually the main cause of bronchiolitis. And we know that there are 2 types, based on antigenic characteristics, sub groups A and B, and they cause winter outbreaks of respiratory illness.

We have disease in all ages, although it does cause significant problems in infants, especially in young children, we know that another at-risk population is elderly adults. And importantly, although we do develop an immune response in antibodies that allow us to get through the infections, you see how this response might not be sufficient to prevent recurrent infections, which happen throughout our life. And they tend to be milder as we get older, except once we age or we have other underlying medical problems.

But certainly, as I mentioned before, those antibodies, neutralizing antibodies against the S protein, particularly more than the G, although those surface glycoproteins are targets, are going to be what prevents -- make us get through the infection and prevents further infection. And these to be antibodies that are induced by the infection itself, but we also know that maternally-derived antibodies can protect babies as well as passively administered antibodies.

The next slide is going to show you some of the work of pioneers in the field of respiratory viruses. Caroline Hall had the very early descriptions of RSV as the most important cause of infant bronchiolitis. Looking at the epidemiology of bronchiolitis, as you can see in the '90s there, and showing how you see outbreaks of bronchiolitis cases that match the identification of RSV in the laboratory from patients that have that syndromic disease.

The next slide is going to tell you a little bit more about the impact of RSV in children, in particular. So for us, pediatricians, this is really the most important cause of lower respiratory tract illness in infants and young children. This is because nearly all children are going to be infected at least once by the time they turn 2 years of age. And we know that this is not just a little cold, 30% to 40% of babies who get this virus are going to have pneumonia or respiratory -- lower respiratory tract symptoms. Mostly, again, in the form of bronchiolitis. This is really a more severe illness than just the common cold.

2% to 3% of these infected children will need to be hospitalized. Now that we're seeing the impact of the COVID-19 disease, these numbers are put into perspective here. This is a higher hospitalization rate, for example, than influenza. And we also have a higher mortality from RSV than influenza in infants. You see that the majority of hospitalizations, 75% are going to happen in actually full-term healthy infants. Although we know that there could be some groups that are at higher risk. And there's also a concern that having early infections with RSV also might predispose to recurrent reactive airway disease and asthma in the future.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

The next slide is another one of the descriptions of RSV hospitalization. So the impact of this disease in children by Caroline Hall. And what you could see here is that, indeed, it is a disease that tends to affect mostly infants in the first 6 months of life, but it can happen particularly throughout the first 2 years of life. Most of disease, up to 50% could happen in the first 3 months of life. And the majority, again, is going to be in the first 6 months.

The next slide is going to show you the -- a little bit more contemporary data. So throughout the United States, there are some medical centers, 7 of them that participate in the CDC's new vaccine surveillance network, or NVSN. And you see in that map, the distribution of the sites that represents, geographically, the entire country, and this is looking specifically at the occurrence of RSV hospitalization, again, as an important impact of this disease.

You see that, as we mentioned before, you have a seasonal epidemics usually with wide circulation from November until March or April, and this is an example of the 2015-2016 season. And you see, again, as contemporary data confirms what has been seen in the past, that the most affected age group is going to be those under 6 months of age, with a rate that is variable nearly 20 per 1,000 in the first 2 months of life and then about 30 per 1,000 in the -- up to 6 months of age. But certainly, you see the toddler age group is also a high-risk group.

The next slide goes into the information regarding the impact in terms of mortality. So we talked about how the majority of affected children and those hospitalized are going to be actually termed healthy infants. The same is true for mortality. So because we have really a small number of premature babies that are born every year, we do see, again, a majority of impact occurring in healthy term infants in the first 6 months of life. This is going to be your red lines in this graphic.

However, you see that if you are premature, healthy -- even healthy preterm infants, just prematurity itself, does increase the risk of mortality from RSV, and that is the green line.

The blue line shows infants with comorbidities and again, a high-risk of mortality in the first 6 months to even a year of life from RSV, usually associated with cardiovascular disease, in this case. But other comorbidities, immune compromise and so on can be affecting these children. This is data that is not just from the United States now, this is global data from 23 different countries. And this is to point out that this is a disease that is of global consequences. The median age is 5 months and a lot of the deaths, greater than 40%, occur in the first 3 months of life.

The next slide, just to finish the discussion about RSV and its role as a major global pathogen in children under 5 years of age, this slide shows 2 different studies, with about 10 years of difference between the 2, 2005 and 2015 estimates of the impact of RSV in the world, so including up to 132 countries in the second study. And sadly, for this graphic that you see here, you see that there is not a lot of change over a period of time because we don't really have a good way to prevent these acute lower respiratory track illnesses, which happened in a number that is as high as 33 or higher million cases a year.

Hospitalizations, you see vary there in children under 5 up to 3.2 million. And those under 6 months represented about 1/3 of those. And that hospital deaths continue to occur in the thousands, 60,000 in children under 5 and about 1/3 of those in those under 6 months of age. So definitely, overall, RSV is an important global pathogen. We also know that these virus can pre-exposed to secondary bacterial pneumonias, which is a big problem as well.

The next slide, I'll start talking a little bit about the other 2 viruses. So parainfluenza virus, again, is also an enveloped single-stranded RNA paramyxovirus. There are actually 4 distinct types. These are parainfluenza 1 to 4. 4 has 2 subtypes. There's actually 5 parainfluenza viruses. And this is a virus that is also well known. We know about it since the 1950s. It causes sporadic inspections, but it can also cause outbreak. And it has a very characteristic circulation as well.

You see parainfluenza 1. I'd like to tell my students to remember that at the beginning of the winter is number one. So in the fall, we see outbreaks of parainfluenza 1, while you also see sometimes parainfluenza 2, and in the spring is when we see parainfluenza 3, which happens later than and tends to be, as you'll see, a little bit more severe.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Parainfluenza 4, we know a little bit less about it. But as similar to RSV, this is a virus that, after infection, does not confer complete protective immunity, and you can have reinfections through the rest of life.

The next slide is another one of the graphs from Dr. Hall, showing again the main clinical manifestation of some of these parainfluenza viruses, and showing you that if you map out in the season the cases of croup, you'll see that croup activity correlates with the finding of parainfluenza 1, and sometimes parainfluenza 2. But parainfluenza 3 viruses are a little bit more diffusely spread out and again, happen after the end of the winter.

So in the next slide, just to complete the discussion about parainfluenza virus and how it presents, para 1 and para 2 give you croup, para 3 give you bronchiolitis and pneumonia, especially in the youngest infants and young children. And we also know that these parainfluenza viruses can cause exacerbation of asthma, just like as RSV, can do that. And also worsening chronic lung disease.

In some cases, you can also have refractory infections. So I work with patients that are immunocompromised. And certainly patients that have received bone marrow transplants or are lung transplant recipients or any other type of immune deficiency, these viruses tend to persist and can have more severe consequences, dissemination and even higher mortality than in an otherwise healthy patient. You have also uncommon presentations, as you can see there, with extra pulmonary manifestations, especially in the central nervous system, such as encephalitis, for example.

Now similar to RSV, most children have been infected with parainfluenza by the time they turn 5. Any of the types, and again, they can have more than one infection. This is a virus that is also having a very short incubation period, and similar to others, can be shed before you even have symptoms. So it's very contagious as well.

The next slide is to give you just a little overview about human metapneumovirus, our third important virus. hMPV is the new kid on the block. It was only discovered in 2001. This was after some outbreaks of respiratory illness in the Netherlands. And it was identified as, again, an RNA paramyxovirus, which has 2 antigenic subgroups. It also has A and B, similar to RSV, that could circulate during the winter season. As a matter of fact, hMPV causes a clinical disease that is indistinguishable from that of RSV. You can't tell by looking at them. They also happen at the same time during the winter, and sometimes in the spring time.

Similar to the others, as you can see, most children have had this virus by age 5. They can have co-infections. It looks just like RSV, with cough, some rhinorrhea, some wheezing illness, and it's mostly, again, bronchiolitis, although you can have like parainfluenza croup presentation, pneumonia, exacerbations of asthma and other problems, where you can see in adults as well and some immunocompromised patients quite a bit of disease. Short incubation period, quite contagious as well, and prolonged viral shedding in some patients.

The clinical presentation, in the next slide, is going to show you something that is actually interesting and different from a human metapneumovirus compared to RSV and flu. And that is the concern about it causing community acquired pneumonia. So when we first learned about this virus, we thought it was actually worse than RSV causing more hospitalization, but it has some distinct characteristics. So among hospitalized children, with community acquired pneumonia, it represents about 6% of the cases. And we know, just like RSV, that children under 6 months are going to be having higher rates of hospitalization.

However, if you look at outpatient and emergency room cases of acute respiratory illness, and you compare children under 5 and children over 5, it's a very similar proportion. It's about 5% to 7%. So unlike the other 2 viruses that we discussed before, human metapneumovirus is more likely to be associated with pneumonia. And this is mostly in the outpatient study, where even children in the first 5 years of age, continue to have similar rates as young infants. So this is important because it could be that it's a more significant pathogen in children that are a little bit older than those who have RSV.

Okay. So let's talk about the next slide, please. Just to show you, again, as a quick wrap-up about what these 3 viruses have in common. So they're all encapsulated single-stranded RNA viruses. We have talked about similar characteristics of the viruses. RSV is a little bit more complex. It has more proteins. And PIV, parainfluenza, is a little bit simpler virus, although it's larger in size.

You see that at the very top of this table, as I've put there, this is from a textbook showing how the fusion protein is really an important target. And that even though there's variability in the different proteins, this is one that is quite conserved.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Importantly, we diagnose these by PCR, and we can do that very efficiently now. We can detect it as part of our viral panel in any patient with respiratory illness these days, but we don't really have any treatment. It's supportive. We don't have any effective antivirals that are used commonly or any available vaccine.

So with that, if we could please move on to the next slide. Just to tell you that, at this point, really, it is urgent for us, pediatrics, to think about a strategy to prevent these respiratory virus infections, both in infants and also in young children.

The next slide, I will focus a little bit on RSV, because, unfortunately, the work for hMPV and parainfluenza has not been as advanced as with RSV. But there's a lot that we can learn about RSV, and what has happened in the last few years.

So for RSV, we have 2 options that have been considered for a long time, one is the use of vaccine and the other is the use of monoclonal antibody.

Next slide, it's a complex slide that I borrowed. That basically is not for you to look at in detail, but it's for you to see how enormous amount of work has occurred since 1957 when this RSV virus was first identified in humans until current days where a number of potential products, again, in the form of antibodies, monoclonal antibodies, more recently, but initially it was immunoglobulin. Two vaccines of different types have been developed or have been evaluated.

The next slide is telling you the current prevention strategies that we have for RSV in children. So again, we don't have vaccine for children or adults, but we do have a way to prevent disease in the most vulnerable through passive antibody. So initially, again, we used RSV specific immunoglobulin. That was a product that was used for a short period of time.

For the last 20 years, we've had monoclonal antibody that, again, binds specifically to the S protein, does reduce mortality and the severity of RSV disease and those who receive it. But unfortunately, this is a product that is only restricted to those who are at greater risk.

So at this time, preterm infants that are less than 29 weeks of gestation, those with chronic lung disease or congenital heart disease, that is hemodynamically significant. And of course, it requires monthly administration. It's costly, you do need a cumulative effect. And most of the children, unfortunately, that need this, as we have seen, who are those who are term and healthy, are not able to receive this preventive treatment.

The next slide is going to just, again, give you a little bit of a perspective, and I ask the question about, why is it that we don't have an RSV vaccine for children, after all these years? We're 60 years now of work. Well, one of the reasons is because our primary target population for vaccination, which that would be starting vaccination in the very young, 0 to 4 months of age babies, unfortunately, does not have the greatest responses to vaccines, in general, partly because of maternal antibodies, which are good because they are protective, but in this case, could prevent them from having an adequate response.

We also know, as we have discussed, that there is incomplete immunity to natural RSV infection, especially in those who are very young. So we would need a vaccine that is able to elicit highly neutralizing antibodies, probably better than the natural infection itself.

And then we have the story -- the history, that we did have vaccine tested in the 1960s, especially this formalin-inactivated vaccine, that, unfortunately, resulted in enhanced pulmonary disease that was a concern and has been a concern affecting the development of RSV vaccine since then.

So subunit vaccines have been identified, tested, but don't seem to be immunogenic enough, although they are safe. And live attenuated vaccines, which would be really given a lot of advantage regarding local immunity, have the challenge that you need to balance immunogenicity and reactogenicity because these young babies might have a lot of mucus and inflammation in the nose from the vaccine, and that results in difficulty breathing and more concerns.

So I have, in the next slide, a couple of points to make regarding this, and we'll just then wrap up by discussing the potential options for vaccines. The next slide is to give you a little bit more of a perspective regarding what could have happened with the RSV formalin-inactivated vaccine.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

So in the 1960s, during RSV outbreak, there were vaccines that were produced. And this table shows you the experience of the formalin-inactivated, one particular lot of vaccine that did not protect, and actually was associated with enhanced disease in children who were young from 2 to 23 months of age when they received the vaccine. These are 4 different studies, and what you can see is that the outcome in these cases was pneumonia or hospitalization, not from the vaccination, but from being exposed to the virus after having been vaccinated.

So in the vaccinated group, which is your second column, compared to the control group, which is unvaccinated, the top study, for example, showed a much greater risk of pneumonia, 69% of the vaccinated developed pneumonia versus 9% in the control group. And you can see this is within 2 weeks to several months after the vaccination.

The third row is important. It does show you a study where in the vaccinated group, 52% of children required hospitalization versus 2.5 in the control group. And again, this happened 3 weeks to 11 months after the vaccination. And in this particular study, 2 infants died when they were 14 and 16 months of age after they had been vaccinated early at 2 to 5 months, and after receiving 3 doses of vaccine. So this is the enhanced disease that was reported with that original formalin-inactivated vaccine.

The next slide shows you some of the theories about why this could have happened. And so it's basically two. One relates to the ability of eliciting adequate functional antibody that is neutralizing.

So in the slide, hopefully, it will come up. You see in the bottom panel, the one that says ELISA, you see that these are what we call binding antibodies that are measured by looking at IDG to the S protein. And the column on the right -- I'm sorry, on the left, so the column on the left is showing you natural infection. The column on the right is showing you the responses after vaccination. And again, where it says ELISA, those are the binding antibodies. You see that after vaccination, you have a good response similar to that of seen during natural infection.

The problem is what was seen in the top panel, which is actually now the fusion-inhibited antibodies activities. So the neutralizing antibodies, where, in the vaccinated group, you see that not everyone responded. Actually, some had no response at all to the vaccination. And this disassociation or discordance between binding and neutralizing antibodies is a concern to be associated with enhanced disease.

The next slide is going to then, again, show you how these aberrant immune responses, again, based on antibody-mediated responses, which I've just described, which results in poorly neutralizing antibodies are a problem and the second arm would be T-cell responses. So we know that newborns, the age group that we're trying to vaccinate, are naturally Th2 biased. And that a Th2 response with the formalin-inactivated vaccine was thought to be one of the reasons this disease was -- enhanced disease was seen, where you have now T-cell proliferation and long eosinophils that are on the Th2 side, resulting in immunopathology in the lungs.

So ideally, what we want, in this case, is priming. So the first vaccination these babies would receive would be with vaccines that induce CD8 and Th1 CD4 T-cells that are not the Th2 responses that we're seeing before. So 2 points, neutralizing antibodies and T-cell responses that elicit the right type of phenotype and specificity.

The next couple of slides is just to show you, again, the changes over time, where you see that we have learned a lot and RSV vaccines have shown us that.

Dr. Barney Graham gives a wonderful lecture and he is at the forefront of this specific structure-based vaccine design. So I borrowed this slide from him, where you can see that in the past, some of the approaches to vaccine development, again, resulted in pure immunogenic vaccines, mostly because of the confirmation of the F protein with modest neutralizing activity and that were not effective in clinical trials in protecting either adults or in maternal immunization trials, those who were vaccinated.

While the newer vaccines are really based on, as you can see, vectors or the nucleic acid vaccines, or even virally modified recombinant vaccine, that we'll be able to stimulate that immunity that is necessary, specifically Th1 balanced with good neutralizing antibody production.

The next slide, I think, I'll just probably skip. So if you don't mind, going to 163, because it's just to show you the development of a number of vaccines that are still occurring. So large field happening right now to try to develop vaccines, still with the idea of protein-based or live vaccine.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

But if you go to the next slide, I do want to focus on the children. Because this table, also from a recent publication and immunity review, shows you what hasn't worked and what maybe we should be focusing on. So at the top is a formalin-inactivated vaccine, as I described before, that unfortunately resulted in severe illness and at least 2 deaths in those babies, with the reasons we described.

We have the F-specific monoclonal antibodies that do protect infants against severe illness that they do not result in immunity or memory responses and are limited to a particular group. And then you see how the live vaccines and chimeric vaccines continue to be a good option because of the potential of inducing local mucosal antibody, but also good T-cell responses and potentially protection in the upper and lower respiratory tracts. And the nucleic acid, where you have DNA and the mRNA vaccines, where similar to vector-based vaccines, you see that you can have the induction of both antibody and T-cell responses that do prevent upper and lower respiratory tract disease. So this is where we are, at this point, and it's very exciting to see the possibilities.

The next slide, just to wrap up again, potential strategies to think about as a pediatrician and an infectious disease doctor. I've been working on maternal immunization. You see that for RSV, a couple of different strategies have been considered. We now have, right now, the ability to give passive antibodies at the center for those infants, who are most susceptible. But the potential for maternal immunization continues to be there just as a given direct immunity to those babies. But that would be a temporary solution. Ideally, one would really want to vaccinate young infants, as we said in the first 6 months of life, with a strategy that could combine either maternal or passive antibodies, depending on the age of the child with infant immunization and then toddler vaccination.

And then to end, we could move to my last slide, please, going back to the concept of a pediatric respiratory vaccine. The nice prospect here about mRNA technology is that, as we've heard, it allows the development of a pediatric respiratory virus combination vaccine, where you could put RSV, hMPV and parainfluenza viruses, that could elicit these highly neutralizing antibodies and the right types of T-cell responses with CD8 T-cells.

Because of the history of RSV, I think it will be important, and it's not unexpected that there will be a need to demonstrate that these Th2 virus response that are not seen with the (inaudible). But ideally with a vaccine that was then used to prevent these 3 viruses that caused really the majority of respiratory disease in infants and toddlers, if you could give it between 0 to 6 months of life as a primary dosing with boosters and up to the first 5 years of life, you can see how a substantial impact could be achieved, reducing lower respiratory tract illness in the first year and the first 5 years of life, reducing hospitalization and mortality in the world, secondary infections, and then an important point right now, into microbial resistance, which is a big problem for us, could be affected, in addition to reducing the transmission to vulnerable populations such as the elderly and immunocompromised.

And with that, I would like to end. And thank you so much, again, for the opportunity to present today.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Dr. Munoz, I really appreciate it. It is a real pleasure and honor to introduce our next speaker, Dr. Mark Denison. Dr. Denison is the Edward Stahlman Professor of Pediatrics, Pathology, Microbiology and Immunology and the Division Director of Pediatric Infectious Diseases at Vanderbilt University Medical Center.

His lab has been focused and has been funded for investigations of coronaviruses for over 30 years. Dr. Denison is one of the world's leading experts on coronavirus replication and pathogenesis, and the potential pandemic threat of coronavirus pathogens.

In addition to his academic contributions, Dr. Denison serves on national and international forums for the development of policies for biosecurity and biosafety, and I know we're all really looking forward to his talk about the current coronavirus.

Mark Denison

Thank you. Please let me know if you can't hear me all right. I appreciate the chance to be on this call very much and to speak with you today. It's a challenge. Many of the questions that came to me over time, over the last couple of weeks, pretty much span hold the gamut and would take



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

about 4 hours of conversation. So I'm confident that you'll go away with new knowledge, but disappointed as well in the things that we were unable to cover.

I'm just starting on the first slide, to really be able to discuss my team. The team that's currently active in the BSL3 lab as well as those old and new, who have helped.

And next slide, please. Our collaborators are multiple, and these represent really our long-term interactions, mostly around antivirals. So I'm not a vaccine expert, but I am a Pediatric Infectious Disease person, so I am a vaccine zealot. But I'm not an expert in that field. Nevertheless, having studied the coronaviruses and really experienced SARS and MERS epidemics and the development of those diseases over time, I feel, at least, competent to comment on the issues and the biology.

I guess, what arose in my conversations with Allison and others were the sort of series of questions. And so I want to just pose all the sort of different kinds of questions that I want to prime you for, and then that we can potentially address as I move forward in the talk.

So where did the virus come from, recombination or mutation? What are unique features of replication and evolution? Is the virus mutating rapidly? Immune response and protection, is there cross protection? Is there protection from pre-existing coronavirus? Is there immunity? And if so, what is the durability of immunity? Will this virus become seasonal or endemic? And what are the implications of that for how we think about strategies for countermeasures? What are our approaches to countermeasures? And what can we do to really integrate those, not just thinking one way, but thinking multiple ways? And then the issues of can we predict if, when and how this pandemic will evolve or resolve?

Well, I'm afraid I'm a little bit of -- not, I hope not a prophet of doom, but I hope one of perhaps clarity and honesty in terms of what we know and what we don't know. And what I'd say is, mostly, we don't know.

Everything that's being talked about, about this virus, about SARS CoV-2, COVID-19, I'll refer to them interchangeably, is really related to models of things that we understand, which gives us comfort and gives us a sense that we have a sense of what's going to happen, but we don't -- we actually have no idea because this is a brand-new human virus. Now coronaviruses are unusual, and all the things that we have been talking to today are those that are endemic, that those that have established pathways and mechanism. This is a new human virus with no precedent in human history that I'm aware of, affecting the whole globe at the same time simultaneously.

Even the influenza pandemic of 100 years ago, really circulated slowly around, and there was some background of immunity. We don't know what its impact was. Obviously, that was a profound and devastating pandemic at that time.

But when we think about 7.8 billion immune naive people, susceptible humans. Even if we assume that there is 10x more than our reported 20 million people, that's 0.25% of the human population. And so this virus is really playing in a playground where it's getting to make its choices, and we are having to respond to it.

I'll just deal with a couple of these issues, and then I'll riff on them more as I go through the talk. But the concepts of seasonality and endemicity arguments are really for highly established endemic viruses. You've been talking about some of them today. RSV, metapneumovirus, parainfluenza virus, influenza, et cetera, that have the patterns. Therefore, they have patterns. Therefore, we assume this virus is going to establish patterns.

I don't think we have any evidence for that. This is a virus that is ready to go. There is -- the evidence for selection or adaptation for better or worse is not present. We think about these things on an evolutionary term, we have to think of it in terms of evolutionary selection.

So what is the pressure on the virus to change? Right now, it doesn't look like there's a lot of pressure on the virus to change because it has these opportunities, and it has a world to explore. And the mechanisms for it to become mild or endemic to establish seasonality are not yet there. And seasonality is also a concept that is really based on our observation of what the viruses do, which is actually more migratory. They tend to move from the northern hemisphere to the southern Hemisphere and back. That's, of course, why we select our flu strains, usually from Australia or China at the time of year when it's active there.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Further, a lot of these viruses are not -- really aren't as seasonal, so to speak, in the tropical and subtropical regions. They tend to persist and have low level persistence at all times in those areas. That, in addition to the idea that these viruses are already preexisting in the southern hemisphere and in warmer climates, is not strong, supportive evidence that these are going to be rapidly seasonal or endemic. We just don't know. Further, there's no herd immunity that's established. So there's no selective pressure on the virus from that perspective for rapid change.

From the perspective of a vaccine, I suppose that could be considered as not bad -- good news, in a sense, that the likelihood of a vaccine then being able to reach this virus more broadly is higher than really encountering obstacles at the get-go. So we must -- I think we must plan for it to not be seasonal or a milder endemic virus.

May it have waves? Might it do that? Yes, it might. But there's no data to support that it will. So how do we think about this in terms of our public health response? Well, I think of this as sort of 4 prongs that are likely more. But those have to do with public health response to monoclonal antibodies, antivirals and vaccines.

And I think a public health response of limiting transmission, limiting genetic variation, assessing mechanisms of transmission. Monoclonal antibodies to really think about attacking or providing some prevention or treatment with temporary immunity, interruption of transmission and prophylaxis of population so vulnerable populations as high-risk groups, antivirals for treating acute infections preventing disease progression, prophylaxing vulnerable populations and limiting local transmission. And then vaccines for long-lasting immunity, prevention of disease or infection, interruption of epidemic, limit on disease and subsequent exposures.

I talked to my friends, we worked on antivirals, which I think are very important, and I think are a key leg on the stool. But as a pediatrician, as an infectious disease person and as a human being, I think, short-term monoclonal antibodies and long-term vaccine approaches, particularly for COVID-19, must be established and have to be successful because our ability -- otherwise, this virus is going to have to establish its own herd immunity, and that's going to take a long time.

So in terms of endemic human coronaviruses, I spent several hours last night, going back and making sure that my deep back brain knowledge from 30 years ago and up to this date is up to date. There are 4 human endemic coronaviruses, 229E, HKU1, NL63 and OC43. HKU1 and NL63 were actually discovered after SARS, when people were surveilling for disease. It weren't previously known.

And so the -- these cause up to 15% to 30% of human colds, depending on the report. They also caused lower respiratory tract infection, exacerbation of asthma, bronchiolitis. They maybe more serious in the elderly or are those who have preexisting conditions. But typically, they haven't been that bad.

Their immunity occurs. What's interesting is it's not really clear -- I went back to the study from the 60s and 70s last night, and looked at this issue of durable immunity. And I think what comes up is, at the time, it was -- there was a lot of mixing of viruses, the mechanisms for looking where HAI or some form of neutralization, but there has been really no good genetic analysis done of the viruses because it wasn't possible.

So I think these concepts that there may be limited durable immunity and/or genetic variation are both still excellent. I think we have to come away with the fact that both of those can occur. In other words, you can get immunity that might not be long-lasting. And there also may be some strain variation that's occurring under genetic pressure of some immunity.

It's certainly clear from the really well done studies, particularly volunteer studies that were done with these, that reinfections can occur in the setting of existing antibodies. There were many people that had existing neutralizing antibodies, and were able to be reinfected. And there was also a very high seroprevalence throughout life in people in their 80s and 90s, there was 80% to 90% seroprevalence of the 2 coronaviruses, at the time, that were being tested, OC43 and 229E.

So that's clear, that we all have these antibodies, which raises questions about their ability to really control this new disease because all -- almost all humans will have antibodies to some level against all 4 of these coronaviruses.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

And certainly, they also are seasonal, cyclic, persisting and alternating. All of those have been described with seasonality, more seasonality for some than others. Cyclic, meaning they, one, is in year 1; A, is in year 1; B, is in year 2; A, is again in year 3; and B is in year 4. So they can alternate back and forth. And really, we don't understand complex ecology between the human coronaviruses that are even endemic.

So then we come to the issue of the emerging coronaviruses, and what does that look like? Well, I think it's clear now. We -- I left a slide out where we've been doing the predictions for 20 years about the oncoming pandemic of a very serious as far as like coronavirus. But I think SARS epidemic in 2004, with 8,000 cases and 10% mortality in 32 countries in 3 months, with the clear evidence that this came from bats into -- likely into humans and back and forth into intermediate hosts, was really the shot across the bow that made us very concerned about this and raised our issues. Subsequently, we started looking at vulnerable targets. And by the time MERS occurred, surprisingly in 2012, we really were committed to this process of looking for countermeasures, again, not just the past coronaviruses, but the ones that might come in the future.

SARS was the concern because it had this capacity for serious disease. Why did it go away? Probably because it really required transmission by a serious pneumonia lower respiratory disease, and so it could be recognized and isolated. In contrast, MERS has also interesting in that, it really doesn't seem to transmit as effectively and requires some interaction probably with camels, probably originally a bad virus.

Fewer cases, there's 4 here and 5 there. But what's interesting about MERS is its mortality stays around 30% to 40%, even now after 8 years of that virus in humans. It still remains that high, likely associated with comorbidities. And then, of course, SARS CoV-2, or COVID, with, as of this morning, probably about 2 million confirmed cases and greater than 100,000 deaths -- 120,000 deaths worldwide and over 23,000 in the United States. Stunning, really. I just got off a call where there was a really nice discussion of this. Clearly, being most likely a bad virus. Not -- the smoking gun, that has not been found, but there are ones that are very close.

Well, this is a bad virus. Did it use an intermediate host? I don't know. But it's definitely a human virus now. And it's one that does not need an intermediate host. And so that search is important. But for this current virus, that search is not necessary for us to understand how this virus is working.

So this accelerating emergence of coronaviruses with pandemic potential. And you can see even the host ones are maybe 800 years old, maybe, which from evolutionary terms, is very young, very, very young. These viruses that have been reintroducing into humans, likely all from animal sources over the last several hundred years, some of them as recently as probably 60 to 70 years ago. And then the dramatic appearance of these viruses, really over the last 20 years, suggest something very different about ecology. It likely does not suggest something novel or changing about the viruses, what it suggests is that we are intruding into ecological niches and into environments where these animals exist, where these viruses coexist.

When we look about bats, especially bats are about 1,200 species, probably 25% of 1 million species are bats. And every bat that's been closely looked at is shedding 2 to 5 coronaviruses asymptotically. Several of those have been identified with the capacity to infect human cells directly.

And I want to just comment briefly on this. This is from Vineet Menachery and Ralph Baric in Nature Medicine, 2015. We -- people talked about this concept of viruses, recombining or mutating and suddenly being capable of infecting humans. The concept of that evolutionary belief is complicated and unlikely, but the concept of the models are that there's a mutation, there's a host range variation that occurs in the virus in nature. And suddenly, it has this capacity to infect a secondary host, either an animal or a human with back and forth amplification.

This is possible, but as an evolutionary event, this is unlikely, particularly since there's models that suggest that really what's happening is more like this. That is that in a diverse population of animals that what you have is you have generalists that occur. And there's laboratory experimental evidence to support that this can occur.

Basically, a virus that has a binding to a certain receptor like ACE2. And it gains the capacity to infect not just one species, but multiple species. And then it really demonstrates the capacity to survive and thrive in that general population.

So what does the virus like that lack? Well, it has capacity. It's like a Swiss army knife of multiple tools for different species. What it lacks is opportunity. It lacks the ability to enter into a new population of animals.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

And so this is -- we think what likely happened here, and is likely the source of probably what are really multiple introductions of coronaviruses into humans that just don't persist for one reason or another. And why don't they persist? Or what would it take for one to persist? Well, I think this is a schematic from one of my colleagues, Marco Vignuzzi, from a long time ago now, but it's still relevant. If you start with an animal virus -- I'm sorry, I'm on Slide 179, I apologize for not saying that more regularly.

If we start with an animal virus entering into a naive host, meaning human, in this case, or another animal, that there's so many things that it has to do to be successful. Jumping is not a good analogy for these viruses. A good analogy is a 1,000 mile race with 10,000 hurdles that the virus has to overcome. So that's why we're all around, and that's why we encountered what we're encountering, hope, very rarely. But when we do, that's a virus that has to have a tremendous capacity for overcoming all these obstacles. In terms of being in the host, not killing the host too much, overcoming immunity, being able to replicate, being able to survive in the environment, being able to spread to new hosts. And of course, being able to spread in ways that aren't easily detectable and identifiable by public health measures.

Next slide, 180. This is just showing -- going back to this concept of the generalist and where these exist. This shows a supply [indiscernible]. It's an older one, and the boxes aren't accurately located except within the genera. But I want to point out mostly is, overall, if you see something on here that says BT, that means it's a bad virus. And you can see that they populate really almost all of the different groups of coronaviruses. The ones in boxes are human viruses, except for the ones with the green -- the deep green filling.

And what I wanted to point out about that is that if you look at the upper right up there, where it says 2b, ready-made, pre-pandemic, that there's SARS-CoV, and then there's the current virus, I'm calling NCOV here. Then there's the couple of viruses here that are located that were identified 1995 as viruses are actually able right out of the bat, to infect human cells and to infect mice using the ACE receptor and to cause some version of disease.

This is the first indication that we have these viruses that are existing in nature aside from SARS within this same group. You can see that since the current coronavirus came from that same group, it really targets this as a region where we have to do extreme surveillance and really identify the other viruses that are to come as well as the one that we're taking care of right now, because this is -- the way the world is changing with population and while animal marketing changes in their demographics, rapid travel around the world, we have established a mechanism by which viruses can be very happy with our opportunities that exist in the world.

The next slide, 181, only shows -- I want to make one point on this. This is a breakout, what's called a phylogeny. Basically, a genetic grouping. And you can in the top of this, where it's SARS, CoV, and those are all sort of different strains or different genetic slightly different geographic or animal variance of SARS, coronavirus from 2000 to 2004. Then there's a group that are called SARS-like coronaviruses, where those premade viruses exists. And then down here, where I call it Wuhan SARS coronavirus, which is not the terminology I'd use now anymore.

And then another one is called BAT Rat -- or RaTG13. This is the virus that's really closest that's been identified. It's about 96% nucleotide identity. Then there's a lot of things to make us think that this is really close as they come to being -- showing why this is likely a bat virus.

And there's also these other viruses and pangolins, which are an animal that's been potentially implicated. There's no real evidence that that's occurring, but you can see there's a grouping of those viruses all grouped together, suggesting where this virus came from.

So I don't want to spend a lot of time on clinical symptoms, and this is an older slide from early in the epidemic. Because I really want to talk to you about the biology and my sense of why vaccines are so critical for this. And I've never given talks before where so many people know so much more about the clinical stuff because everybody has a chance to read about it.

But I would just make a few comments. Obviously, this virus can -- the most important things to say, I guess, is that this virus really can look like other viruses. It can be very mild, it can be very severe, it can -- and it doesn't need anything to help it. It doesn't need a secondary infection to help it along, it's perfectly capable of doing this. And there's multiple phases. One is going to be the viral logic, an initial response to the virus component. And the second is really the immunopathology. Essentially, the body deciding it's going to pour gasoline to try to put out a fire and try to burn it out. And so this is really the components of this disease that make it something that we have to be concerned about.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

So I think the basic clinical symptoms are shown here, and I'm not going to go through them in detail.

Next slide, 183. And I think this is still consistent, even though this was early in the epidemic, is that most of the cases are mild, and at the times, there were the conversations about whether this could be a asymptomatic or presymptomatic, and the answer is yes. I think the answer is that this virus can definitely spread from people who are asymptomatic or don't know they're symptomatic yet because it's so mild or preexisting. It can also have a long train of time before and after, which some rare people can shed. This suggests a virus that's really trying to find its niche, and the body is trying to find mechanisms to really respond to it. And I won't go through this. I think people have talked about all the different ways of transmission. I will just say that I'm in favor of masking -- I'm in favor of social distancing. I think that these are our best tools that we have right now to move this along. And I wish I could say when that would be possible to end.

I want to talk a little bit -- now I'm on Slide 185. I want to talk a little bit about the coronavirus replication. Just to take you through, to give you an understanding of what directions we need to go with this virus and things that we can do. The most important thing to understand perhaps are the simplest, that the virus binds to receptors, that's called entry and uncoating on the upper left. The virus will go in by 2 mechanisms. One is called direct fusion, where you can see the particle fusing with the cell membrane in light blue and then dumping its genetic RNA into the host cell. The other is an endosome. An endosome is an uptake vesicle that takes the virus into the cell. And then the interior of that endosome changes its chemical character, which causes for release of -- which causes for release of the RNA. After that's done, the viral RNA is copied into proteins because it's an RNA. Those proteins are processed by viral proteases. The bioproteins all assemble and modify the host cell in what I call double membrane vesicles. And then it begins to copy the RNA, genetic material, make new proteins, assemble the virus particles and release them from the cell. And coronaviruses are really capable of releasing lots of virus from the cell without killing the cell. So I'm sorry, that was just way too fast of a molecular biology class, and I understand if you aren't following that closely, but I just want to make a few points.

One is I won't spend time on this because this has been covered so well this morning, the issues of the spike protein as the target. This is, of course, protein that's really targeted for immune -- for antibodies for vaccines because -- and ideally, for some forms of antivirals, because it's so important and so critical for the virus to get into the host cell. It's required for entry, it's required for fusion. It's required for virulence. It's required for host range. It's required for severity of disease. So all of these things are necessary for the virus to work. And of course, these are the target for monoclonal antibodies, which are being developed in multiple labs. Monoclonal antibodies are essentially bypassing the vaccine strategy and developing the antibodies directly that would work. The advantage is that they could be maybe rapidly deployed, that they can provide temporary immunity. The disadvantages is that, that immunity is not going to be long-lasting, and they would have to be re-administered. And then, of course, the vaccines, including the RNA vaccine that's being developed at Moderna as well as others such as those vectored by measles and adenovirus, and there's many cultures that are being used, and all of which really with the goal of expressing the spike like a protein. In some version, that's immunogenic, native-looking and gives good immunity and, as was said earlier, avoids that immunity from presenting the spike in the wrong way.

I want to make 1 comment about chloroquine and where it might or might not work because this has been so popularized. Basically, chloroquine acts to block the internal changes within the endosome. This is how it's thought to work, although this hasn't been studied in excessive detail. And it essentially prevent the virus being -- from being able to uncoat its RNA and put it into the host cell. That's the key mechanism. It probably has multiple other effects on the host cell. It's definitely not acting as a direct antiviral. It will act as an indirect antiviral. And my concerns with it have a lot to do with it just not being studied in a controlled manner, but also the idea that, in some cases, for example, for chikungunya virus that had paradoxical effects where it enhanced replication and decreased immune effects, along with its cardiac and psychiatric side effects. So I'm glad it's being done in a careful manner, and I think that would be weighed in the information about its efficacy at all.

So then I wanted to just mention a couple of points about viral RNA synthesis because this is the area of our focus. And since you asked me to talk, you have to hear at least 2 slides on antiviral strategies, partly because 2 of them that are in consideration, all the preclinical work was done in my laboratory. And so I just want to give you a sense of this as a -- and I can come back to talking about back to the virus again. So the stage of the virus where replication occurs is called viral RNA synthesis. It's the stage where the viral genome is in the host cell, the proteins have been made by the virus from the virus and now they're copying the genetic materials, so Slide 189, that they are -- the replicate proteins assemble. And there's a protein called the RNA-dependent RNA polymerase. That is the enzyme that all viruses have, all organisms have that have to copy genetic material or the polymerases. Ours are called RNA-dependent RNA polymerases because they copy RNA into RNA. They're highly conserved across coronaviruses and significantly conserved across all RNA viruses in general.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Next slide, 190. This is -- it appears complicated, but let me try to simplify it for you. The top panel on this is a schematic showing the coronavirus expressing proteins that it expresses that are called replicase proteins. These are all the proteins that assemble into a complex. Coronavirus has assembled a really novel, large, complicated complex, and that includes what's called RdRp, that's #12 in red, as well as multiple other proteins. What's impressive about that, if you look down below, the model suggests that these assemble in a way that's really unique for an RNA virus. That is that they create a complex that looks really more like a DNA virus polymerase, with 1 particular feature that was -- this first discovered in my laboratory, which is basically the coronaviruses are to date, the only known RNA virus family that undergoes RNA proofreading. One of this dogma that if you follow any of the science at all is that RNA viruses are so good at what they do because their polymerases make mistakes, but they can't correct them. They lack proofreading. This is true for every other RNA virus, except coronaviruses. So we have discovered that coronaviruses encode a protein. We call it nsp14-ExoN. That actually gives them about 20-fold greater fidelity than other RNA viruses. Meaning, they make 20x less mutations. In fact, they can be very, very stable. We know this because we've genetically inactivated that enzyme. And what we see is that we have a virus that makes lots more mutations, and those mutations are associated with damaging the virus, they make the virus less able to replicate and culture, they make the virus attenuated from causing disease in animals. They impair its overall fitness. And so this is a key element. And I bring it up for the following reason: One is that there's arguments that come up about the virus mutating. Well, we've passaged wild-type coronaviruses in laboratory for over a year, and we may see 5 mutations in the whole virus genome. But if we apply a selected pressure, for example, a drug or an antibody or something else, we can see changes in the virus in a very, very short period of time. Why is that? Well, our model is that because the virus has this proofreading function as a part of a big complex that sometimes that function functions and sometimes it doesn't. So this is our model for the evolutionary role of proofreading. The idea that under no selective pressure -- remember, this is all about evolutionary selected pressure. The virus doesn't sort of do anything. It doesn't care. It just responds to the environment, okay? And that biochemical response that leads to evolutionary change. So under no selective pressures, say, a new virus out in human beings, and there isn't any immunity, and there isn't any pressure on it. And it says, this is cool. I'm doing fine out here, that, that complex may be intact, and that virus may be very high fidelity with very few mutations because that enzyme, that proofing enzyme is working so well. That's a stable genome with limited variation. In contrast, if you apply selective pressure like herd immunity or a drug, a temperature change, a new host, that is possible that, that complex gets disrupted biochemically. And now you have a polymerase making lots of mistakes without corrections, and you make lots more mutations, and the virus can adapt more rapidly over time. It's a -- I hope this isn't too complicated a concept. So basically, the idea is it might be able to have its cake and eat it, too. It can be high fidelity without mutations in some circumstances and low fidelity with lots of mutations that help it to adapt under other circumstances. So this is a feature that is, so far, as we know, unique to coronaviruses, and may, in some ways, explain their capacities to persist in nature and to change host species as often as they appear to do.

So the implications for us from antivirals to spend 1 or 2 -- just a couple more minutes on that, are that we have disrupted this proofreading because we had seen that many different antiviral nucleosides that work to get their polymerase didn't work against coronaviruses. And so this is an example. The black lines here for 2 drugs called Ribavirin and 5-Fluorouracil, which both interfere with the human polymerase. The flat black line running across the top with the circle says that we can increase these drug concentrations as much as we want, and we don't see any impairment in the virus. Going down would be impairment. But when we knock out that enzyme, we see the virus has become very sensitive to those drugs. So this is important

(technical difficulty)

thinking about other issues related to mutations that might be introduced in the presence of vaccines.

And so I'm not going to spend a lot of time on this, but I wanted to let you know that 2 of the compounds that are being in testing or prepared for testing that we worked on in our laboratory into the preclinical testing on, one is called remdesivir, which you may have heard of, which is in active trials. And hopefully, we'll have the results on that soon. What you can see here is even in the presence of proofreading on Slide 194, you can see that even in the presence of proofreading, that drug is very active. The top graph just showing that you increase the dose, even low -- very low doses, sub micromole doses that you get a really dramatic effect on the virus. The other compound is called EIDD-2801, which I just noticed yesterday, was identified as going into humans. I think it was started last Friday for safety and tolerability testing, and it shows a very similar effect of high activity.

Just going to summarize them. I have lots of slides I could show you, but I'm not. I guess what I could say about both of these compounds is that remdesivir is IV and EIDD-2801 is oral. And that they both potentially inhibit multiple divergent coronaviruses, including that bat coronaviruses that



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

have potential for infecting humans. They both surprisingly put up quite a fight against resistance by the virus. So they seem to have high genetic barriers. And resistance is detrimental to the virus. The viruses don't do well when resistance mutations arise. They're both useful for prophylaxis and for printing disease given early in infection. And they both appear to be active against SARS-CoV2, and they have different mechanisms of action.

So I guess I just wanted to come back to finish up with a couple of things about these issues of implications for vaccines because I am -- having shown you the slides about antivirals, I have to say that if I'm rooting for anything, I'm rooting for vaccines as a strategy that we have to have. It's absolutely critical. Why? Well, I think there are precedents for vaccine success in good responses in animal to multiple approaches for SARS and MERS-CoV. Some of these are vectored, some of them are live virus strategies. Some of them are sub units. And that this is important that there can be antibody responses, which are generated, either monoclonal antibodies or other things that can be useful. So I think there are precedents for it. I've mentioned what the concerns were, obviously. So -- and broadly neutralizing antibodies can exist against SARS. The cross reactivity of antibodies is not well demonstrated. Certainly, nothing that's really, really broadly neutralizing and active across SARS and across MERS. And now when people are starting to look at SARS-CoV2, I think that remains to be determined. But I think it's likely that vaccines will have to be developed. I think what this virus points out is the need to develop these in ways that really are capable of really crossing over between virus strains and looking broadly at SARS, SARS 2 and bad viruses, especially in this 2B group. How now universal vaccines can be identified that can really target across those strains, not just the one we're seeing today, but the ones that are going to be coming tomorrow. It's really a cry for a Manhattan Project on vaccine development for this virus group.

I think there's also evidence that immunity doesn't necessarily have to be sterilizing or even comprehensive. I think the data really support the idea that coronavirus immunity is not likely to be lifelong single strain. That's purely speculation on my part, but it's based on models that we have from other coronaviruses. But it does suggest that immunity, even if it's incomplete or non-sterilizing, is likely to lead to infections that are mild or even if you can't get absolute protection. I think that's a better primary goal in some ways than a perfect vaccine that stops everything. I think that may be more achievable. The capability of the virus to adapt and change is well known. So I think we have to understand that responses to this virus, it's possible that it can show the kind of variation and persist, which would lead to modifications or adaptations that might be necessary for vaccines as well. Certainly, vaccines are essential for control and changing the dynamic of the virus. I think there's absolutely no question about that. I think there's also, as I mentioned, the likelihood this virus will persist, flare and recur, feel like better terms to me than direct seasonality. It might be both. [Allusionarily], I don't know how long it will take. But I think that, that -- in the absence of that, I think we need to act as if these are going to be the factors that are going to persist.

And so coming back on Slide 197 to sort of the response. I think what you can see is I'm an advocate or fan of these multiple strategies that would have to be used to approach it with the concept of vaccine development moving forward as rapidly as possible. And I think the model that's being used with the RNA vaccine is one that I'm excited about as a scientist, and very hopeful about as a human being that we're all persisting in this current environment, which is so fraught with concern. We're certainly driving forward with our own work on antivirals and strategies to test the drugs that we have tested, to test them in combination, to test combinations of antivirals and monoclonal antibodies, to look at the response to vaccines and to see how that changes, if that changes the virus, and then how we could potentially target.

So -- and then finally, the last slide, I won't dwell on it, and I'll just stop there. I think we entered -- we talked about a lot of these issues. I hope we addressed the questions, many of the questions that you have. I'm confident you have many more, but I really appreciate the opportunity to present here today and to be involved in the opportunity to really make a difference in vaccine design and testing. And thank you very much for your time.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Dr. Denison. I really appreciate the overview, as I'm sure our listeners did. That was quite an eye opener. I think it underpins sort of our sense of both commitment and responsibility to what we're doing. And I'd like to just take a few moments to walk through what our strategy is for mRNA-1273, which is our vaccine against SARS-CoV2.

On the next slide, on Slide 200, I'm not going to speak. We've heard this. I think the important -- the salient part for us is the focus on this Spike protein. People often ask us whether we should add additional elements, whether we're worried that this is too narrow focus from an immunogenicity standpoint. I think our belief, based on the science, and I think you heard Dr. Denison allude to this, is that this Spike protein is really where the

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

action is. We believe scientifically all the data points to it, not just important for adherence in transmission but for virulence and disease severity. And so from our perspective, and this is also based on our history with MERS and in collaboration with the NIH, it was clear that this should be the place where we're focusing.

On Slide 201, I'm just sharing a little bit of information that is the background of MERS, which is a distant cousin, but yet, I think, informative to our efforts as it relates to the Spike protein. These are data that were done in collaboration with the NIH. And what you see here on the left graph is our ability to induce neutralizing titers. So this is a preclinical model and you can actually see the titers rise up to about day 20, day 21, they get rechallenged. So the group that got dose 2 goes up to about 1,000. The group that got just a single dose continues to stay more or less flat or go slightly down. Then they all get challenged on day 43 and they get challenged with the virus. And what you can see now on the right is the ability of 1 or 2 doses to actually protect, in this case, from viral replication, both in the throat and nose. And then if you look at the bronchoalveolar lavage, which is the ability to inhibit viral replication or measure viral replication in the lungs, you can see that we are able to significantly decrease viral replication. There's still some virus there, but it's a 3-log reduction. Even the single prime here already has an effect. And certainly, a prime boost is quite effective. So it's these kind of data that had given us the confidence, based on previous work, to go after the Spike protein.

Our vaccine here on Slide 202, if you've seen everything else we've done, you'd recognize that, actually, from a molecular biology standpoint, this one is relatively simple, I almost hesitate to say. But this is a single protein, when it's made, it aggregates as a (inaudible) complex on the cell membrane, pretty much expected to do the same way it would if it were in a virion, presents the right epitopes. This one has been stabilized with a couple of mutations based on work done by Barney Graham's team at the NIH, understanding how to best stabilize the (inaudible) confirmation that should lead to neutralizing antibodies. And so while they don't have yet any preclinical data or clinical data to share, this trial, the Phase I, is well on its way. And we look forward to those results. The design of that Phase I is on Slide 203. And this is really a 45-subject trial to begin with that is dosing at 25, 100 and 250 microgram. Dosing at the 250-microgram dose level started over a week ago, and so it's enrolling well. The trial has been amended to include also an elderly population as a small Phase I to start to demonstrate the safety and tolerability and immunogenicity in that population, which is obviously a vulnerable one. In Slide 204, I want to spend a couple of minutes to discuss sort of what's the development path and what should we expect. This is obvious.

As we are seeing the Phase I enroll. We anticipate data in the coming weeks and months from that Phase I that ought to teach us about immunogenicity. And as we in collaboration with the NIH and the NIH are building the preclinical models and the assays required to demonstrate surrogates and correlates of protection based on neutralizing and inhibiting inhibitory antibodies, the question is, okay, how does one continue to develop this? And how do the clinical trial paradigm, how does that jive with the eventual availability and access? And this is an ongoing conversation we intend as the next step to start a Phase II that we'll be able to take us from sort of tens of subjects exposed to Phase I, to hundreds in Phase II. The endpoints for the first Phase II are still going to be to confirm the immunogenicity and continuously expand the safety and tolerability. But I do want to speak to sort of what's the ultimate goal here and how I see this evolving.

On the left is sort of the clinical paradigm of developments. If you go through Phase I, II and III, this has been discussed earlier this morning by Dr. Heath. And as you go through these trials in Phase IIb or Phase III, you're starting to look at clinical endpoints where you're trying to prove that you indeed can prevent disease, prevent disease severity and perhaps leading into less infection. And as you're doing that, you are building the safety database, you're trying to demonstrate that the vaccine is well tolerated. You don't have any untoward safety events. And in that context, people have been talking about the risk for enhanced disease, which I'll come back to in a second.

On the right-hand side is sort of ways in which we could see population usage of people who need it, starting perhaps with the people who needed the most. And in between is sort of the dialogue that has to happen between the sponsors and the regulatory authorities and the other government bodies that ultimately we trust to intervene and support us here in the case of the pandemic. And it sort of goes -- it runs the gamut from a regular approval, which you have once you have clear clinical efficacy. There's a potential for accelerated approval that sort of refers to the alternative pathways of approval that Dr. Heath spoke about this morning. In the case of this pandemic, one would anticipate that, that should be something along the lines of neutralizing antibodies that can be shown to prevent disease in relevant preclinical models and then that one can actually correlate ability of those antibodies back to the titers that we see in humans. And I think there is a growing body of evidence based on clinical disease and transfer of convalescent serum from people who've had this illness. There's a big push by FDA these days to kind of harmonize those efforts and support them under the belief that passive transfer may actually reduce disease severity. And so somewhere, if you connect all those dots, we should be able to, as a field, actually determine what is the appropriate surrogate of efficacy somewhere between Phase II and III that one

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

could envision this leading to an accelerated approval pathway here once we reach that threshold of something, a surrogate that is reasonably likely to predict benefit, and different people will have different definitions of what's reasonable.

And all the way at the bottom, in very exigent circumstances, which this pandemic obviously is one, one can envision an emergency use authorization. And for that, what we need to demonstrate is that this vaccine may have benefit in that language taken straight from the guidance. This, of course, is problematic because typically, we can demonstrate that a vaccine may have benefit fairly early on when we haven't yet fully demonstrated the safety and tolerability profile. And so somewhere between our ability to advance trials on the left side as rapid as we can, and the stepwise demonstration of potential utility all the way through to full clinical efficacy, I think there will be a dialogue with the regulatory agencies as to when and how is the right time to enable broader access to this vaccine. And I think that's a dialogue that's ongoing. In terms of time line, I expect that in the summer, we will start to see the immunogenicity of the Phase I, and then hopefully thereafter, hopefully, within Phase II, such that we should be able to hone in on a dose and start our Phase IIbs and potential Phase IIIs in the fall of this year. And the success in terms of demonstrating safety and efficacy there will obviously depend on the efficacy of the vaccine, our ability to enroll subjects who are still at risk and who unfortunately will still have an attack rate so that we can compare rates within placebo and vaccinated people.

So this is sort of the development plan ahead. I don't want to spend -- I want to spend 2 minutes on this notion of enhanced disease. It has received a lot of noise. The concept here, as Dr. Munoz had alluded to, sort of goes back to the history of formalin and activated vaccines back in the '60s. And people have come up with various animal models that may or may not be accurate surrogates of the pathology seen in the case of enhanced disease. What is pretty clear to me, I'll make the following 2 statements. Number one is enhanced disease is a clinical phenomenon. So really, the way to think about it is, one has to rule out the fact that [vaccination] will indeed cause enhanced disease. And as such, it is something that we will continue to monitor for in clinical trials.

Now to date, what we've seen with our platform in the cases such as hMPV/PIV3 is that we do not see the preclinical correlates and, in fact, our platform, when the antigen is designed right, as we believe is the case here, has a propensity to cause the right type of neutralizing antibody with the right kind of T cell responses, which Stephen Hoge has shown earlier today. So I don't have any untoward concern that this is an issue with the antigen and the platform that we've designed to date. That being said, it does remain a theoretical risk. And until we can prove it in the context of large randomized trials, it just is part of the safety that we need to demonstrate. I do want to make a distinction, though, of enhanced disease as a safety event because it's different from the way we typically think about safety of vaccines. So vaccines go into healthy populations, and they need to be -- they need to demonstrate in a stepwise manner the safety and tolerability. And so when one thinks of safety and large populations of healthy people, one needs to rule out infrequent and rare and then very rare adverse events that are sometimes end up at having been associated with vaccines.

Now the concept of enhanced disease is not something that one can demonstrate as a safety concern in an individual patient. It ultimately has to be a population determination and it's encapsulated by the benefit/risk. So if we can indeed show that our vaccine, with use of disease severity cases, reduces hospitalizations, et cetera, then by definition, it does not

(technical difficulty)

disease. In fact, it protects from disease. And so all of that is a long-winded way of saying that this will remain a clinical question. However, it should not hamper our ability to rapidly in a step-wise responsible manner address the potential utility of this vaccine, and that's the way we're thinking about the development of mRNA-1273.

With that, let me then give the floor to my colleague, Juan, who really has the major task of getting all of us ready to supply the need out there for the people who are going to need this the most.

Juan Andres - Moderna, Inc. - Chief Technical Operations & Quality Officer

Hello. Thank you, Tal. Hello, everyone. Can you hear me okay? Okay. So I've been in Moderna almost 3 years, leading manufacturing, technical development and quality. As a way of introduction, I've been in the industry over 30 years. 18 years working for Eli Lilly across a number of different



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

countries, 12 years in Novartis, and my last job there was leading manufacturing worldwide across all Novartis divisions. So what I will do today is provide an overview of manufacturing in Moderna and how it applies to our candidate for coronavirus vaccine mRNA-1273.

Slide 206, please. So we make mRNA and LNPs in a very similar way across all our products in development. And we start with what we call a starting material, which is our DNA template of plasmid that we use in very small quantities, together with enzymes, nucleotides and buffer at the right temperature to create mRNA. And it happens very similar to what -- to the way it happens in the body. Once we have mRNA, obviously, we purify it through a downstream process. And then we form the lipid nanoparticle that is going to surround and protect the mRNA as its final drug product to be injected in the body. So we fill the LNPs inside vials and into the formulation that it is ready to be done. This process is cell-free. We don't need big bioreactors, like in traditional biotech industry. We use the body as the bioreactor. And this means we are much less asset intensive as the normal biotech industry, which makes this platform also faster in the way you scale up and you make product. Next slide, please.

So as a new platform, we have had to solve a number of different questions from the beginning. And we have made a lot of progress understanding our process, but what I want to highlight is also how we measure the different properties of the product that we make. Essentially, we have focused first on quality.

Next slide, please, 208. Integrating platform research, technical development and manufacturing has been a key success criteria. And I will talk a little bit later how this comes together in our manufacturing site in Norwood. At the end of the day, when you're creating a new platform, it is all about teamwork. Many disciplines come together in creating this new platform. Next slide, please, 209.

So let's look at how we started. Before we had our own manufacturing site, we have to use several third parties across the world. And obviously, they helped us significantly, but our supply chain was in a number of different places. It was divided into -- in Europe where we made mRNA, then we did LNPs in the United States. We got the plasmid from another location of (inaudible) material. And then we did fill/finish also in another location, and then we ship the samples to do QC in another place. And we have to integrate all of that together through a small number of people.

So Slide 210, please. We decided to build our manufacturing site and integrate all the different elements of our manufacturing chain that I described before in only 1 location. And we did it as well with 1 obsession. And the obsession was about learning. As a platform, what we learned for a product, we can quickly replicate for others. And that's why we built not only all the different elements of the supply chain, but also we build it in a digital way so that we could apply this, and we can gather the data and apply it from one part to the other, or one product to the other.

Next slide, please. Now while our side main mission is to make clinical trials, that's where we started, we built it with the standards and scale to allow us to launch and commercialize from here if we needed to. So the platform is very scalable. And it has, inside the same footprint, inside the same manufacturing site, 3 engines. We call it -- we call them 3 engines in Slide 212. The first one is the preclinical engine, and this is where we make material for research, for all the preclinical testing that we need to do. The second engine is the personalized vaccine unit, and in that locations, we make 1 batch per patient, 1 batch per product. So 1 patient equals 1 batch. And the third engine is our clinical engine. This is where we are using in good manufacturing practices with GMP standards to supply our clinic at this stage.

Slide 213. So what I'd like to do now is describe a little bit each one of these engines. The preclinical one, just to give you an idea, we have made over 23,000 different constructs of mRNA. A research scientist can tie the sequence of mRNA, send it electronically. It is received in preclinical, and a few weeks later, 4, 5 weeks later, there is a vial that is received with the product that was ordered. All the data in there is integrated, so we can learn from one and the other. And we can, through artificial intelligence, see then main suggestion to the scientist in terms of the structure of the mRNA. The equipment is -- there is fully robotized.

So the second engine, in this case, as I mentioned before, we use it to make our personalized vaccine unit, we have made around 100 batches to date. And of course, the scale is a little bit larger than in preclinical. And this is -- this has the repetition in the number of batches that allows you to do very fast replication because it is personalized. So think about, in my experience, think about the number of batches that you make when you're in commercial. You reach 90 batches, 100 batches in your second, third or even fourth year when you are commercial. So we have had the opportunity to make all these many batches that it is allowing us to learn, to optimize and to become more efficient.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

The last engine is our clinical engine. And here, we make one batch for many patients. Our scale varies depending on the different program and depending on where the development candidate is in the clinical process. And this allows us to scale up as we need and use it for a number of different patients. Here, you can see that the 5 grams to 75 grams is what we've been doing to date, and I'll speak a little bit later as well on how we are thinking to scale that beyond those numbers.

So Slide 214, please. So what we know now in terms of our platform technology is that we have similar processes, we can implement fast the process improvements that we have. We are cell-free, which means also that we need less -- we are less capital-intensive. We need a lower amount of money to scale our process. And then we also know that our path has been focusing on quality, on speed. Now we are with scale and, in turn, that will give us the economy of scale that we need in the future as well, making this affordable.

Next slide, Slide 215. So now that you have an overview on our process and our platform, let me take it to our candidate for coronavirus, our mRNA-1273, which is part of our pipeline, and we didn't plan for it. It just came at the beginning of this year, and we tackled it very decisively.

Slide 216, please. Now interesting enough, we had to use for this product the 3 engines that we had in -- that we have in Norwood, and that helped us go very fast. So we made -- we used the preclinical to make a few constructs very, very quickly. We used the personalized vaccine unit in order to manufacture the first clinical batch that we are testing at this moment in time in Phase I, and we are using now the clinical area to make our Phase II material and also do all the scale-up activities that will allow us to continue developing the product.

Next slide, please, Slide 217. So let me take you through the time line so that you can appreciate the speed at which we were moving. Day 1 here in the slide was January 13. We called that day 1. We, in collaboration with NIH, we selected the amino acid sequence that we were after. A few days later, we have the digital sequence, and we started making this in our preclinical area. We put all the documentation together that will allow us to make the first clinical batch directly. And by February 7, we had manufactured the first clinical batch really, really fast. We have to wait for a couple of weeks, get all the different testing done, including sterility. And then we eventually shift to the clinic. And then the first patient was dosed 2 months after January 13. We have initiated at this stage our Phase II manufacturing, obviously, going in parallel, and also scale up activities that will allow us to go much higher in scale as we progress the development of our candidate.

Next slide, please, 218. So what we are planning at this stage is to scale capacity in 3 different stages. Obviously, we have our existing capacity in Norwood that provides us with tremendous advantages, as you have seen, and we are going to scale that we have already used in other construct for what we call now the Stage 1. This is where we are. In Stage 2, we want to build several nodes of capacity in addition to Norwood with the help of government industry and private institutions and then make millions of doses. Stage 3, it will be later, we are only in this conceptually, which is obviously having our own manufacturing sites if that is needed.

Next slide, Slide 219. So one of the points that I want to make is that we cannot solve these sequentially. We have to act in parallel in a number of different fronts. So working in the scale that we have and working in the next scale at the same time that we perform the clinical trials, at the same time that we invest on different nodes of capacity cannot happen sequentially. It needs to go in parallel if we need to go for speed.

Next slide, 220. And I am going to bring in this last slide the human factor. I cannot emphasize enough the passion of everyone involved in this journey today. It is not only employees who have tackled these with a tremendous excitement from the beginning, but also suppliers and partners. People are working nonstop with tremendous motivation to basically to take this forward and help people.

So let me stop here. Thank you for your attention. And Tal, back to you.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Juan, for that overview. It's now my pleasure to introduce Kathy Edwards to the panel. Dr. Edwards is the Sarah H. Sell and Cornelius Vanderbilt Professor of

Pediatrics at Vanderbilt University Medical Center. Dr. Edwards is a pediatric infectious disease expert who has contributed to the field of vaccinology for more than 40 years through her service at the CDC, the NIH, the WHO and the Infectious Disease Society of America. In recognition of her

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

extensive contributions, she was elected in 2008 to the National Academy of Medicine. And in 2016, she was further recognized with the Charles Mérieux Vaccinology Award from the National Foundation for Infectious Disease. Dr. Edwards, the floor is yours.

Kathryn Edwards

Well, thank you very much. I've enjoyed participating in the several hours before and have learned much. And obviously, some of the issues that have been discussed are really helpful because they are going to be things upon which I discuss -- actually what happens next.

So what my focus today will be on what is the role of the Advisory Committee on Immunization Practices or the ACIP in formulating vaccine recommendations for the United States. So the objectives of my presentation are going to be several. First, I'm going to talk with everyone and discuss what the ACIP is and how it works. I'm also then going to talk about the role of the ACIP and plan that it plays in formulating vaccine recommendations. I'm going to provide you the specific criteria that are used to formulate these recommendations and how pharmacoeconomic data are considered. I'm going to use the CMV vaccine as a model upon which to plug into this process. But certainly, other models and other burden data that we've seen today would also be very applicable for applying to how the ACIP will look at a myriad of vaccines. And then finally, is there an equivalent of the ACIP outside of the United States.

So on this next slide, 224, this is a nice overview of how vaccines are developed, tested, licensed and recommended. As you see at the top, vaccine development and testing occurs when a company or a biotech firm applies to the FDA for a Biologics License Application or BLA. This BLA then certifies the manufacture of vaccine and also within that, conducts and works with the company to formulate a series of studies going from Phase I to Phase III, as you have heard, which then will allow the vaccine to be submitted for licensure. The FDA will take the dossier that the company prepares and will only take the dossier that the company prepares, so that has to be inclusive and really give all of the data that are needed for the FDA to make a decision. The FDA will then go over that dossier very, very carefully, and will have several questions that they will present to an advisory committee called the Vaccines and Biologic Product Advisory Committee or VRBPAC. I was chair of that committee last year for several years. And what that committee does is a committee of academics, of scientists, of clinical trialists, of epidemiologists that will address the questions that the FDA asks prior to licensure. And usually, those questions are, do you think that the vaccine has been shown to be safe? Do you think the vaccine has shown to be effective? Do you think that the vaccine plan for post licensure is adequate to assess the vaccine? And the VRBPAC votes on all of those measures, but ultimately, it's the decision of the FDA whether they want to accept the vaccine information and to actually license the vaccine. Nearly always that licensure does require post-licensing or Phase IV data to be prepared as well. However, once the FDA license the vaccine, it really becomes the purview of the advisory committee and the ACIP to recommend how that vaccine will be used. As you see underneath the FDA licensure, there is a column that says CDC consideration, and there is a column that says the American College of Physicians Board of Regents consideration. What happens is that slightly over half of the vaccines that are produced and made are purchased in the public sector. So all of the public sector use and approval for payment comes from CDC recommendations within the public sector.

In the private sector, the recommendations are often the purview of the American College of Physicians for adults, the American Academy of Pediatrics for children, the American College of Obstetrics and Gynecology for obstetricians and gynecologists. And they all have advisory committees that advise the Board of Regents as well.

I'm going to focus mostly on the CDC consideration, however. And over the past decade, there has really been a lockstep between the CDC recommendations and the recommendations of other advisory groups such as the Academy of Pediatrics. And so I think that understanding the public sector will really be pivotal in understanding all of it.

I'm going to now then go to the next slide. Now this is a slide that summarizes AAP approval and ACI recommendations. And you've heard on several occasions, first, very nicely from Dr. Heath, about how vaccines are approved, either the traditional or accelerated pathway or the animal rule, and we've gone over some of those. The traditional approval generally includes an efficacy study were vaccinated and unvaccinated, but certainly accelerated approval or approval with a correlate of protection of an actual immunogenicity marks can be done with accelerated approval and animal rule approval, which is approval based on animal testing. There tends to be much more extensive post licensure safety assessment with accelerated approval and animal rule because, obviously, we still want to make sure that the vaccines are safe. But as I said before, then the recommendation comes from the ACIP, how the vaccine is going to be recommended for people at various ages and risk groups.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

So the next slide, Slide 226, outlines the functions of the ACIP. The ACIP advises the Director of the CDC regarding the use of vaccines for effective control of vaccine-preventable diseases in the civilian population of the United States. And the ACIP just had its 50th birthday. So it's been doing this important function for a number of years. Secondly, it also provides advice regarding the use of a new vaccine when it is licensed in the United States by the FDA. And third, it establishes and periodically reviews the list of vaccines for administration to children and adolescents because what the ACIP votes on then is approved for the entitlement program -- program vaccines for children. And then it allows the vaccines batch that are recommended, then will be purchased in the vaccines for children program. The membership of the ACIP is very controlled and very stringent. There are a total of 15 voting members in the ACIP. 14 of them are subject matters in vaccinology, immunology, pediatrics, internal medicine, nursing, family medicine, virology, public health, infectious disease and preventive medicine. I personally have been a member of the ACIP, and my focus is on vaccinology, pediatrics and preventive medicine. There is also 1 consumer representative who represents the perspectives of the social and community aspects of vaccination. The voting members are -- will vote on each vote, and a simple majority is required for a vote to pass. There are several ex-officio members, in fact, there are 8, and these individuals are nonvoting members, but they are important members of the vaccine community. So they are the director of the vaccine injury compensation program, a member from the Assistant Secretary of Defense, the undersecretary for the VA, they -- a representative from the CBER at the FDA, Medicaid, NIH, DMI -- CIM and the Indian Health Service and also the Vaccine Program. So these members are also in attendance at each of the 3 ACIP meetings that are held every year.

There are also, on the next slide, 228, there also are ex-officio members that are members of communities that are very important and nonvoting members, and you'll see those are listed there as well. I'm having a little trouble advancing my slide here. There we go. Okay.

And so this is -- there are 31 liaison representatives from professional organizations, as you see, and they also are in attendance at the ACIP meeting. The real work, however, of the ACIP in preparation for voting occurs in work groups, and the work groups are subgroups of the committee, and they review relevant published and unpublished data and develop recommendations for presentation to the ACIP. They are responsible for collection, analysis and preparation of all the information, which ultimately will be discussed and voted on by the ACIP. They not only will be privy to the information that the pharmaceutical company that has licensed the vaccine provides them, but they also will be privy to other studies to other literature, and a lot of the actual work that is accomplished in the collection of these are by members of the Centers for Disease Control. The work groups review specific topics in detail, they clarify issues in a way that really helps the ACIP voting members to make informed and efficient decisions, and with the best and most current information.

There are 4 permanent work groups, the Adult Immunization Schedule Work Group; the Child/ Adolescent Immunization Schedule Work Group; the General Best Practices Work Group; and the Influenza Vaccines Working Group. There are -- the remainder of the Work Groups are task-oriented, and these are developed in response to specific needs and are disbanded when the task at hand has been completed. A Work Group has already been established for COVID-19 in the ACIP.

The composition of the Work Groups are also very controlled. It must include 2 or more ACIP voting members, 1 of whom will be the Chair. It must include CDC staff members who are very active in acquiring and assimilating data. It also includes an FDA member who will be knowledgeable about the licensure process. And it may also include ex officio members and liaison representatives. It also often includes experts, and currently, I am a member of the expert Work Group for tests. Only the appointed ACIP voting members may chair the Work Group, and on occasion, vaccine experts are -- can serve as consultants as I do.

Members with a potential conflict of interest cannot serve on the Work Group. If an individual has a unique experience, then that person may serve as a consultant, but will not be able to participate in any policy deliberation. The conflict of interest declarations are signed by the Work Group members, and they are repeatedly reviewed so that there is not a concern that there has been a conflict in the voting and in the preparation for the voting.

The functions again are to review the data and to come up with options for voting to present to the ACIP during the public meetings. And they then are formed when the update about existing recommendations are anticipated based on new data or when a new vaccine is licensed. The ACIP, however, is very forward-looking in that it closely follows vaccines that are under development, and in general, Work Groups begin reviewing data at least 12 to 18 months prior to the decision for licensure. And indeed, this length of time depends, in some ways, with the complexity of the topic and the available data. And as I mentioned to you before, currently, there is now a COVID-19 Work Group.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Once the ACIP findings are deliberated upon and a vote has been taken at the ACIP meeting where the question is approved, and we'll go over that in just a minute, then the ACIP has a very standard way upon which its recommendations are disseminated. The committee's recommendations are forwarded to the CDC director for approval. Generally, those occur quite expeditiously and certainly, in an epidemic, would occur very expeditiously. These also have to be reviewed by the HHS. And with the approval, then they are posted on the CDC's Morbidity and Mortality Weekly Report or the MMWR. This represents the final and the official CDC recommendation for the immunization policy for the U.S. population. Professional organizations will also work with the ACIP to develop annual and childhood schedules as we mentioned before.

Now I want to spend the last part of this discussion talking about how the recommendations are actually formulated. And this is done in a very systematic way called "grade". So as you'll see in this schematic for the "grade," the questions are formulated. There is a systematic review of the literature for each outcome that is anticipated on the vote. There is an assessment of the quality of the evidence. A randomized clinical trial, placebo-controlled, would certainly have a great quality of evidence and observational study.

Then in the next approach, there is an assessment of the value of the vaccine, its health economic data and actual implementation issues that would need to be surmounted and dealt with in order for the vaccine to be delivered to the individuals who are recommended to see it, and then finally, formulations of the recommendations through the ACIP meetings.

In the past 2 years, there has been a form that is used very strictly for the -- collecting the evidence and looking at the aspects that are needed to make a recommendation for a newly licensed vaccine. First of all, the question has to be where -- what population, the target population, the age, the sex, the immune status and pregnancy. We're on Slide 234. The intervention, the vaccination, the comparison that will be used, and what is the outcome that will be assessed, both in terms of prevention of disease and also adverse effects. As is shown on Slide 234 by the arrows, the question in the criteria, is the problem of public health importance? That will be assessed by available scientific evidence on the burden of disease, the target population, and if there is no published evidence, then expert judgment on public health priorities will need to be accumulated.

Secondly, how substantial are the desirable effects? Is the vaccine effective? What is its duration of protection? Is there evidence of herd immunity? On Slide 235, how substantial are the undesired anticipated effects? Are there undesirable effects of the vaccine on the individual or the population? Do the desirable effects outweigh the undesirable? Is the benefit of the vaccine greater than the risk? What is the overall certainty of the evidence for the critical outcomes? Are the data conclusive?

And finally, on this slide, what is the target population? And does that target population feel the desirable effects are large relative to the undesirable effects? No vaccine that remains in the vial without being administered to the -- to targeted populations is effective, so it's important that it will be something that will be accepted by the target population.

Next slide, 236. Is there important uncertainty about variability on the value? Is the intervention acceptable to the key stakeholders? Is the intervention reasonable and efficient use of allocation? And is the intervention feasible to implement?

The final scorecard upon which a vote will be formulated and will ultimately be decided will be formed here. So what the Work Group will say is what type of recommend -- first of all, is there sufficient information to move forward with a recommendation? If the Work Group says yes, then they will formulate the type of recommendation. They do not recommend based on clinical decision-making or recommend depending upon the doctor. Or finally, do you recommend the intervention universally widely to all individuals? And so those are the buckets upon which the decision can be made.

I'm now going to walk through expeditiously some ways that this may -- might indeed be used as a model for the cytomegalovirus testing. Obviously, all of the other vaccines that were talked about could be addressed in this way and will be addressed if they are licensed and recommendations are made.

So first, is the problem of public health importance? What is the burden of disease? Well, we've already heard today that congenital CMV has a significant disease burden. Each year, in the United States, 1 in 200 infants are born with congenital CMV. That's around 20,000 babies. Most of the infants are asymptomatic. However, they may go on to have hearing losses. But about 20% of those infants have significant long-term health problems, microcephaly, early death, severe retardation, hearing losses and various degrees of developmental disability.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Secondly, how substantial are the desired anticipated effects? As you heard earlier, gB, which is a protein of the CMV vaccine, is a vaccine candidate and was actually introduced in a vaccine trial that both Dr. Munoz and I participated in and was led by Dr. Bernstein. As circled below, you'll see that after 3 doses, prevention of CMV infection in seronegative adolescent girls was shown to be 42% effective. However, the confidence intervals were very wide, suggesting that this vaccine could not definitively be stated that the vaccine is efficacious. So obviously, it's highly unlikely that this vaccine would have ever been licensed, but I'm just giving you an example of how vaccine efficacy might be used.

For another example, we might look at when the pneumococcal conjugate vaccine, the 7-day vaccine, was licensed. The vaccine efficacy was 98% for prevention of invasive pneumococcal disease, with very tight confidence intervals. So the more efficacious the vaccine, the more compelling that it will be. However, if we're going to say that a COVID-19 vaccine were licensed and it were 50% effective with clearly confidence intervals that show that, that would be its efficacy, I think, at this time, that would be a very appealing kind of efficacy. So depending upon what we're seeing and the confidence which we can predict the efficacy, obviously, the interpretation and the level of efficacy will not always be the same.

Secondly, I want to just cite some adverse events, how substantial are undesirable adverse events. And on the left, on the bottom, you'll see these are adverse events that we're seeing in the placebo recipients in red, and in the purple, in the gB vaccine, recipients from Dr. Bernstein's study in the purple. As you can see here, that there was a little more fever or a headache or other symptoms, but by and large, this vaccine was highly well-tolerated. In the CMV vaccine to the right, which was not used in normal healthy people but was used in patients that had cancer and had bone marrow transplant, you will see that the drug-related adverse events were much higher. And so when a vaccine is given to normal healthy people and certainly normal healthy little kids, it's very imperative that the safety profile be excellent. If it is given in individuals who have underlying conditions or have cancer or have underlying problems that you want to use the vaccine for, then the tolerance for adverse events will obviously be much greater.

Next slide, on Slide 242, the overall certainty, the target population needs to be addressed. And I want to spend just a little bit of time talking about target populations. And there was recently a supplement to the Journal of Infectious Diseases, that just came out earlier this week actually, that looked at issues to consider when you target various people. And so for the CMV vaccine, certainly, many people in the trial that I participated in, we targeted women of child-bearing age, so that we could immunize the women so that they could have the antibody and they could be protected from getting CMV while they were pregnant. So certainly, the issues when you consider -- when you vaccinate women of child-bearing age, you have to screen them and make sure that there's seronegative. You have to tell them that -- about the risk of CMV, so placebo may -- participants in the study may be more cautious about hand-washing and may actually reduce the number of infections that might be seen in the placebo recipient. And then also, you have to look at the vaccine in terms of intrauterine transmission. So again, thinking about this will be important, and as we all know, pregnant women are very, very intent on protecting their babies, so that the motivation for a pregnant woman to take a vaccine to prevent disease in their baby may indeed be very great.

We could also, however, prevent CMV disease in toddlers, and we could prevent CMV disease in toddlers and toddlers are often those who give their -- the CMV to their seronegative mothers. So we could immunize the toddlers. But if we did that, we would be immunizing the toddlers to protect others. So is that ethically fine for us to immunize little children who can't tell us that they want to be vaccinated to prevent the disease in their mothers? Again, these are issues that are dependent upon who is being targeted and what the benefit is to each individual person.

And then finally, there does have to be an assessment. Is this a reasonable and efficient allocation of the resources? So there does have to be cost-effectiveness analysis that is done on each of these vaccine candidates.

And on Page 246, this is a summary slide that was just taken from an article that summarized the cost-effectiveness model in the past 12 vaccines that were licensed for the ACIP. And it's not important to actually look at all of the issues, but I think you'll see that from the cost perspective, that a lot of the costs that were assessed were societal, the direct cost, but also a number of the assessments assessed indirect cost as well. So this is a big part. And a lot of this is driven by the literature, but also the CDC has a number of economists that also address this. But many times, companies when -- are -- also sponsor these economic assessments so that they can project what the benefits will be and also the potential for compensation about -- for the vaccine.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

And then finally, just as I said before, after going over all of these things, the Work Group will have to say, is there sufficient information to move forward? And then there will be a vote and the ultimate vote will be, do we recommend? Do we recommend it based on clinical decision-making? And do we recommend the intervention universally?

I'm going to give just very -- a couple brief examples of how this has worked over the past several years. So in 2015, there were actually 4 vaccines that were licensed by the FDA. One was a flu vaccine, was an adjuvant for older people. One was a DTP and polio vaccine for children. One was BEXSERO, which was a vaccine for serogroup B meningococcal disease. And one was an anthrax vaccine. And as you can see here, that FLUAD has an accelerated approval, that Quadracel had traditional, but both the BEXSERO, based on immune correlates, and the anthrax, based on the Animal Rule, based -- those were recommended and -- or those were licensed in that way.

However, I also wanted to point out that an A recommendation is a recommendation from the ACIP that the vaccine will be given to all individuals and recommend it to all individuals to which its directed. And that's in contrast to B, which is BEXSERO or bio anthrax (sic) [BioThrax], and that is, that in that -- that the decision is up to the doctor and to the patient. And by and large, when you have a B recommendation, the uptake does not -- is not the same as when you have a universal recommendation.

In 2006 (sic) [2016], there were more vaccines that were licensed. And as you can see here, that by traditional accelerated pathways, almost all of them, except for one, were recommended by -- for, A, for everyone, and there was no recommendation that was given for the H5 vaccine, but was put in the stock.

Finally, there is a global vaccine advisory group for the WHO, and that is the Strategic Advisory Group of Experts or SAGE. And they have much the same function as the ACIP does for the global community. There has been a push for every country to have a vaccine advisory group like the ACIP called the NITAGs, and at this point, about 140 countries have, but it's not universal.

So thank you very much for the -- this opportunity, and I would like to say that, I guess, the bottom lines are that the ACIP recommends how licensed vaccines are to be used. This decision is done in a systematic and data-driven approach based on epidemiology and burden, vaccine efficacy, effectiveness, vaccine safety, the quality of the evidence, economic evidence and implementation issues that the recommendations for all the vaccines, CMV, hMPV and PIV, will be guided by these very clear and well-articulated factors, and that the global advisory group for the WHO is SAGE.

Thank you very much. I appreciate being a participant of this on this day, and I have learned a lot. And thanks again.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you very much, doctor. This is Stéphane. So on behalf of the Moderna team, I would like to thank our guest speakers, and I would like also to personally thank my team for the presentation and all their hard work here.

Let me just close with a few slides, starting on 253. I won't spend too much time on it as you got it in the introduction and through the day. We are extremely excited about the potential of mRNA vaccine to disrupt the industry, a very large product opportunity, higher probability of technical success, a velocity that is compared to none of the old technology and a greater capital efficiency, which we are excited about.

If you look to Slide 254, the current development pipeline could have potential peak sales of \$6.5 billion to \$12 billion. If you just put that in perspective to Slide 255, that could make Moderna one of the largest players in the vaccine space. And if you look at 256, this is actually without even counting all the exciting new programs that Stephen Hoge and his infectious disease teams are working on in the labs. There are more vaccines that the team is trying to optimize so that we could take them to the clinic to go prevent important infectious diseases.

So if you look at Slide 257, we spent the last 5 hours together looking only at the prophylactic vaccine on the far left of Slide 257. And this is why we are so excited. We see infectious disease vaccine as the backbone of the Moderna growth. As we shared in our shareholder letter of 2019, we think this is how we're going to potentially get our first BLAs and build the company and turn into a cash flow-positive company. But look at



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

everything else we have. We have a systemic secreted and cell surface therapeutics modality that can do infectious disease antibodies, like with therapeutic MAB, that can go after a rare disease, that can go after an autoimmune disease.

Then you have all the exploratory space that we are still investigating and are very eager in the months and quarters to come, to get the additional clinical data to decide if those technologies can graduate into commodities or not. This is going to be exciting times. And then there are things, as we discussed, that are not even on the slide that complement our preliminary work with Vertex.

So to close on Slide 258, the company mission is clear. We believe that we have a once-in-a-lifetime opportunity to create a new class of medicine to help millions, to prevent diseases through vaccination and to treat diseases.

Our mRNA and formulation science is strong. We continue to learn weekly. We continue to be at the forefront of these new science fields. I believe that no other group has the scale that Moderna has to do the type of science we do.

Our process development team or technical development is making incredible progress, and I'm confident in the ability to scale the company into a commercial company from a manufacturing standpoint. We have great teams across the company of highly motivated employees that have energy, passion, commitment, who see this opportunity to create a new class of medicine. The company is well capitalized, with close to \$2 billion of capital to invest in a business between cash and grants, allowing several years of runway into our ability to invest and keep investing in these challenging times. And we are getting focused on getting ready to file several BLAs. I have never been more optimistic about Moderna's future.

With that, we would like to take your questions. Given we are all social distancing in different locations, it will be helpful if you could tell us when you ask a question who you're asking the question to. Thank you. Operator?

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) And our first question comes from Maxwell Skor with Morgan Stanley.

Maxwell Nathan Skor - *Morgan Stanley, Research Division - Research Associate*

This is Max Skor on for Matthew Harrison. I had 2 questions. First, in regards to manufacturing, can you elaborate on the current capacity for manufacturing the COVID-19 vaccine? At your Norwood facility, could we assume you're currently producing hundreds or thousands of doses per month? And also, in regards to antibody levels, how antibody levels from COVID-19 serological surveys impact your view on potential vaccine success?

Stéphane Bancel - *Moderna, Inc. - CEO & Director*

Thanks, Max. So maybe I suggest Juan to take the first one and then Tal.

Juan Andres - *Moderna, Inc. - Chief Technical Operations & Quality Officer*

Okay. So thank you for the question. I'll take the one about manufacturing. So right now, we are scaling up the process to be able to produce in Norwood millions of doses. Obviously, the amount will depend a lot on the outcome of the first clinical trials, where we will know the dose that we are shooting. But the facility is ready to have or to produce doses in the medians. We are already working, as I mentioned before, with very experienced CMOs that -- and we are evaluating the potential to even scale further in parallel in a number of different nodes.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

And then the last point is the technical development to scale up to levels that we have not done before that is happening right now. And that will take us to even higher levels of capacity. As I mentioned, we are working in parallel. We are working with raw material suppliers. We are working with equipment manufacturing, technical development. We are making several assumptions to succeed with those. And those will tell us whether we have tens of millions or hundreds of millions of doses available, working with the different institutions.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thanks, Juan. Let me take the question on antibody levels. We're looking at it, but it's early days in the sense that the ability to qualify and understand the assay performance and what antibodies we're looking at is still emerging. And so we're busy collaborating with hospitals even here in Boston to test convalescence serum and understand the antibody levels that are expected to be associated with protection and immunity and see how it correlates to our ability to then -- the vaccine's ability to generate neutralizing titers and as I said, down the road, potentially connected to the demonstration of the ability of those neutralizing antibodies to prevent disease in animal models. So I expect all of these data are going to come together in the coming months in a way that will be more clear. But I think, today, it's premature to -- we don't yet know that.

Operator

Our next question comes from Ted Tenthoff with Piper Sandler.

Edward Andrew Tenthoff - Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Thank you very much for all of the details today. My first question is actually maybe a little bit of a naive one. And I apologize, I forgot the doctor's name who gave the presentation on SARS CoV-2. But with the antiviral strategy of destabilizing the virus, do you run the risk of potentially mutating into a more virulent or more infectious form of the disease? And then a question just for Carol, if I may. You had mentioned, I think, briefly, that the Phase I NIH study is also starting now to enroll elderly subjects. Is that in an additional cohort? Or are they sprinkled amongst the first 45 healthy volunteers?

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thanks, Ted. So I think the first question goes to Dr. Denison.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

So Stéphane, this is Tal. I'm not sure if Dr. Denison is still...

Mark R. Denison

Oh, I am. I am present.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Oh, right.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Mark R. Denison

Sorry. I was on mute. My apologies. I was talking to myself. We have -- we had done extensive publications and work. That was the question that, of course, arrives if you inactivate the exonuclease-increasing mutation rate. Is it -- but that's more science fiction than fact. The fact is that the virus is optimized for its mutation rate and destabilizing it actually irrevocably attenuates the virus. So we've actually had proposed it a long time ago as potentially a vaccine strategy because it appears irrevocably attenuated in animals, unable to fix that mutation, those mutations that we introduce, more sensitive to antivirals and incapable of apparently repairing that in a way that allows the virus and never generates more virulence because the more mutations the virus has a certain amount at once, it doesn't want more. And so this is actually a disadvantage to the virus.

Edward Andrew Tenthoff - Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Excellent. Thank you for that work. It's really interesting.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

I'm sorry, could I ask you to repeat the question?

Edward Andrew Tenthoff - Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Yes. No worries, Tal. So I think you had mentioned that in the Phase I study, you are now also enrolling elderly patients. And is that an additional cohort, or are they sprinkled in amongst the first 45?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Yes. I apologize. I was clearly having an elderly moment here. The -- it's an additional cohort. So clearly, this is a vulnerable population, and so getting safety data in that age group is important. Yes. So...

Edward Andrew Tenthoff - Piper Sandler & Co., Research Division - MD & Senior Research Analyst

And are you evaluating -- yes. Are you evaluating the same doses within that patient population?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Correct. Yes. That's the intent.

Operator

And our next question comes from Salveen Richter with Goldman Sachs.

Salveen Jaswal Richter - Goldman Sachs Group Inc., Research Division - VP

So in regard to manufacturing of the COVID-19 vaccine, just given the large global need here, I mean, over 600 million doses in the U.S. alone, could you speak to the public and private partnerships and the timing when you intend to pursue them in the context of the data? And on the public side, can traditional biopharma vaccine manufacturing plants be transitioned over to manufacture mRNA vaccines easily? And I have a follow-up to this.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Stéphane Bancel - Moderna, Inc. - CEO & Director

So let me, Salveen, take the first one, and then I'll have Juan talk about the manufacturing strategy. On the public-private partnership, we're having quite a number of discussions. It is too early at this stage to be able to share the progress on this front, as you can imagine, having already the vaccine in the clinic. And as we've shared, Tal and his team are working hard to prepare for Phase II. Juan is already making the Phase II material. We have quite a number of discussions. As those materialize, we will, of course, be sharing those. But at this stage, there is no news to discuss.

Juan, can you talk a bit about the ability to -- what's the strategy for transferring maybe outside of Norwood to adding capacity nodes?

Juan Andres - Moderna, Inc. - Chief Technical Operations & Quality Officer

Sure. So what we are doing is, first, is we are scaling up the process. And then in parallel, we are producing with our current scale. We expect to be around the new scale relatively easy around the summer. And then we will -- our strategy is thinking to replicate that scale in a very similar way into different nodes that we mitigate. As I said before, inside Norwood, working with other CMOs, both in the United States and in other parts of the world, and the idea would be to have very, very similar, if not identical, equipment processes so in a couple of different locations. We want to minimize the number of locations for manufacturing to make it faster and don't dilute the supply chain.

And then lastly, for fill-finish, we will need even more locations. We will have to do aseptic filling in a number of different areas. And we believe that by partnering with existing nodes of capacity for aseptic filling and finishing across the world, it will get us there with the numbers that we will need.

Stéphane Bancel - Moderna, Inc. - CEO & Director

And maybe, Salveen, maybe just to add to Juan. As we've said in the past, I think what we're trying to do, first from Norwood and then with potentially additional nodes, is to potentially produce millions of vials per month, I would say, this side of Christmas and then in the '21 time frame, to be able to produce tens of millions of vials. And then as you had noted of manufacturing sites kind of "like another Norwood capacity" times a few times to just be able to scale from there, and I think that is what Juan and his team are trying to do now.

Salveen Jaswal Richter - Goldman Sachs Group Inc., Research Division - VP

Great. And then 2 follow-up questions here. One is can you speak to where the preclinical COVID studies you're running with the NIH stand and then how to think about correlates of protection with regard to your human trials? And then secondly, when you look at the presentation today, the development time line-associated nucleic acid vaccines are about 4 to 7 years. And so we hear about this 12 to 18 months time line, that seems to be debated by some epidemiologists. Where do you think the disconnect is there?

Stéphane Bancel - Moderna, Inc. - CEO & Director

Tal, you want to maybe take all these ones.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Yes. Yes. Thank you for that. 3 great questions. So let me start with the preclinical work. There is work that the NIH is doing. It's primarily, right now, in murine and nonhuman primate models, although we're -- we and others are actively looking at additional species, and it is characterizing the immune response preclinically as well as the ability to protect from a challenge study. So what you do is you immunize the animals and whichever model it is. Those that are susceptible to clinical disease, you measure clinical outcomes and in any case, you measure antibody levels and you try



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

to elucidate the qualitative aspect of those antibodies, i.e., do they just bind or can they actually neutralize in various in vitro neutralization assays? So that's the work that's ongoing in collaboration with the NIH and with other groups.

In terms of correlative protection, at a high level, as Dr. Heath had explained, the goal here is to demonstrate that the same antibodies that you can elicit in humans with the vaccine are the antibodies that are protective in the nonclinical species, and there are essentially 2 ways to do that. One is to show that you're achieving the levels of neutralizing antibodies, that on the same assay or actually, at the levels that you can achieve with a vaccine, the one next step that people often take is to then do passive transfer studies and actually demonstrate that you can take the serum from the humans vaccinated with a vaccine and then prevent the biological and clinical end points in the relevant animal models. The challenge here is, of course, that it takes you 2 to 3 months to just run a cycle if you're doing a prime boost and then you need to look at disease.

And so you can imagine, starting in January, there were no models, right? So all the work had to start from scratch and then in parallel. And I think Barney Graham and John Beigel's team at the VRC and DMID, both branches of the NIH, get a lot of credit for really stepping into the breach right from the get-go and starting this critical work. And I think there's progress being made, but obviously, it's early days. All of this has to come together, hopefully, in the summer time frame for us to get wiser in terms of the potential of the vaccine we're developing.

Now I think that answers the first 2 questions. Let's talk about the time line. I think there are 2 elements that could potentially make the development of this vaccine more rapid, or 3. I think the first is the ability to start quickly, which we've already demonstrated. The second is the ability to run and expanding a clinical program relatively rapidly, which is going to require regulatory flexibility. And I think the one thing that doesn't change is the risk-benefit paradigm. However, in the case of a pandemic, the unmet need is so huge that the potential benefit becomes huge. And so I think the tolerance for the unknown risks are increased alongside with that, at least that's what you would expect rationally, right? And so while I have no expectation of an untoward risk of the vaccine, we don't know what we don't know. So there's always the potential, and that's why it's typically done more in a stepwise manner. You wait to the end of Phase I, you start a Phase II, you wait to the end of Phase II, you start a Phase III. And here, we're trying to compress the time lines by really continuously expanding the safety database and going from phase to phase to phase before the prior phase had finished. So that's sort of the second element where you start to see compression of the clinical development plan.

And I think the last element is an expectation that you will be able to demonstrate benefit quickly for 1 of 2 reasons, either there is a surrogate that's acceptable for an accelerated approval. So those always come faster than full approvals because as Dr. Heath noted, you need smaller trials and the readouts are much quicker. Or the incident, the attack rate remains so high that our ability to take this into a pivotal trial, a placebo-controlled trial, where the end point is a clinical case-driven event rate is actually possible to do in a short amount of time.

So take our CMV. We think CMV is going to go relatively fast, and we're going to accrue that in 18 months. And we expect to follow people for 2 years because you're accumulating cases, and that's all predicated on the expected incidence of the target population of, say, 1% to 2%.

Now if we're able to actually -- if the pandemic is still raging in the fall when we get there and we're able to launch our pivotal trials in a population that has a high attack rate, then cases are going to accumulate much faster, and that leads to further compression of the time line for you to be able to demonstrate a difference in clinical outcomes. So all of these sort of all come together to potentially -- again, this is on paper. The only thing we've demonstrated so far is the ability to start quick and get quickly into the clinic. I think from here on out is going to require working closely with the regulators within this paradigm and being effective in launching trials in areas and sites where there still is a high attack rate to be able to demonstrate that benefit.

Operator

And our next question comes from Cory Kasimov with JPMorgan.

Cory William Kasimov - JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst

I guess, initially, for Juan, I wanted to follow up on some of these prior manufacturing questions. And assuming you eventually get to Stage 3 in your manufacturing plan, how much has to be outsourced? Or would the company, in fact, build additional facilities? And then also, if you are



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

successful with the COVID-19 vaccine, what does that mean with regard to your ability to manufacture and supply your other proprietary vaccines you're working on? And then I have one follow-up.

Juan Andres - Moderna, Inc. - Chief Technical Operations & Quality Officer

Okay. Thank you, Cory. Let me address the last one. First, as of this moment in time, we are not going to change our ability to manufacture any of the other products we have in the pipeline. And so we are doing this in parallel to scale. So we are going to be different. We're scaling for this at a much faster pace in the -- and so the rest of the processes will continue.

This product would be on a liquid vial basis. Recently, we talked about the CMV, which would be lyophilized. So there are clear separations that would make them not complete. As I also mentioned, our Stage 3, in terms of world manufacturing sites and how big and locations and things like this, we haven't decided that yet, and we are not working very actively. We are concentrating in our Stage 2. That is where we are focusing right now, which is scaling up the process and partnering with others in building those nodes of supply, in addition to expanding the capacity model.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Yes, Cory, I just wanted to add to Juan. If you think about the -- building something new, just the lead time to do it and to validate their opening, doesn't fit into the window. So that is why it's really how we maximize now with output, making every additional minimum value that you can turn off, and then how do you help the CMOs that potentially have a lot of capacity so you can scale quickly there using similar process nodes.

Cory William Kasimov - JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst

Okay. Makes sense. And then regarding your \$6.5 billion to \$12 billion estimate of peak sales potential for your current vaccine candidates in the clinic, is COVID-19 included in that? And if so, can you talk at least broadly about how you're thinking about that opportunity, even though I know that's not the initial priority with this program?

Stéphane Bancel - Moderna, Inc. - CEO & Director

So at this stage, we will not split the product. We've done it for CMV in September just because CMV was going into Phase II and so on. We think it's still a bit too early. As we've shared in the past, we view 2 different phases for our product. We believe there's a pandemic need, which is what we are all talking about now, which is how do we vaccinate as many people as we can in the next 12 to 24 to 36 months. And then we believe, as you've heard from some of the scientists on the call today, we believe there's a high likelihood, and we want to be cautious because it's a new virus, we don't know what we don't know, but we think there's a high likelihood that this becomes endemic. And so we don't know yet how long vaccine protection will last. We anticipate that in the elderly setting just because of a weaker immune system, as people age, there might need to be regular boosts. So we have pretty broad-based assumptions on this one. As we learn more about the virus scientifically, as we get some human data on the vaccine, I think we should be able to refine this. We put some basic assumption on COVID in that forecast, but they are not very high.

Operator

And our next question comes from Geoff Meacham with Bank of America.

Alec Warren Stranahan - BofA Merrill Lynch, Research Division - Associate

This is Alec on for Geoff. A couple for Tal on Zika. You said that you're starting to see activity already at the 10-microgram dose, which is certainly encouraging, given the outcome from the first iteration. Do you have a sense of what might be an approvable level of neutralizing-antibody response if it is implemented as a surrogate end point? Or is this still something you're working out with BARDA?



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

And then on study timing, could you remind us what the planned length of follow-up is for patients in the Phase I and how quickly you think you can move into a subsequent Phase II?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Hi, Alec. 2 good questions. On the level of activity, the truth is, I don't know yet. I think we have to complete the work on the nonhuman primate models and then talk to BARDA and eventually FDA to align on that. So I think it's premature to say whether because I think what you're getting at is the question of whether I think the data already hit the mark. And I hope so, but I don't know that yet.

In terms of timing, length of follow-up. So these trials, really, the length of follow-up is typically FDA access for 6 months. And certainly, beyond showing the durability, there's not much of a value to doing it much longer. So I think we're well on our way to designing and getting ready to start the Phase II. Of course, it's a healthy volunteer trial. So I think we need to make sure we can conduct it in sites that are able to facilitate elected procedures in the current environment. But it is slated for the summer, and I'm hopeful that if there is a delay, it's not too long to get started.

Operator

And we have a question from Hartaj Singh with Oppenheimer.

Hartaj Singh - Oppenheimer & Co. Inc., Research Division - Research Analyst

I just had one question on CMV. Tal, you had mentioned we've been talking a lot about serological and surrogate end points. A question just asked about Zika, where you think you can possibly go down that route. Is there a possibility with CMV for you to get a kind of a surrogate end point sort of approval between Phase II and Phase III? Or is that just a difficult kind of animal? And then I just have a follow-up on COVID-19.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Hi, Hartaj. Getting back to you, Look, I think that the agency likely is expecting a clinical end point for CMV. Recall that women who are seronegative still have some risk of transmission. And so given that there is no vaccine approved, even though the gB came awfully close, I think there is an expectation that we would demonstrate benefit. The other reason is that the real unmet need here that we're going after is transmission from moms to babies in utero, as has been discussed. And so while the agency understands that now asking for that is really unrealistic, I nevertheless think it is a realistic expectation for them to expect us to demonstrate prevention of disease women who are seronegative or prevention of infection. And in that case, when there is a Phase III that is feasible than typically other ways of approval that are based on surrogates are shall we say, frowned upon. You had a question on COVID, I think.

Hartaj Singh - Oppenheimer & Co. Inc., Research Division - Research Analyst

Great. Yes. Great, Tal. And then just on COVID-19, a couple of questions. One is you're targeting the Spike protein reviewer with the vaccine. I just wanted to ask Dr. Denison that in his research on coronaviruses, how has he seen mutations to the actual Spike protein and the virus is still viable. And then specifically, a second question on COVID-19 individuals that actually already had been infected and so therefore could be considered sort of, I guess, seropositive. Is there potential for some kind of reinfection or other risks associated with that?

Mark R. Denison

Would you like me to address that as best I can?

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Hartaj Singh - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Yes. Please.

Mark R. Denison

Just quick comments on Spike. I think Spike is -- mutations like this, as stuff happen, mutations happen. And like I said, the -- and coronaviruses do generate them. They tend to not generate them under stable conditions, like I said, under no selected pressure. But the Spike is certainly able to adapt. It's able to adapt to -- and we've been involved with publications with Barney Graham and others looking at MERS and monoclonal antibodies and adaptation and selection for resistance. So they certainly can happen under -- it certainly will occur under selection. Coronaviruses are very good at that, under those selective conditions. So I think that can, and there's an expectation that there will be some response to that. I think the main points are what you want to do is you want to generate enough neutralizing antibody and high enough levels that correlates with protection to stop it in that setting. And ultimately, I think the idea of anything is to thinking about ways to do things that allow for you to sort of overcome that or prevent it in such a way that you basically prevent, you prevent disease. And I can't remember the next question, but I remember what the other question was.

Hartaj Singh - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Yes, sir. It's just a question on the -- on individuals who have already been infected with COVID-19. So I guess they would be sort of, I guess, called seropositive COVID-19 patients. Are those patients -- do they have the potential to be reinfected? Or maybe are there other co-morbidities associated with these patients with something like that observed with SARS or MERS or anything else?

Mark R. Denison

There wasn't enough experience with SARS because it went away, its limitations, and allowed for public health emergence. So MERS reinfection hasn't really been studied. But I don't know that these are prevalence to us. These have been carefully enough done to know that, and the background of the environment hasn't really allowed to understand that. I think with this one, there is a hope and expectation that an antibody will be neutralizing and protective. I think with the coronaviruses, it's -- like I mentioned, you may not need sterilizing immunity, right, either with disease or with the vaccine so much as you want to do is you want to prevent replication enough that you would prevent transmission and you protect people from disease.

So I think -- but all of that data remains to be answered. At this point, any of it is speculation that people are saying. It probably represents that they're not measuring it accurately enough or they're not really knowing what's going on if they say there's reinfection right now. I think it's just too early to say.

Operator

And our next question comes from Yasmeen Rahimi with Roth Capital Partners.

Yasmeen Rahimi - *Roth Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Co-Head of Biotechnology Research*

Thanks to the Moderna team for organizing this day and many of the excellent speakers. We have 3 specific questions. The first one is directed to Dr. Paul Heath. Can you share with us what makes mRNA vaccine approaches better equipped to handle mutational viruses? That would be helpful. And then the second question is directed to Stéphane and Stephen. Thank you for sharing the preclinical data on MERS. Can you comment on how strong was the simulation of T cell response? And how important is that as we think about overall in regards to coronaviruses? And then we have a follow-up also for Stéphane and Stephen.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Stéphane Bancel - Moderna, Inc. - CEO & Director

So maybe, Stephen, take the first question because Dr. Paul Heath is not on the call anymore. So Stephen, do you mind taking those 2?

Stephen Hoge - Moderna, Inc. - President

Sure. Yes. So first, on the question of adaptation of the platform. I think it boils back down to the uniform process that we use for manufacturing all of our vaccines. One of the advantages we have is that we can make small subtle changes in sequence or even substantial changes, moving vaccine to vaccine, in sequence and use largely the same -- essentially, the same manufacturing process. When you go to think about a highly rapidly evolving virus, take something like influenza, as a pandemic, it's obviously conceivable to use that same technological advantage to rapidly change the antigens you're expressing in the vaccine so that you can adapt to evolution of the virus as it moves to a human population.

Yasmeen Rahimi - Roth Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Co-Head of Biotechnology Research

And then in regards to that simulation of T cell response in the MERS, the clinical...

Stephen Hoge - Moderna, Inc. - President

So I think we showed the data that I presented. We focused our conversation on T cells today, it was mostly on the CMV vaccine, where we showed just both preclinical data and clinical data there, showing balanced CD4-positive as well as the preclinical space, CD8-positive T cell responses, that were interferon-gamma positive, so Th1 type. I think in the MERS context, we -- that was a challenge model where we're looking at replication end points, whether or not you could generate sterilizing immunity through vaccination with a MERS vaccine. Now again, this is -- while it's a coronavirus, it's not the closest cousin. But in that case, we were able to show sterilizing immunity. I don't know if we've characterized in detail the T cell responses, but clearly, given the high neutralizing titers, we were able to establish, and given our experience across the platform, we are seeing balanced humoral and cellular immunity in almost every instance we look. And so we would expect it to be there, and that was probably essential for protecting those rabbits that challenge well.

Yasmeen Rahimi - Roth Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Co-Head of Biotechnology Research

And then one last question. Can you maybe remind us how the LNPs used in the prophylactic vaccines are optimized to add immunogenicity?

Stephen Hoge - Moderna, Inc. - President

Yes. So the first feature of most import is you've got to get the mRNA into the correct cell of interest, right? So our -- the first feature we have in the delivery technologies that we use, the LNP that we use for the vaccines context, is we want to drain out of the muscle, we don't want to express locally in the muscle, down into the lymphatics and then transfect the antigen-presenting cells in the lymph node. Those are macrophages. Those are dendritic cells. And so that trope is of not getting stuck in the muscle, draining efficiently because of surface charge and chemistry, down into lymphatics and then rapidly getting efficiently inside of those antigen-presenting cells is key. I think the second feature that we optimize is for a very, very efficient delivery of the messenger RNA to those cells. Once you get inside those cells, you want to actually get your messenger RNA out and make a very large amount of protein. And the reason that matters is actually the presentation of antigen by these antigen-presenting cells is a bit of a kinetic game, right? They have a number of MHC molecules, but they're constantly sampling and presenting, I think. And you want to get a very strong and dominant presentation of a large amount of antigen, which, ultimately, is the fastest way to get an immune response is you want to present antigens that actually create a signal for the naive T cells and B cells in that lymph node.

There are other things that we have not published on but that we've talked about generically around our process for making both the LNPs as well as the mRNAs themselves, which provide a small amount of immunostimulatory signal in the context of our vaccines platform. Obviously, we do



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

not do that. We do something very different in a therapeutic context. But that also just ensures that there is a productive immune response once that antigen is there. But probably the most important features, I would argue, the most important features, at least from my perspective, are getting the mRNA to those cells in the lymph node, not getting distracted along the way and making a tremendous amount of antigen, as much antigen, as much protein as you can, once you get into the antigen-presenting cells.

Operator

Our next question comes from Geoffrey Porges with SVB Leerink.

Geoffrey Craig Porges - SVB Leerink LLC, Research Division - Director of Therapeutics Research, MD & Senior Biotechnology Analyst

And again, congratulations on just a comprehensive presentation. Given the -- my assumption that your excellent experts are going to be inaccessible for the next few months, I thought I would pose a couple of questions to Dr. Denison and then one to Kathy Edwards, if she's on the phone. First, Dr. Denison, it's clear to everybody, the children and adolescents, maybe in young adults, are just less sensitive to CoV-2. And I'm just wondering if any of your research has identified why that might be. And on a related basis, do you believe there are any genetic or other markers of sensitivity or natural resistance in the CoV-2 because that might help us understand the potential for vaccines? And then to Dr. Edwards, can you talk about...

Mark R. Denison

Kathy is not still on the line. I don't think that she...

Kathryn Edwards

I actually got back on.

Mark R. Denison

Oh, you're back on the line. Okay. I'm sorry, Kathy. I apologize.

Kathryn Edwards

It's okay. I got here.

Geoffrey Craig Porges - SVB Leerink LLC, Research Division - Director of Therapeutics Research, MD & Senior Biotechnology Analyst

Great. Terrific. Well, Kathy, could you talk about whether there might be stratified recommendations from the ACIP to use of a COVID vaccine based on risk of exposure because -- and maybe talk about what safety might be necessary, for example, as you go from health care workers, to high-risk adults and the elderly, and then finally, going to sort of healthy younger adults and even adolescents and children? What kind of safety would be required, and might you conceive of stratified recommendations?

Mark R. Denison

Kathy, why don't you answer first your question.

APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Kathryn Edwards

Okay. Well, I think that there may indeed be different recommendations for different populations. I think, certainly, we -- and most all other pediatric ID people haven't seen a lot of disease in the -- serious disease in the middle-age children and even in the littlest children, but certainly about 17 or 18, then they become sort of like adults. So I think that, probably, the initial studies would need to focus on adults that are at risk. And certainly, you would want to be able to find if the vaccine was effective, so you're going to need to target high-risk groups that are going to be infected in the study. I think that the safety signals that you would need to look at are, certainly, the usual ones that you do, but I think there would also need to be any kind of accelerated respiratory symptoms or any exacerbated symptoms. And also, I think that you would also need to look for safety for probably 2 years because we want to make sure that, that is immunity range, there's not a signal there. But I also hope that there may be some more information from the preclinical trials or from the nonhuman primates that might give us some idea about how to look at safety as well.

But I think that given the risk of this disease for -- certainly, that we won't have all the answers for safety before it's licensed, probably, but I think we'll have to look very, very carefully yet and continue to look as time goes on with duration of immune responses. I think also, the -- one of the problems is that it becomes more difficult as to look at high-risk populations because also you're trying to protect those from getting disease, so the next efficacy study is more problematic as well. So it's certainly going to be interesting in terms of risk and stratifying in terms of safety for those that are at the greatest risk. And certainly, I don't think this would be a vaccine that, right away, we would target for children.

Mark R. Denison

The answer to your question is that we don't know about children. As parents, as people, as grandparents, we're grateful -- and as pediatricians, we're grateful -- and we're very happy that this not appear to be targeting children in the same way. I think it's most likely a human development issue. It can clearly be, in fact, that they can clearly shed virus diseases, less common, less severe, although sometimes, it is in younger children, that is still occurring. I think this is why you would see if you put chicken pox or measles in a completely immune-naïve situation, you would see normal childhood disease with those viruses and you would see profoundly severe disease, likely in adults, who had never seen the viruses before. So it would probably like represents a developmental evolutionary issue in terms of the immune system. I think what you raised is the point about are there key components we can identify in adults, which would allow us to target better vaccines and or antivirals that would combine to really knock down the immune components at the same time that we're treating the virus.

Geoffrey Craig Porges - SVB Leerink LLC, Research Division - Director of Therapeutics Research, MD & Senior Biotechnology Analyst

Okay. Genetic markers, any, Dr. Denison?

Mark R. Denison

There's no evidence. At this point, the genetic markers, if we look at the population around the world, the vast global span of this, that -- you mean markers or indicators of severe disease, I guess, is the question from a -- potentially, there's markers, but I don't think there's any evidence yet, certainly, that there's going to be genetic proclivity.

Operator

Our next question comes from Umer Raffat with Evercore ISI.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

Stéphane, you mentioned the COVID study is obviously being run by NIB, but it is open label. I guess my question is do you -- are you aware of the GMT titers on the first 2 cohorts? And then also, have you generated any preclinical data investigating the impact of adjuvant? I would be very curious if you have that.



APRIL 14, 2020 / 12:00PM, MRNA.OQ - Moderna Inc Corporate Analyst Meeting

Stéphane Bancel - Moderna, Inc. - CEO & Director

So we have not commented on the preclinical work we are doing with or without adjuvant, so I will not go there. And on the data, we will share the data when we have a complete set of data. We don't have data at this stage. As soon as we have the data, you guys will get the data.

Operator

And I'm showing no further questions at this time. I would like to turn the call back to Stéphane for any closing remarks.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Well, first of all, thank you again for our guest speakers. We really enjoyed having you today. It was very instructive. So thank you.

Thank you for joining today. If you want access to the slides, they are already on our website in the Investor Relations section, and there will be also a webcast available. Thank you very much, and have a great day. Bye-bye.

Operator

Ladies and gentlemen, this concludes today's conference call. Thank you for participating. You may now disconnect. Everyone, have a great day.

DISCLAIMER

Thomson Reuters reserves the right to make changes to documents, content, or other information on this web site without obligation to notify any person of such changes.

In the conference calls upon which Event Transcripts are based, companies may make projections or other forward-looking statements regarding a variety of items. Such forward-looking statements are based upon current expectations and involve risks and uncertainties. Actual results may differ materially from those stated in any forward-looking statement based on a number of important factors and risks, which are more specifically identified in the companies' most recent SEC filings. Although the companies may indicate and believe that the assumptions underlying the forward-looking statements are reasonable, any of the assumptions could prove inaccurate or incorrect and, therefore, there can be no assurance that the results contemplated in the forward-looking statements will be realized.

THE INFORMATION CONTAINED IN EVENT TRANSCRIPTS IS A TEXTUAL REPRESENTATION OF THE APPLICABLE COMPANY'S CONFERENCE CALL AND WHILE EFFORTS ARE MADE TO PROVIDE AN ACCURATE TRANSCRIPTION, THERE MAY BE MATERIAL ERRORS, OMISSIONS, OR INACCURACIES IN THE REPORTING OF THE SUBSTANCE OF THE CONFERENCE CALLS. IN NO WAY DOES THOMSON REUTERS OR THE APPLICABLE COMPANY ASSUME ANY RESPONSIBILITY FOR ANY INVESTMENT OR OTHER DECISIONS MADE BASED UPON THE INFORMATION PROVIDED ON THIS WEB SITE OR IN ANY EVENT TRANSCRIPT. USERS ARE ADVISED TO REVIEW THE APPLICABLE COMPANY'S CONFERENCE CALL ITSELF AND THE APPLICABLE COMPANY'S SEC FILINGS BEFORE MAKING ANY INVESTMENT OR OTHER DECISIONS.

©2020, Thomson Reuters. All Rights Reserved.

