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EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc Vaccines Day

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PRESENTATION

Operator

Good morning, and welcome to Moderna's Vaccines Day. (Operator Instructions) Following the formal remarks, we will open the call up for your questions. Please be advised that the 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. - Senior VP & Head of IR

Thank you. Good morning, everyone, and thank you for joining us for our second Annual Vaccines Day. This morning, we issued a press release that you should access along with the slides we will be presenting by going to the Investors section of our website.

Before we begin, please note that this conference call will include forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Please see Slide 2 of the accompanying 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 these forward-looking statements. We undertake no obligation to update or revise the information provided on this call as a result of new information or future results or developments.

With that, let's now begin with Stéphane introduction to the event.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you, Lavina. Good morning, or good afternoon, everyone. Welcome to Moderna Second Vaccines Day. Thank [Audio Gap] the industry for more than 100 years since (inaudible) had the first rabies vaccine has been an analog industry.

As you all know, mRNA is a formation molecule, and this changes everything. So where do we go next? We believe our mRNA vaccines will have a profound impact on human life and so we want to go bigger. We have a very exciting pipeline today of first-in-class vaccines, but we're not standing still. We're investing in research to develop more vaccine, we're investing in development to accelerate and expand our programs.

We want to go fast because patients are waiting for those important vaccines. And so we have built and continued to invest into a fully digital enterprise, are investigating heavily now into AI, so that we can learn faster. And we want to do it better. We want to design our manufacturing processes to minimize our impact on the environment. We'll come back to that topic in the next few weeks.

We believe this is a large commercial opportunity. First, because the vaccine market already is large at around \$35 billion annual sales. But what is most exciting to us is that we believe we will grow the market very materially by bringing new vaccines against viruses for which there are no vaccines on the market today.

We also believe we can develop new vaccines to materially improve efficacy and all the safety of currently approved vaccine and disrupt those and bring new solutions to consumers.

On Slide 8, let me start by talking about new first-in-class vaccines opportunity. As you can see in this bar chart, in the last 40 years since 1980, the scientific community had discovered more than 80 new viruses that hurts humans. And as of now, there are only 3 vaccines approved against those 80-plus viruses. Vaccine against HPV, vaccine against H1N1 and we have 2 authorized vaccines -- sorry, for vaccine in the U.S. against SARS-CoV-2.

And then if you look below the blue line, you still have a selection of viruses that we described here. That have been discovered before 1980, but for which, in blue, you have viruses for which there is yet to this date, no vaccine available to protect people. If you look at the commercial opportunity and the direct medical annual cost, these are in excess of \$100 billion. We believe there's a great opportunity to impact human health by bringing those vaccines to market.

If I go on Slide 9, we also believe that there is a great opportunity to improve vaccines that today underserve markets because of low efficacy. And the example that everybody is very familiar with is, of course, influenza. As everybody knows, the efficacy of the influenza vaccines depends year-on-year, as you can see on the slide. But as you see, the best years are in the 60%. And as you can see, the worst years are in the 20%, 30%. And so we think there's a great opportunity to impact care by being able to reduce the risk of hospitalization and thereby, having much higher efficacy vaccine. So when you look at this market, we believe there is a very large total addressable market ahead of us.

On Slide 10, we believe that many platform has very important competitive advantage, speed, capital efficiency. If you look on Slide 11 of our pipeline, we are really excited about the pipeline. But first, as you saw in our announcement last night, we have great news on mRNA-1273, the Moderna COVID-19 vaccine currently authorized. It has high efficacy that we can sustain with a high level of antibody that we can sustain over time. It is well-tolerated.

We have been able to scale up manufacturing and we have a demonstrated speed in 2020 with this historic achievement by the team, 11 months from sequence to authorization. And we are continuing to move fast, as we'll talk about later around the variance.

We're also trying new programs like mRNA-1283 to be able to have a fridge temperature storage, in 2 to 4 celsius. But if you look at the pipeline, cytomegalovirus could be a first-in-class vaccine. hMPV, PIV could be a first-in-class vaccine. Zika, same thing, no Zika vaccine in the market, no RSV vaccine in the market, no EBV vaccine in the market. Flu, we talked about great opportunity to bring the high efficacy to the market. No Nipah vaccine on the market; no HIV on the market; no influenza H7N9, a virus that is a high-risk for pandemic on the market either.

Today, I'm very pleased to be joined by an extraordinary team. Stephen Hoge, that many of you know, the President of the company, who runs R&D today; Dr. Melanie Ivarsson, who is our Chief Development Officer; Corinne Le Goff, who is our Chief Commercial Officer; Dr. Jackie Miller, who's in charge for the development for all of our vaccine portfolio; Dr. Lori Panther, who is also working in the development group, and she's going to talk about CMV today; and of course, Dr. Tal Zaks, our Chief Medical Officer.

If you look at the agenda quickly, you're going to have a quick overview by Tal of 1273. And then Corinne is going to talk about the commercial strategy. Stephen is going to talk about the vaccine strategy. And then we're going to go around 9:30 into respiratory diseases where Jackie has a few guest and also, we'll give you some update. We'll take a coffee break and then Jackie will come back after the break to talk about [topical] vaccines, and we're very excited about some of the work we're going to present on HIV.

Then we move to complex antigen. And then Corinne will come back again to talk about the commercial vaccine business model. I will do a quick close before we go into Q&A.

With this, let me hand over to Tal. Tal?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Stephane, and good morning, everyone. It's a pleasure to be here and to speak to you about the safety and tolerability profile of our COVID-19 vaccine to date, as I believe it is relevant not just for COVID, but for the future of our mRNA vaccine platform.

And this next slide is just to remind us that our Moderna COVID-19 vaccine in the United States is currently authorized, not yet licensed. Now if you look back at the accelerated clinical development plan, it was really enabled by a number of factors, not the least of which is the safety and tolerability profile. So let me review that clinical development for those who may not have followed the progression of our vaccine from the start of Phase I through to the emergency authorization.

We were able to design a vaccine, conduct a large clinical program, enrolling over 30,000 participants that subsequently read out a successful trial, apply for and receive authorization in approximately 11 months. This was largely due to the remarkable public-private partnership between industry and the U.S. government. But there are also key aspects of vaccine development as well as Moderna's ability to take on the business risk, given our prior clinical development experience with our mRNA vaccine.

The 2 key clinical development elements that allowed us to proceed quickly were first, the understanding of the dose ranging, and this was based on the experience of having successfully induced neutralizing antibodies against all 8 viruses that we had previously immunized against in prior Phase I trials.

And second, it was the safety and tolerability profile of our vaccine. For vaccines, it is well-accepted that the 6 to 8-week follow-up period after the last dose is really the relevant period to look at for the vast majority of attributable adverse events. Indeed, the FDA asked for 8-week safety and reactogenicity data from our Phase III trial before evaluating the risk-benefit profile of our vaccine.

Now this meant that we could start the Phase II study after reviewing the safety data from Phase I, but before having the full immunogenicity results. And we could then start the Phase III trial as soon as we have the safety data from the Phase II, now being able to select a dose based on the data from Phase I. Now of course, this was possible because the safety and tolerability were supportive of continued development. And that the prior studies, meanwhile, continue to generate important clinical data.

Indeed, we've recently seen the 6 months immunogenicity update from that original Phase I trial, which has now been published in the New England Journal of Medicine, and which we will review later in the program. Of course, we're grateful for the ongoing collaboration with NIH and the U.S. government at large. And particular, the timely guidances and reviews by FDA, without which this development could not have proceeded. Coming back to the safety profile, it is telling that the reactogenicity profile we saw in Phase I which is, by and large, similar to what we've seen in all of our mRNA vaccines, was the same as that described in Phase III and is maintained in the current post authorization database as has recently been reported by CDC.

As of yesterday, more than 85 million Moderna COVID-19 vaccines have been given in the U.S. and in many other countries. And we as well as global regulatory bodies continue to monitor closely any and all adverse events. The surveillance is working. These days, everyone is focused on these thrombotic events, and I can tell you that for us, a comprehensive assessment of the totality of the available safety data for mRNA-1273, after over 64 million doses have been administered globally, does not suggest an association with cerebral venous sinus thrombosis or thrombotic events.

Let me make one last point in closing. We had always anticipated that high levels of neutralizing antibodies should lead to clinical efficacy. This is predicated on the science of immunology and experience with many other prior vaccines. That said, for COVID-19 and early 2020, it was not known what titers we should consider as high and what is achievable in terms of clinical efficacy.

Well, we now know. High antibody titers are those that match or exceed those induced by natural infection and high clinical efficacy exceeds 90%. And these two are clearly correlated with our COVID-19 vaccine being our first mRNA vaccine to establish this translation of high-level of immunogenicity to unimpeachable clinical benefit. I believe this is the first of many to come. Thank you, and let me now turn it over to Corinne.

Corinne M. Le Goff - Moderna, Inc. - Chief Commercial Officer

Thank you, Tal, and good morning or good afternoon, everyone. As all of you already know, Moderna's COVID-19 vaccine is our first authorized product and one that thrives the company into becoming a global commercial entity very quickly. I am delighted to be here and to give you a commercial update on the Moderna's COVID-19 vaccine.

On the next slide. Throughout the course of 2020, as we were developing our vaccine in clinical trials, we entered into many advanced purchase agreements across the globe. And we are truly grateful for the confidence the United States, the European Commission and other countries have demonstrated in our mRNA vaccine platform by including our vaccine in their portfolio vaccines early on and ahead of any available clinical data.

From the middle of 2020 through late March 2021, we announced advanced purchase agreements totaling in excess of 800 million doses to be delivered to the countries that are listed here on the slide. And of course, we continue to engage with governments around the world, and we are in discussions for additional supply of our vaccine.

Next slide. We have established supply capacity to enable broad access to our COVID-19 vaccines across the globe. Moderna has set up two independent supply chains to address the U.S. market and the ex-U. S. market. In the U.S., our own manufacturing facility and those of our partner, Lonza, produce a vaccine. And our partners, Catalent and Baxter, filled and finished the vaccine vial prior to shipment for the market.

Now given that our experience as a manufacturer prior to COVID-19 was in the U.S., production at our U.S. facilities processed earlier than it did outside the U.S. So for markets outside of the U.S. all international, the U.S. Lonza facilities in Switzerland manufacture the product, and our partners, Rovi in Spain and Recipharm in France fill and finish the product for market release. Thanks to our global manufacturing footprint, you'll see on the next slide, that we have been able to rapidly address this pandemic.

To date, we have successfully delivered approximately 132 million doses of our vaccine. Including approximately 117 million doses to the U.S. government and approximately 50 million doses delivered from Moderna's ex-U. S. supply chain. As I mentioned previously, the U.S. production started earlier, and you can see from the chart on the left-hand side, on this slide, that the U.S. is roughly 1/4 ahead in production ramp. As such, in the second quarter of 2021, we expect the ex U.S. ramp to be similar to that of the U.S. ramp in the first quarter. As a reminder, we have guided to supplying between 700 million and 1 billion doses on a global basis in 2021.

Next slide. So as we continue to produce and roll out vaccines into the global market, we are proud and humbled to be part of the solution. And we look forward to ending this pandemic and helping bring life back to normal. As Tal mentioned earlier, more than EUR 85 million of Moderna COVID-19 vaccines have been injected into arms. Arms that belong to some famous people, as you can see on this slide, but also less famous people. And we have received so many messages of encouragement and testimonials from people who received our vaccine. It has been heartwarming for our teams. I wanted to make this point.

So on the next slide. The pace of immunization campaign is picking up around the world. However, we continue to monitor the situation. And look to experts on the state of the pandemic and the possibility of the formation of an endemic market, and we are in a position of adapting our strategies accordingly. We currently believe that the coronavirus is here to stay.

And I'm putting here a recent paper published in Nature a few weeks ago, where 89% of immunologists surveyed, consider likely or very likely that COVID-19 will become endemic. Our own market studies confirm this point. So what is likely to happen is that SARS-CoV-2 will not be eradicated and will continue to circulate in pockets of the global population for years to come, potentially causing outbreaks in regions where it had been eliminated. So according to these experts, they are four top factors that are driving endemicity. Immunoscape, winning immunity, but also the -- an even vaccine distribution around the world and the fourth factor is vaccine hesitancy, which is fading, but is still a factor.

The Kaiser Foundation, most recent poll shows that 20% of the U.S. population is still not convinced that they should get immunized. So all of these factors can lead to additional variance to arise, and you will hear much more about this in the scientific presentations from Stephen and our guest speakers in a few minutes.

Next slide. So with the potential of COVID-19 becoming endemic, Moderna is committed to staying vigilant against this virus and its variant strains. We believe our mRNA vaccine technology positions us very well to address variance of concern. The key advantages of the Moderna vaccines technology that enable us to stay ahead of this coronavirus are threefold. One, rapid development and rapid manufacturing that facilitate a fast pace updating process; two, the ability to produce multivalent vaccines, vaccines that have less strains, and therefore, can protect against these trends and improve vaccination coverage; and three, the ability to be used potentially as a heterologous booster, meaning that the Moderna booster vaccine can be administered after prime vaccinations done with other vaccine technologies.

So as we understand, on the next slide, the evolution of the pandemic in the coming months and next few years, it is clear to us that speed and adaptability are paramount. Since the start of the rollout of the vaccination campaigns around the world, close to 800 million doses have been administered, which is enough to vaccinate. A little bit more than 5% of the global population. These are the data from the latest Bloomberg tracker.

So what we expect is that COVID-19 vaccines deployment across geographies in 2022 will be driven by the continuing ramp-up of the humanization campaigns for adults, 18 and above, and it will expand into the adolescents and children as we extend age cohort coverage. And it is likely that the countries that have already achieved high vaccine coverage are going to be ready to shift their focus to boosters in 2022 and possibly even starting at the end of this year.

Next slide. So we at Moderna, want to be in a position of maximizing the impact of our COVID-19 vaccine on population health, and we are set up to do so. The COVID-19 vaccine has been a clear accelerator for the company, and it allowed us to scale up our commercial operations at a rapid pace. Today, we have achieved a large geographic footprint with 8 currently operational subsidiaries, and we plan to grow our commercial presence with the opening of three more subsidiaries in Japan and Asia Pacific.

So building a direct presence by establishing a subsidiary in a key strategic market also signifies our intention to build strong and long-term collaborations within local ecosystems and notably with the clinicians and scientists who are passionate about extending the therapeutic use of mRNA. In addition to setting up these subsidiaries, we are also partnering with distributors in Israel, Eastern Europe, Latin America and Asia, with the ambition to build a broad global commercial network. Most importantly, we are building now for the future. We plan to leverage our commercial infrastructure. That is currently set up for our COVID-19 vaccine with other vaccines that we are developing because as Stéphane just said, beyond SARS-CoV-2, Moderna continues to go big in vaccine, and you will hear more from our Moderna scientists about the progress that we are making in developing these vaccines.

On the next slide. So I have covered a lot so far during my introduction of Moderna's commercial organization and commercial strategy, but I would be remiss if I did not cover a key aspect of vaccines, which is the clear impact and value of immunization. Vaccines are among the most successful and cost-effective public health tools for preventing diseases and death.

As we all know, but sometimes forget, they have led to the eradication of small pox, the elimination of polio from most continents and the control of many other diseases. And we certainly have been reminded of the value of vaccines with the COVID pandemic. The IMS estimates COVID-19 total societal costs to be between \$20 trillion and \$25 trillion. Now even if the entire world population of 7.8 billion people is vaccinated with 2 doses at an average of, let's say, \$20 per dose. The total immunization cost would be negligible, less than 2%, and about 1.3% of the total cost of the pandemic.

But most importantly, the value of vaccines goes way beyond health care cost savings. It goes way beyond positive economic impact on labor and productivity. Vaccination has real benefits on individual social and psychological well-being, on political and economic stability of nations, just to name a few. So coupling this clear value proposition with the advantages of our mRNA vaccine technology, leading to many more innovative new vaccines coming to market. We believe that Moderna is poised to become a disruptive force in the vaccine market.

And as Stéphane said, for us, this is just the beginning.

So with this statement, let me transition to Stephen Hoge, our President and Head of Research and Development, who will present the Moderna infectious disease vaccine strategy.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Corinne, and good morning, good afternoon, everyone. It's probably an understatement to say that 2020 was a transformational year for Moderna and the field of mRNA-LNP vaccines that we've been building. But it's an important moment to sort of pull back and ask, how did we get here? In fact, given some of the recent reporting, people could be forgiven for believing that the idea was had decades ago, and just sprung into existence in the last year with this success.

But many of you who've been following the story over the last decade with us know that actually much, much more work has been done to get to this moment. And I'd love to cover that in just a few slides. So the -- the idea of mRNA vaccines has actually been around since the early 1990s. But none of the prior approaches had translated into any clinical success until 2013. And that's when the discovery of the combination of mRNA and LNP technologies change the story forever.

In fact, all successful example since of mRNA vaccines have relied on the combination of lipid nanoparticle and mRNA technology to make those vaccines work. Put simply, prior to 2013, there were no successes and after 2013, all successes depend upon the combination of those technologies. That story, the story of -- from 2013 to now and the advancement of those mRNA and LNP technologies is one that Moderna has really led the development of.

In fact, the first mRNA and LNP vaccine was put into rodent in 2013 by scientists at Moderna led by a scientist by the name of [indiscernible]. That result was so significant that they almost didn't believe it and actually repeated the study before they would share it more broadly. Knowing that so many things previously had not translated, Moderna worked hard to demonstrate quickly the following year, but that translated into primate. And at that moment, we came to believe wholeheartedly that mRNA and lipid nanoparticle vaccines would be a disruptive force in the field.

Now we continued a lot of preclinical work. But actually, Moderna focused most intensely on advancing the human translation to prove the power of this technology. That started with the first-in-human clinical study of an mRNA and LNP vaccine, which happened in 2015, actually in Europe and was against a pandemic influenza strain called H10. That was followed shortly by the first vaccine trial in the United States in early 2016 against a totally different pandemic influenza strain. In this case, H7.

Those milestones, important as they were, were followed quickly with others, including our RSV vaccine series of clinical trials, where we drove successive improvements, most recently into mRNA-1345, in our RSV vaccine platform. A Zika vaccine followed shortly thereafter towards the end of 2016, and that was the first demonstration of the opportunity to use mRNA and LNP vaccines to respond quickly in an epidemic.

Now in that instance, we actually went from sequence of the Zika virus to IND filing in 1 year. And that, at the time felt, like quite a milestone. But looking back, it looks quite quaint given what's been able to happen in 2020. Now moving forward, that we didn't stop there. The first -- that was followed quickly with a vaccine for chikungunya virus into the clinic in 2017, and the first combination respiratory vaccine in 2017 as well against 2 respiratory viruses, human metapneumovirus and the parainfluenza virus, which we'll talk about in the rest of the presentation.

That was followed by the first vaccine for a complex antigen, our cytomegalovirus vaccine towards the end of 2017. This was a 6-mRNA protein, 6-mRNA antigen vaccine, which formed a 5-protein component called the pentamer and then very complex antigen that we've spoken about previously. That was followed quickly with the first pediatric study, in this case, which started in 2019, an age de-escalation study for hMPV/PIV3 combination vaccine. And the first vaccine trial using a refrigerator stable vaccine, our CMV vaccine, which was lyophilized, also for the first Phase II study at the end of 2019. And of course, everybody knows the story of SARS-CoV-2 now started in 2020.

But importantly, the large number of milestones and foundational technological and scientific work that had happened over the preceding 8 years, potentially laid the foundation for how we move forward with SARS-CoV-2. That also was communicated in a range of publications. In fact, the first publication of clinical data using an mRNA and LNP vaccine happened in early 2017, using the 2 vaccines are 2 influenza vaccines that were first-in-human in Europe and the United States.

It was followed quickly in 2017 by 3 foundational publications that we did, in collaboration with the Karolinska Institute in Europe, and Dr. Lori's lab there, showing the mechanism of action of mRNA and LNP vaccines and ultimately, laying the foundation for almost everything that happened afterwards. We also engaged in substantial publications across a wide range of vaccines, including Zika, flu, Ebola, CMB, chikungunya, dengue and even in 2020, following up with RSV, HIV and VZV publications, laying the preclinical foundation demonstrating the power of this technology across a very wide range of vaccine opportunities.

And what you started to see more recently in 2017 forward, is the emergence of third-party validation of this approach. First, with the first academic publications where they combined messenger RNA and lipid nanoparticle technology, as Moderna had been doing, and showing the potential in their hands of this combination.

And it's not until 2020 that you see the first non-Moderna mRNA-LNP vaccine clinical trial. That was the Pfizer BioNTech vaccine now is helping combat the pandemic of COVID-19.

Now importantly, if you look back on that history, that foundational work of advancing the state of the technology for messenger RNA and lipid nanoparticle vaccines also, we think, informs where we go from here. Because in many ways, the strategy has been preparing for the moment of 2020 and the transformational things that we think will come thereafter.

So looking forward, where do we think mRNA and lipid nanoparticle vaccines will make the biggest impact on human towns? We think there are 4 principles, as we've talked about before. The first is, we think combination vaccines are essential. We've already advanced 1 in hMPV/PIV3 and expect to advance many more.

The second, as we've said previously, is we think complex antigens are going to be a key feature of mRNA vaccines. One of the challenges has been making multi protein antigens like the cytomegalovirus pentamer antigen. And mRNA is uniquely capable of doing that, we believe, in a very quick and high fidelity way.

Third, the speed of development, as demonstrated in 2020 with COVID-19, we think is uniquely a feature of our technology. And we think capital efficiency, the ability to do many things in parallel, will also be foundational for the strategy of vaccines using mRNA and LNP. So how does that translate into pillars?

The first big pillar of our vaccine strategy is respiratory combination vaccines, where we think the combination of different viruses, the ability to rapidly respond to the evolution of those respiratory viruses, like flu and COVID, and the capital efficiency with which we can do that will underpin our success in that strategy. And the second, vaccines against complex antigens like CMV and others that I'll talk about in a second where we can combine multiple things and benefit from the capital efficiency of messenger RNA technology.

And third, vaccines against public health threats. If we needed any reminder, 2020 was more than enough, but we believe that public health threats are essential and protecting against public health threats are essential to our vaccine strategy because of the opportunity to show that we can generate complex antigens, do rapid development and do so very efficiently. I'd like to talk about these 3 pillars to our vaccine strategy in the coming slides.

So first, the respiratory combination vaccines. Our respiratory combination vaccines are going after one of the major burdens of disease in the world. In fact, it may surprise you to learn that lower respiratory infections are a top 5 killer globally, leading to almost 3 million deaths. Approximately 1/3 of those are from tuberculosis, but the other couple of million are largely related to infectious -- other infectious cause, including antiviral infections. Approximately 1 million deaths annually occur in high and upper income countries as a result of these lower respiratory infections. And just to give you a sense of the magnitude of the unmet need, in high income countries, respiratory infections kill more people than colorectal cancer. It's an incredibly high burden of disease.

Now that burden of disease is really divided in 3 areas. First, the very young children, those under the age of 5, often getting their first infection. Second, older adults, often those over age of 65, which experienced waning immunity of these viruses as they age. Now there is less disease in the middle stages of life, but there still are populations at higher risk of infection, including morbidity and mortality. And those are generally seen in cancer patients, immunocompromised patients or those that are pregnant. All 3 represent important opportunities and unmet need in respiratory infections.

Now as we look forward to those viruses, it's important to characterize which of these viruses drive the majority of that disease. And in fact, as you can see here, 5 or 6 viruses account for a substantial majority of them. Many of these you'll recognize from our pipeline. Looking at this data from Washington in 2018, 2019. What you can see is a large number of infections acquired in outpatient settings, across both the young and old, and focusing on 65 plus, you see high rates of infection every year in influenza, respiratory syncytial virus, human coronavirus, the rhinoviruses, melanoma viruses and parainfluenza viruses.

In fact, I'll call your attention to that third line, human coronaviruses. This is not SARS-CoV-2. These are actually the endemic viruses that we're circulating in 2018, 2019 and leading to approximately 2% of people that season over the age of 65, having an attack of an acute respiratory infection. I'd like to double-click on that population of over the age of 65 and these viruses that are driving a majority of that burden of disease.

If you look at those top respiratory viruses, actually, just in the United States, and just in the 65 population -- 65-plus population, they drive over \$15 billion of annual cost prior to COVID-19. Looking at the annual inpatient per 1,000 in the middle column here, in total, these viruses represent [17.8], approximately 20,000 people annually being inpatient hospitalized as a result of this disease.

That's about 1 in 50. In-patient mortality is quite high. You can see ranging between 3% to 7%, particularly in the 65-plus population, these opportunistic infections can lead to significant morbidity. And the total estimated costs is \$15 billion just for these viruses, and that's before SARS-CoV-2 starts to add to those totals.

If you look at what that means globally, estimated cost in just 65-plus year old adults are \$20 billion to \$40 billion annually. And even more importantly, those diseases lead to approximately 19 million years of lost disability adjusted light years each year or in 2019 alone. Obviously, there are huge and dramatic unmet need. Now our pipeline, not surprisingly, aligns pretty substantially to these areas of unmet need. And so if you look at those same viruses, and where we have programs. You'll note that in 5 of these virus families, Moderna has already developed clinical data against that pathogen. In total, the pathogens for which we have clinical data, accounted for about \$10 billion of annual cost in the 65-plus population alone. And again, that was before the COVID-19 pandemic.

Now of course, we'll continue to look at other viruses and other opportunities but also, as we've often shown in images like the right, looking at opportunities to combine pathogens into single vaccinations, something we've already done with the metapneumovirus parainfluenza vaccine, and we expect to do with many other combinations in the future.

Now that is just looking at the burden of disease in older adults on the right-hand side here. But it's just -- it's important to remember that older adults are just the beginning of the potential impact of these vaccines. There is significant additional disease in the young children, as we've spoken about previously and a need to protect high-risk populations, both cancer patients, immune-compromised and (inaudible). All of these represent key aspects of our respiratory vaccine strategy.

So now moving forward, I'd like to speak about a complex antigen, the second pillar. These are a number of diseases where we think there's incredibly high unmet need but for which vaccines have not historically been able to be developed because the combination of proteins necessary was a burden to vaccine creation with older technologies. So first one we'll speak about extensively today is the cytomegalovirus, and specifically our vaccine, 1647.

CMV, as we shared before, the leading cause of birth defects in this country, leading to 20,000 congenital CMV cases annually in the United States alone. It is a major driver of immune dysfunction with aging and a significant cause of disease in transplant population and other immunosuppressed populations.

The second is the Epstein-Barr virus vaccine, mRNA-1189. EBV is a major cause of malignancies globally, leading to 160,000 deaths due to EBV-related volumes in 2017 alone. It is also a major driver of multiple sclerosis risk. In fact, EBV infection can increase your lifetime risk of multiple sclerosis by 10 to 15-fold. So clearly, an important unmet need. In both of these vaccines, we are developing multiple mRNA vaccines with up to 6 mRNAs in a single vaccine to encode for these complex antigens, something that we think our platform is uniquely capable of doing.

The third is HIV. HIV needs no introduction as the cause of AIDS, and substantial morbidity and mortality resulting from that disease. Approximately 700,000 people die worldwide annually in 2019. In addition -- in collaboration with IAVI, NIAID and Gates Foundation, Moderna is advancing a pair of novel approaches to try and shepherd the immune system towards what we hope might be a first-in-class functioning HIV vaccine. Much work to do there but obviously, critically important.

Now third, I'd like to focus on our vaccines against public health threats and briefly speak to that. Following the traumas of COVID-19 and our experiences throughout 2020, this probably needs no justification. But it's important to note that it's been a long-term commitment of Moderna to continue to advance vaccines against pathogens or public health concern because we think they are critical to health security.

Our work with the Middle Eastern Respiratory Syndrome virus, MERS, which happened many years ago and was in part in collaboration with the National Institutes of Health, actually dramatically helped accelerate the global response to SARS-CoV-2. MERS, like SARS-CoV-2, is a coronavirus. And in fact, the improvements that were made there that are subject of a publication referenced here, were allowed Moderna and the NIH and others using mRNA technologies to rapidly and confidently move forward in advancing vaccines against COVID-19.

Now in this space, we are looking at 2 additional pathogens and 2 development programs. The first is our Zika vaccine, which was a major in mosquito-driven epidemic in 2016. That program is planning to enter Phase II; and the second is a perhaps less well-known pathogen, the Nipah virus which has high outbreak potential. And when it does break outbreak, it has a very high mortality risk, with 40% to 75% risk of death. We're hoping to enter that program into Phase I in the coming year.

So here in total is our vaccine strategy. 3 big pillars where we think mRNA-LNP vaccines will make the biggest impact to human health new decade ahead. Respiratory-combination vaccines; complex antigen vaccines; and third, vaccines against public health. We also think these take full advantage of the inherent strengths of mRNA and lipid nanoparticle technologies.

Now as an innovator, we also have the advantage of being able to protect many of these innovations over the last decade and have over 200 issued patents across our platform, including many that cover vaccines. One advantage of being a first mover and having many of these first milestones

in our experience set is that we've been able to file these foundational inventions and achieve protection for them. Just a few examples of that are shown along the bottom, including where the earliest priority dates are.

But for instance, on the left, first, the idea of mRNA and lipid nanoparticle vaccines and methods for vaccinating subjects against infection with lipid nanoparticle encapsulated mRNAs for infectious disease antigens; that we also have issued composition of matter covering influenza A vaccines in lipid nanoparticle encapsulated mRNA for the influenza AH1 strain.

Back in 2016, we have -- from 2015, I should say, you'll find compositions against coronavirus and particularly, compositions of lipid nanoparticle encapsulated mRNA, including beta coronavirus spike proteins, anticipating very much the world we're in and COVID-19 in 2020 and '21. And also see compositions against important programs like CMV, CMV vaccine compositions of lipid nanoparticle encapsulated mRNA and methods of vaccinating and also against hMPV and PIV3.

These are just 5 examples of issued United States patents that cover compositions or, in some cases, methods of our key technology improvements. The important note is that we were able to file those many years ago based on the work that we were doing. And in fact, over the last 4 or 5 years, have continued to add to that with additional patent applications and filings. We're quite proud of this portfolio and think it helps support the foundations as we build the company.

So what is our vaccine strategy in summary? First, the 3 pillars I've spoken about. Respiratory combination vaccines, complex antigens and vaccines against public health threats. We're proud of an industry-leading portfolio with 2 Phase III programs, including our soon-to-start CMV program, 9 programs with positive clinical data, and we'll be adding to that substantially; 5 more, first in humans expected in 2021 alone. And this is in the face of all the challenges of the current pandemic.

Lastly, we think we have an unrivaled foundation as the creator of the mRNA LNP vaccine field over the last decade, and that has given us a chance to have strong technical and manufacturing capabilities that we've built over those years and have come to bear in responding to the current pandemic. We also have the broadest clinical and preclinical experience as evidenced by our pipeline, and over 275 issued patents, including extensive coverage of our vaccines portfolio. We're quite proud of our strategy and look forward to a bright future broadly across our pipeline.

Now in covering our strategy, it's nearly impossible not to do a double-click on COVID-19. And particularly, how we think the COVID-19 pandemic will continue to evolve in the coming years and what it means for our strategy and product development against SARS-CoV-2.

Now in order to get into this, I'd like to take a half step back and reference what we think we can learn from the broader story of human endemic coronaviruses that I'd referenced in the previous slides. So let's start with the prior pandemics in beta coronavirus. There was a pandemic that originated in Central Asia during the 1889, 1890 winter. It happens to be, we believe, the first beta coronavirus pandemic.

It was driven by a strain of human coronavirus that's called OC43. Subsequent publications and work has suggested that, that OC43 strain actually jumped out of its bovine host, cows, into humans, approximately 130 years ago. And right around that time, there was a Russian flu pandemic of 1889 and '90 that led to millions of deaths globally. It was the first pandemic that moved very quickly because of increased mobility around the world. And that pandemic with OC43 -- which we believe is OC43, can be instructive as we look forward. So 130 years later, OC43, where is it?

Well, it still causes 3% to 5% of acute respiratory infections every year. In fact, this is a figure from a publication from scientists from the CDC showing the frequency of OC43 or other beta -- or other coronavirus infections, NL63, 229E and HKU1 over the course of time in the United States. And what you can see is approximately 3% to 5% of infections every year are identified as OC43. And that has a particular seasonality to it, as you'll note, referenced around the January or winter season every year, very similar to other respiratory infections like influenza. Those diseases -- that disease most often shows up in young children and older adults over the age of 65.

So clearly, 130 years later, OC43 is still causing some disease. And how severe is it? Well if you look at actually the severity in the over 65 population that has the highest risk, you see that there's actually quite substantial disease. I'm showing some data again from 2018, '19 here in a publication based on observations in New York City at the frequency of community-onset respiratory virus associated hospitalization. And this is again looking at the 65-plus and 80-plus populations.

And as you can see, highlighted on the left, endemic human coronaviruses, including OC43 lead to more hospitalizations than RSV or either of the influenza H strains, H3 or H1. In fact, it's approximately 1 in 200 people in the community over the age of 80 would be expected to be hospitalized as a result of 1 of these endemic human coronavirus infections.

If you estimate that impact economically across the 65-plus population, across developed markets or the OECD, that translates into over 1 million outpatient visits every year, approximately 350,000 hospitalizations and 20,000 deaths. The total direct medical expense accounting for that is estimated to be between \$3 billion and \$4 billion every year. And 50% of that is driven by OC43, 131 years after, we believe it caused that pandemic.

So looking forward and informed by that example, I think the question we should be asking is not when, but if -- but not if, but when the human coronavirus will continue to come forward. So what can we learn? Human coronaviruses cause seasonal disease in the young and the old. And reinfections will happen at varying rates. Although I haven't showed examples here, there's extensive publications suggesting between 1 and 3 years is when you would expect an endemic human coronavirus to lead to a reinfection.

A disease can often be mild or asymptomatic, particularly in the healthy, but it can also be lethal for older adults even if they're seropositive. So what are the open questions for SARS-CoV-2? Well, again, as I said, it's really when, not if reinfections will happen. And to some extent, what is the role of variants in accelerating waning immunity and those infections?

The other questions are, when will more severe disease reemerge even when those reinfections happen, particularly in high-risk populations? But clearly, the lessons from endemic human coronaviruses would suggest that you will expect eventually emergence of severe disease in those populations.

And the last question is will endemic SARS-CoV-2 mortality rate continue to be higher? Or will it drop towards the more endemic human coronavirus mortality rate of, let's say, 3% to 7% for in-patient populations that have been described previously? Clearly, these are important questions to answer.

Now how does that translate into our view looking forward at SARS-CoV-2 and how we think the situation will evolve? Well, if you look at morbidity over time, morbidity and mortality, we are clearly in the pandemic phase of the vaccine, where in 2020, there's been a quite substantial increase. And illustratively, that spike has gone up.

What we expect to have happened over the coming 1 to 2 years is a series of variant-driven epidemics, where the evolution of the virus will continue to push an opportunity for reinfections, perhaps earlier reinfections in the face of waning immunity. And that will continue until we are able to achieve broad 0 positivity in human populations. Until we're able to protect the majority of humans and achieve something akin to herd immunity, that pace of evolution and reinfection seems likely to continue. That will transition at some point into a more seasonal and endemic picture, and we think maybe 2023 plus, when you will continue to see reinfections every year more akin to what you see with the endemic human coronaviruses like OC43.

So what does that mean for vaccine? Well, during the pandemic phase, we think there's going to be a high -- heavy focus on protecting high-risk populations, and most vaccines are likely going to be based on ancestral strengths. But as we move into the variant epidemic phase, where you're going to be seeing the earliest reinfections as well as first infections in populations which still have not been protected, because they have not had access to the vaccine or been previously infected, and the focus there will be on suppressing transmission of those variants.

How do we stop that evolution in all the places it's happening? Speed and adaptability are going to be critical during this phase because the virus is going to be evolving and our vaccines and our countermeasures need to evolve just as fast. And then eventually, during the endemic phase, we think we will move to a period where multivalent vaccine approaches will provide the broadest immunity. That means not just against 1 strain of the virus, but against many strains of the virus, to make sure that we're fighting the full waterfront, protecting all the places that the virus has tried to evolve. During that phase, the focus will probably be mostly on protecting toddlers who are still seronegative, every year, birth cohorts and seasonal protection against those who are at high-risk and are seeing waning immunity, particularly, for example, the 65 plus.

So what is our strategy for combating COVID-19 and that picture of continued evolution that we described? Well, in short, it's to stay ahead of SARS-CoV-2. We think we do that in 3 ways. First, we need to continue to closely monitor emerging variants and waning immunity associated with those at high risk. Second, we need to rapidly move to update our vaccine for variants of concern, with breakthrough potential whenever we identify them. And third, we need to partner with governments to ensure access to the most up-to-date boosters. With coronaviruses, as I said, the question is when, not if they will lead to reinfections and disease. And we can't afford, with SARS-CoV-2, to lose control of it again.

So how are we doing on those 3 pillars of that strategy? Well, first, on closely monitoring emerging variants and waning immunity, there are early signs coming out of the public literature and public health reports that reinfections are happening with some of the emerging variants. I'm showing 1 example here from Brazil, but similar reports have been coming out of South Africa and other geographies.

Now in this case, 1 of the early waves of infection, has been suggested, led to seropositivity of upwards of 75% in Brazil over the summer of 2020. But the evolution of a new strain, P1 led to a second wave of infections approximately 8 to 9 months later. Again, similar stories have been told against other strains, particularly those in -- those first identified in South Africa, called the B1351 strain. That strain has been associated with increased transmission, higher viral burdens and possibly reinfections and increased mortality in infected persons.

All vaccines that are based on the Wuhan strain have reported reduced neutralizing activity against this B1351 strain. And sero from individuals vaccinated with mRNA-based vaccines, including the figure on the left, had about a 6-fold reduction in that neutralizing activity. That's good news and bad news. We were still seeing high neutralizing protection, and there's good reason to believe that our vaccines and other vaccines continue to be effective immediately after vaccination. But the reason for concern should be that as you start lower with neutralizing titers, waning immunity or the loss of those titers over time might happen faster. And that's one of the reasons that we particularly want to remain vigilant.

So as we closely monitor those emerging variants and that concern about waning immunity, we think that there's a convergence on these new strains. There are lower neutralizing titers, which does suggest that there's a chance that we'll see earlier reinfections and maybe even a hint in some data that that's happening within the year. We see increased transmissibility from these variants of concerns through public reports and that could increase the exposure risk to hyper-risk populations. If the virus is jumping between people with increased transmissibility, that might mean that those who have been vaccinated might be exposed more frequently or to higher viral loads, and that could pose a threat even if you've been vaccinated.

And it's important to know that we're not standing still with this virus. The immune pressure of vaccination and prior infection in the selection of the virus is just beginning. It's going to continue to evolve and see new variants. And if we wait until it's too late, it would obviously be a mistake.

So that brings to the second piece of our strategy. We do need to rapidly move to update a vaccine for variants of concern. And in particular, we've identified 2 that we think have some breakthrough potential in terms of earlier waning immunity and eventual reinfections.

I'm showing here 3 of the key strains and a picture of the spike protein across them. The spike protein is shown -- it's actually a trimer, 3 parts of the protein and the 3 parts of color, the tan, the purple and the pink, actually are those 3 identical parts of the spike protein coming together.

On the left, you see the B117, often called the U.K. variant. In the middle, the B1351 variant, which is often called the -- a variant first identified in South Africa. And then P1, the variant on the right, that was first identified in Brazil.

Now I'm highlighting 2 key portions of that protein, the receptor binding domain RBD and the n terminal domain NPV at the top. These are places that interact with the cell in a human as the virus tries to infect them. And they're incredibly important places where the virus continues to evolve its spike protein. They're also important because the spike protein is what we express in our vaccine and all of the vaccines. And therefore, it's a place where we need to be most vigilant in making sure that we're tracking evolution.

Now all of the different mutations that have been acquired by these different strains versus the ancestral Wuhan virus that is the basis of our vaccine are highlighted in red. And the numbers identify the amino acids that was changed, for instance, 501 and the change from n to y. All of those are annotated throughout.

I'd like to focus for just a minute on the receptor binding domain mutations. Now we had shown this slide back in January when we first started down the path of developing an updated vaccine. So quickly, we're now looking down from the top part of the spike protein and just the receptor binding domain. And as people probably know, the receptor that these virus bind is called the ACE2 receptor, A-C-E-2 here, and that's shown as these 2 yellow ribbons. And again from these pictures, what you can see in the red is where has the virus been evolving and changing its strengths, where are the mutations that might be impacting either its ability to bind the receptor or your immune system's ability to recognize the virus based on its prior experience with the ancestral Wuhan strain or a vaccine.

Now the U.K. variant on the left-hand side, B117, has 1 mutation that's been widely reported, N501Y. But what you can see is both the B1351 variant and the P1 variant, the first reported in South Africa and Brazil, respectively, have acquired that mutation as well, as well as 2 other critical mutations, E484 and K417 changes. Based on those changes, many people have been identifying an increased risk of [current visibility] infection associated with this virus. And they've also been reporting that this has decreased the neutralizing potential of both prior infection and vaccines.

So clearly, RBD changes are essential, but they're not the only ones happening. And I'd like to take a moment to talk about the N-terminal domain, the other part of the protein that interacts with a human cell.

So the internal domain mutations are less convergent, less consolidating into a few changes. And that probably reflects the fact that they're not facing a receptor alone like the ACE2 receptor and have a little bit more flexibility. That also poses a bit of a challenge because more of these mutations, as they diverge from each other, leads to an important need to look for where are the N-terminal changes that we want to update in the vaccine.

Now as you can look left to right, the U.K. -- first described in the United Kingdom variant, B117, had a relatively small number of changes in its N-terminal domain. But the 351 variant and the P1 variant both acquired substantially more mutations. And in fact, the 351 variant has the largest number of them. As we and others have looked at cross neutralization between them, often, because of these variations in the N-terminal domain, 351 actually has been the furthest to escape, even more so than P1.

And for that reason, we announced a strategy in January: update the vaccine to include 351 in our purchase. That included a Phase II trial that's already underway and 3 boosting strategies. The first was mRNA-1273.351, a variant-specific booster candidate that was based on that variant first identified in South Africa and included the RBD and NTD mutations described there. We've been evaluating that in 2 dose levels, 20 micrograms and 50 micrograms. The second strategy was a multivalent booster candidate, which combined our older vaccine 1273, with 1273.351 into a single dose of 50 micrograms. We looked at that multivalent vac booster as an opportunity to increase the broadest amount of immunity across the evolution of the virus, both ancestral and new strains. And then third, given the remarkable efficacy that we've seen with our mRNA vaccine in mRNA-1273, we also tested a third dose of the Moderna COVID-19 vaccine, but as a booster this time, importantly, only 50 micrograms.

All of that has been moving forward, and we'll be providing updates as we go, but I wanted to share some recent preclinical data on those 3 strategies and how we've been learning from this as we shape our clinical strategy going forward.

So first, we were able to show in a preprint that was posted recently that we were able to improve neutralizing titers against the B1351 strain with mRNA-1273.351. That's the strain specific vaccine when it was done as a primary series, and that's illustrated here in the blue, with higher neutralizing titers against B1351. But importantly, we were able to also show that the multivalent vaccine, that's a vaccine that includes both the ancestral strain, the Wuhan-based strain and the most recent and most advanced 351 strain into a single vaccine, actually had the broadest neutralizing immunity. That's evidenced here by the red bars. And particularly on panel D on the far right of the figure, you'll see balanced immunity between the older D614G, that's the Wuhan Ancestral strain and the more recent strains, B1351, particularly the South African Variant.

We think that bears -- bodes well for the use of the multivalent vaccine in the future. And we also looked at the ability to boost immunity to folks who have previously been vaccinated, in this case, mice, and looking to boost 6 months after a primary series of our 1273 vaccine. We showed that a boost of the 351 variant booster closed the neutralizing titer gap for the variant of concern.

On the left-hand side, you can see the relative titer chain. It was a 15-fold increase against the B1351 variant. And on the right-hand side, you can see the result of that, comparing both the ancestral strains, again, D614G and the 351 variant. And you see, again, the emergence of balanced,

more balanced immunity between those strains with a third dose, a booster, against the new variant of concern. Obviously, that bodes well for the ability to develop vaccines and boosters against the new variant of concern before.

So where is our strategy for combating COVID-19 going forward? So first, as I've shared, we are closely monitoring variants and waning immunity. And we think there are 2 variants of concern that do pose a risk for earlier waning immunity in high-risk population. We'll keep looking for others. The virus is by no means done evolving and other presenters today will share their thoughts on that.

Second, we're going to rapidly move to update the vaccine as soon as we think there's a variant concern that has some breakthrough potential. Again, breakthrough in terms of waning immunity, not immediately after vaccination. The addition of the 351 strain to our vaccine provides good coverage against the current variants of concern as evidenced in that publication. And multivalent vaccines, we believe, are going to provide the broadest neutralizing immunity, including against other variants that are going to continue to emerge.

We're evaluating 3 strategies in the clinic right now, and the initial dosing is complete. And what we've already started to do is scale up for commercial manufacturing of these new strain-updated booster vaccines to make sure that we're able to meet our third objective in our strategy, which is partnering with governments to ensure access to the most up-to-date boosters so that we can continue to fight this pandemic together.

So I think -- thank you for your time, and I'm sure that we'll be getting a number of questions on our overall COVID-19 strategy. But before getting to that section, I'd like to turn it over to Jackie Miller to speak to our COVID-19 data to date. Jackie?

Jacqueline Miller - Moderna, Inc. - SVP of Infectious Disease Development

Thank you, Stephen. Good morning, everyone, and thank you for the opportunity to review our progress in our vaccine pipeline this morning. For the first focus of our agenda will be the worldwide development of our COVID-19 vaccine.

Next slide, please. So the COVE study or COVID-19 efficacy and safety study is our pivotal study for the authorization of COVID-19 vaccine. As a reminder, we enrolled 30,000 participants who were randomized one-to-one to receive Moderna COVID-19 vaccine, 100 micrograms in a 2-dose series or placebo. We have now unblinded and crossed over placebo recipients with over 27,000 clinical trial recipients or participants now having received the Moderna COVID-19 vaccine as of April 9, who will continue to follow-up as part of the COVE study.

When our vaccine was originally authorized in December, we reported a vaccine efficacy of 94%. And we are now getting ready to update that analysis in the coming weeks with the full unblinded data set. And we have reported that we anticipate the efficacy to be greater than 90% against cases of symptomatic COVID-19 disease and greater than 95% against severe cases, with approximately 6 months of median follow-up post dose 2.

Next slide, please. Next slide. So we will continue to provide updates on the COVE study throughout 2021. We have a number of important updates in the coming weeks, including information on the efficacy of the vaccine against asymptomatic infection, genotyping of the strains of SARS-CoV-2 that we have detected in our clinical trial, and the work we are doing to identify a correlate of protection. We have recently published our 6-month antibody persistence data from the Phase I study, and we'll continue to provide updates on antibody persistence from all of our studies as they become available.

Next slide, please. We also have ongoing clinical trials, which will generate the data needed to expand our vaccine to other at-risk populations. Our TeenCOVE study has been designed to evaluate the safety and immunogenicity of Moderna COVID-19 vaccine at the 100-microgram dose, compared to placebo in children 12 to 17 years of age. We fully enrolled this study, which includes over 3,000 children in the U.S. KidCOVE is another companion study to COVE and is designed to select the appropriate vaccine dose and then evaluate the safety and immunogenicity of Moderna COVID-19 vaccine in children 6 months to 11 years of age. This trial is expected to enroll over 6,700 children in the U.S. and Canada. Finally, our partners at Takeda are conducting a Phase I study in Japanese participants, which is a regulatory requirement for authorization in Japan.

Next slide, please. We're continuing to follow the participants from our Phase I, II and III studies with Moderna COVID-19 vaccine. In a recent letter to the New England Journal of Medicine, our colleagues at the NIH reported on the persistence of antibodies after a 2-dose schedule of Moderna COVID-19. Binding and neutralizing antibodies were reported in 3 assays.

The results on this slide are from the pseudovirus mutualization assay. Each COVID line represents 1 of 3 age strata, 18 to 55, 56 to 70 and over 71 years of age. Antibodies persisted in all 3 assays for all 3 age strata, although titers were noted to decline further in the older age cohorts as compared to the group 18 to 55 years of age. These data highlight the importance of future booster doses to maintain protection against COVID-19, which we are evaluating both with Moderna COVID-19 vaccine and with mRNA sequences modified to address variants of concern, as Stephen previously reviewed for you.

Next slide, please. While all of this development work is ongoing for mRNA-1273, we're continuing to innovate with the vaccine formulation. mRNA-1283 is a next-generation construct intended to improve vaccine potency at lower doses and improve the length of shelf life and stability at refrigerator temperatures. The mRNA sequence includes the receptor binding domain and the N-terminal domain, which, as Stephen explained, are the 2 sections of the spike protein containing the most important epitopes for the immune response. Our Phase I dose-ranging study was initiated in March.

So that concludes the discussion of Moderna's ongoing development activities for COVID-19 vaccine. We're now going to invite 2 of the leaders in infectious diseases to speak to us about ongoing research into viral mutants and analytics to predict protection against COVID-19.

It now gives me great pleasure to introduce Sir Jeremy Farrar, the Director of Wellcome since October 2013. Prior to that, Sir Jeremy served as the Director of Oxford University's Clinical Research Unit in Vietnam for 18 years. As the author of more than 600 publications, he's widely recognized as an expert in global health and infectious diseases.

So Jeremy, thank you for joining us today, and over to you.

Jeremy Farrar

Yes. It's a great pleasure, and it's -- I hope you can all hear me. It's -- I'm speaking down my phone. If you go to the next slide, please. And just to pay tribute to what you've all done over the last year or so, been little short of remarkable since -- I remember meeting some of you in Davos, in end of January 2020. The first slide shows you what I think where we are, and I'll come back to this later in the talk. But I -- what amazed me is -- with a background in emerging infections, actually, it's just how predictable 2020 was.

It was often made more complicated, I think by politics, is the truth. But the reality was, I think, from the middle of January onwards, when we knew this was an animal virus that had come across to humans, that essentially humanity had no immunity, that it was spread by the respiratory routes with a natural R of maybe as high as 3 or a little bit above.

So we had, at that time, no diagnostics, no treatment and no vaccines. And then it happened in a major urban center, which was highly connected with the rest of the country it was in and the rest of the world. And that was an asymptomatic transmission all the way through to very [severe and death]. Those are the features, which any undergraduate program of concerns about the emerging infection would make you worry. And from that moment on, which was essentially from the 24th of January, I think it was very clear, the pathway that 2020 took. I think we're in the reasons we just heard, in part, in for a much less predictable 2021 and beyond. And that's part of the topic of what I want to talk about.

Next slide, please. I think it's always helpful to have a little bit of who's talking to you, especially when it's virtual and even down a phone. That's me on the left of the screen there, slightly younger than today. Born in Singapore, lived in a host of countries as a child. My father was an English teacher. Came to the U.K. as a teenager, studied medicine in London and then in Edinburgh, Oxford, Melbourne and at UCSF in California. And then was planning to be a neurologist, in my original trade of neurology and immunology, but took the opportunity to go to Vietnam in 1995 for what I thought would be 13 -- 3 or 4 years, but actually stayed 18 worked all the way through that.

Next slide, please. Essentially, at this hospital in Ho Chi Minh City in the south of the country. This is The Hospital for Tropical Diseases, I think it's the largest infectious disease hospital in the world, dedicated to infectious diseases in the world. Originally built during the French (inaudible) in the 19th century, but then upgraded at the very end of the Vietnam War. And Vietnam was a very special place to do clinical research and had an amazing 18 years there, but also became very involved in -- from 1999 onwards, with the Nipah outbreak in Malaysia, then to Singapore and of course, now to Bangladesh, but also SARS 1, and lost a lot of very good friends to SARS 1. And those scars stay with you for the rest of your life, through bird flu, through Ebola, and of course, now coming into 2020 and SARS-CoV-2.

Next slide, please. For reasons which I do still sometimes question, I left the beauty of Vietnam and the beach scene, not so far from where I worked for 1.5 hours commute every day from where I live here in Oxford into London until we shut down in March 2020. But it's been a great privilege to be head of the Wellcome for the last 7 years. The Wellcome is the second largest research charity in the world with assets of some \$45 billion or \$46 billion and dedicated to science, to innovation and to society to improve health through the best research that's possible.

So personal view here, next slide, please, of the new global health. And I think it's in this context that we all need to think. I'm very interested in what role in future organizations such as Moderna might play into it. And I think for me, the interesting thing here is actually the convergence that's going on.

The world is undoubtedly becoming smaller. The international travel and trade is obviously making things spread more quickly in emerging infections. But also in the noninfectious disease area, there is a convergence of illnesses, of health, of disease with the growth of the noncommunicable diseases at a global scale, cancer, diabetes, impacts of obesity and everything else that goes with it, autoimmune disease as people's lifestyles and others change.

And therefore, there is less of a demarcation between what happens here, wherever here is to everybody in the world listening and what happens over there, because of that travel and connectivity and the ability of pathogens to spread around the world. But also because the underpinning health is changing and actually converging. And I think it's very important for us to appreciate that convergence is going on and will come to be the dominant effective global health of the 21st century.

But also a reminder that we remain very, very vulnerable. And we've seen that over the last year. Many of us, as you know, have warned on this for the last 20 years. And if you just look back over those last 20 years, and it goes back, as I mentioned earlier, to Nipah in 1999, and that is just a list there in front of you that I put forward without going through a literature or anything else. So that's just epidemics that I've been involved in, in the last 20 years. And there is many that I've not been involved in that is not on that list. But each and every one of those, in either national, regional or global ways, caused enormous disruption.

You've got to remember that health systems around the world, as in the picture on the right there of the list, are very fragile, very vulnerable, and we've essentially underinvested in our health systems, particularly preventative health systems around the world. Societies are changing. Animal human interfaces are changing. And when animal human interfaces change and then they're part of these enormous cities that we now mostly live in and then those cities are very connected, then the ability for something to spread very, very quickly at the speed of COVID and even quicker potentially, is the world that we now live in. And it's that world that we must prepare for rather than the world of the 20th century.

Next slide, please. This is just a reminder, I was very involved in the Ebola crisis in West Africa in 2014 to 2016. And a good friend, Peter Piot, of course, was very involved in the original Ebola description of 1976. And what's important to remember is in that -- it's a single person's career. Peter is still very active. And in that 30 or 40 years, the world has changed in ways that are simply remarkable.

And if you just take the impact of Ebola, the picture on the top left there is of the Ebola River on which the virus was named in 1976. For the next 30 or 40 years, Ebola was essentially a disease of rural populations. And yet over that time, and this is what led to the crisis of 2014 to 2016 in West Africa where 11,000 people died, we almost forget that now in the context of COVID, but we must not because the virus has not changed in those 30 or 40 years.

The Ebola virus today is very similar to the Ebola virus Peter described in 1976. The genetics of the individuals infected has not changed. What had changed is society had changed around it. The environment has changed, the way we live changed, migration patterns have changed, technology

changed and indeed, society had changed. And so in 2014, Ebola not only spread in the context of a very rural community that could be isolated, and it could be contained as an epidemic, but the Ebola reached the big cities of West Africa.

In Ebola in 1976, the average person with Ebola met 6 to 7 other people and had the chance to infect 6 or 7 other people with Ebola. In 2014, that same individual, infected with Ebola, met over 200 people. It is that interconnectivity, that ability to pass it on to a much larger number of other people that has led to the Ebola crisis in 2014 and indeed has led to COVID of 2020 and ongoing.

Next slide, please. I was not alive in 1918 during the influenza pandemic. But obviously, as a great believer in history, in the impact of history, I've read many, many books on 1918. These are 3 graphs from London, Paris, New York and Berlin in 1918. On the right, I hope you can see, is a graph of the start of the H1N1 pandemic in Mexico City in 2009. And I was in Mexico City at the start in May of 2009, at the start of the pandemic. And at that time, I was very, very worried.

The hospitals of Mexico City were full of young people with very severe respiratory illness and tragically died of that influenza. And when I went there as part of a WHO-linked assessment of the situation, it seemed to me that we were facing the pandemic of influenza that we all feared. Now as events turned out, of course, that proved to be not true. It was transmissible, but it was not as -- it did not cause such a high-case fatality rate. And therefore, many people said, you've cried once again.

Just come forward now to Wuhan in 2020 at the bottom. And the thing I want to take away from these 3 slides is in your first phase of an epidemic, things happen very, very fast. 42 days is a number to remember. If you look at the curves, London, Paris, New York and Berlin, the first wave, when it is so important to learn what you have to learn in order to protect the public was 42 days. There were, of course, subsequent waves, the pandemic of 2018 -- '19, '18 spread around the world over the course of the next year. But the first wave, which is so important to intervene in and learn from, lasted about 6 to 7 weeks before subsequent waves.

The Mexico outbreak of 2019, in Mexico itself, lasted 6 to 8 weeks. And then it started to come down. Subsequently, there were further waves. If you look at Wuhan, again, the first opportunity to learn about the virus, the clinical syndrome, the ability to prevent transmission and indeed, the starting of vaccine development lasted that short 6 to 7 to 8 weeks.

The message here is that epidemics do follow a trend. Of course, they're all different, but the rules of epidemics are fairly generic. And speed is of the utmost importance, speed and the ability to implement. And you -- if you get behind that epidemic curve, you will always be playing catch up, and that's extraordinarily difficult.

Next slide, please. If you live in Oxford, as I do, or London or New York or Washington at the moment, China as well, you may be forgiven for thinking the worst of the pandemic is over. This goes -- this graph, thanks to the John Hopkins Group goes through to the 1st of April. This is a horrifically worrying curve in my view. We can see peaks in -- around the November, December, January, which was effectively the second wave in many parts.

But if you go forward to the right side, into April 2021, that expansion of the epidemic to me is as worrying as at any point in this pandemic. You can see that the growth is happening in Central and South America, in Europe, tragically at the moment. In Asia, particularly in India at the moment, Pakistan, Bangladesh, Sri Lanka, the epidemic curve is going up. And that area of Southeast Asia, remember, is home to about 1.6 billion to 1.7 billion people.

Africa may be protected by younger demographic and by being not so connected as other continents. But nevertheless, I still think Africa could be at grave risk of a future upswing in this pandemic in the future. I don't think Africa has yet been affected as it might well do.

But those epidemic lines are really frightening, I think. Because what has happened through 2020, and I'll just go to the next slide, which has been beautifully explained already about mutations. And I know everybody at the donor is giving a huge amount of thought to the mutations and the viral mutants.

But if I go to the final -- the next slide of that graph again, the ability to mutate a virus is driven by the evolutionary pressures that are under it. During 2020, those pressures were mostly as the virus was catching hold in humanity. It was adapting to the receptor, it was increasing its binding. It was perhaps increasing its ability to transmit from 1 person to another. It was increasing its biological capacity to gain a foothold in humanity.

And over the course of 2020, of course, increasing numbers of people were infected. As we're now in 2021, that biological adaptation is being, if you like, added to by the immunological adaptation as this virus now faces both the biological need to adapt or evolve but also the biological need to escape from natural or vaccine-induced immunity. And so the virus is now under more than the biological adaptation pressure. It's also under immune pressure.

And I think what that will lead to, especially if we allow this pandemic to expand into very large populations where transmission is not controlled and vaccines are not available to keep ahead of the vaccine variant -- virus variants, then I fear that we are opening up the possibility of variants that truly escape natural immunity and, indeed, vaccination. And our ability to stay ahead of that new variants concern is hampered if we allow transmission at global level to continue on that upswing that you can see in that graph.

And that's why the ability, next slide, to appreciate that the health issues that we face, the great challenges we face in the 21st century are going to be about the convergence of health. Health will look less like different here to different somewhere else. The speed at which one needs to act, the speed of ability to innovate, the ability to take that innovation to scale, the ability to use platforms so technological advances have a regulatory pathway, which is facilitating, not an impediment. That we will see increasingly in the future, I believe, the convergence, but also the blurring of definitions. I think in the future, what we currently think of as a vaccine and what we currently think of as a drug will be increasingly blurred, and we will be delivering what we might think of drugs being an approach that might look more like vaccines. And I think the RNA technology will open that up in ways that we can't even yet really consider, but which I think is incredibly exciting. And the platform technology behind that are going to be crucial.

And I suspect the future is going to be in the innovation around that and the software, if you like, rather than necessarily in the hardware of the manufacturing and the processes. That is very important, and we need to advance and technologically innovate on manufacturing. But the ability to innovate around what I call the software, the intellectual underpinning of innovation, I think, is going to be crucial. But equally in the last comment there, is unless we also learn to distribute and make accessible these innovations in an equitable as possible way whilst protecting all of the intellectual property and skills that go behind it, then I fear we are -- as we are now in COVID, opening ourselves up to an even worse situation in the future.

And last slide, please, and I mentioned Peter earlier, we -- some of you actually sent me this recently. This was from 2014. And I think it still rings true, so I won't read it all out. I'll let you read it as it's there on the slides. But just to say that as a result of biological shifts and changing of society, fragile health systems, what might have once been a limited outbreak can become a massively potentially uncontrollable epidemic. It's remarkable to -- it's sad to read those words today. But critically, the next paragraph, we have to be prepared for this future with the diagnostic tools, therapies, but crucially also the vaccines for these relatively rare but inevitably potentially devastating epidemics.

And although we have had better surveillance, we've got to get quicker at acting, and that goes back to my comments about convergence, about speed, about innovation and the ability to work through platforms with new regulators and get manufacturing at scale.

I finish by, once again, going back to the final slide. We've been through a remarkably predictable 2020. We must have the humility to think that the future is going to be less predictable, and we're going to have to prepare for whatever nature throws at us. We can mitigate that by reducing transmission and making vaccines available globally, but those curves at increasing transmission in Asia at the moment, Central and South America and essentially Africa, I think, are very sobering and very concerning.

Thank you for the invite to joining you. I hope that was of some interest. And I'll pass back to the team at Moderna.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Thank you so much, Sir Jeremy, for that excellent and sobering talk. I'd now like to hand the podium over to Professor Miles Davenport. Dr. Davenport is Professor of Medicine and Head of the Infection Analytics Program at the Kirby Institute of the University of New South Wales. Professor Davenport will be speaking to us about using advanced analytical methods of existing efficacy and immunogenicity data to predict protection against COVID-19.

So Professor Davenport, please go ahead.

Miles Davenport

Thank you for the opportunity to speak today and present our work using mathematical modeling to try and predict future protection from SARS-CoV-2 infection.

Many of you will be familiar with the traditional vaccine development pipeline, that is Phase I or safety studies involving small numbers of patients. Phase II or immunogenicity studies involving tens of hundreds of patients and measuring immune responses in the laboratory to check that the vaccine is inducing the responses that we want. And finally, Phase III or protective efficacy studies where tens of thousands of people are often involved and patients are studied to see that the vaccine reduces infection.

Now a number of vaccines have been through that pipeline, and we find ourselves at a stage where there are some additional questions we'd still like to answer. In particular, how long will immunity to infection last and how long will the vaccines work against new viral variants? And one way to address this question is obviously to perform more Phase III studies looking out longer over time or looking at infection with the different variants. And that work is ongoing but obviously quite expensive and it takes a while.

An alternative is to try and look at how immunogenicity, the level of immune response we get to a vaccine, might predict efficacy. And this is referred to as a correlate of protection, something that will predict protection. And for those of you that are interested, I'll refer you to a presentation by Professor Paul Heath at last year's Moderna Vaccines Day where he talked about this in quite some detail.

So for our studies, we were interested in analyzing the neutralization titer to SARS-CoV-2 because the ability of antibodies in the blood to neutralize the virus have been shown to be predictive in a number of other viral infections.

So what is the neutralization titer? Well, essentially, it's the dilution of a patient serum that is still able to neutralize the virus in an assay performed in the laboratory. So for example, if you take the serum and you can dilute it 1 in 10 or 1 in 20, obviously, the antibody level is getting lower as you dilute this serum. And you finally create a dilution at which you can still neutralize the virus. And that's the thesis that it might be 1 in 40 or 1 in 80 dilution, for example, that can still neutralize the virus.

That's great, and that's been measured in all of the vaccine studies. But the key question is, how does this level of neutralization in the test tube predicts protection from infection in a patient? So the available data out there is neutralization titers measured across all of the different vaccine studies as part of their Phase II trials. A significant challenge is that quite different ways of measuring neutralization was used. So some different viruses, different cells and different laboratory methods. So you can't directly compare the number from one trial with the number from another. However, all of the trials also tried to standardize the neutralization of the vaccine against the neutralization of a convalescent cohort of patients who've being recently infected.

So if we standardize all of these neutralization levels against the convalescent, that will at least maybe allow us to compare between studies with the -- again, a caveat that there was a slightly different definition of convalescent patients in the different studies.

In terms of the efficacy, there are also slightly different ways of measuring protection in the different Phase III trials. But all of those limitations, notwithstanding, if you look at the average neutralization titer measured in the Phase II studies against the protective efficacy measured in the Phase III studies, you can see there's quite a strong relationship. Right in the middle there in blue is the convalescent cohort. Of course, it -- average

neutralization titer is 1 because we've standardized everything against that. And convalescent subjects have 89% protection in the study. We looked at there are some different estimates out there also.

So if this is the relationship between neutralization and protection, we can answer the question, does neutralization predict protection? Yes, it does in this circumstance.

The next question we'd like to ask is how large a response is needed for protection so we can predict how good a vaccine needs to be, for example. So to go about this, what we use is the fact that there's a distribution in the level of neutralization amongst the population. So if you vaccinate a group of people, they don't all have the same neutralization titer. And we would suspect that those that have a higher level of neutralization on the right will be more protected than those on the left.

So if we have a situation where, for example, we find 95% of people were protected and 5% was susceptible, then we might suspect that, that level of neutralization that divides off the bottom 5% of titers is going to be the level that provides protection. Studies in other viruses suggest that the cutoff is not quite so sharp. So there's not a level where you're fully protected just above that level and not protected below it. In fact, there's a range in which people start to acquire protection and have different risks. So we'd like to find the level of neutralization that provides 50% protection from infection.

So using this approach, we took data from the 7 published vaccine studies at the time and from the convalescent study and used modeling to try and fit across all of those studies what the optimal cutoff for 50% protection would be that would accurately predict the protection observed in those studies.

So when you do that, we find that the 50% protective titer is equivalent to a level of about 20% of the normal convalescent titer. And so that would explain the level of protection we saw against all of these studies. So now we can take that mathematical relationship and we can plot what that would look like on this graph of neutralization titer against protective efficacy. And the solid red line is our best fit of this model and the shaded area indicates the confidence intervals around that.

So now we have that relationship, we can ask, could we predict the efficacy of a new vaccine? So right around the time that we finished that modeling on the 7 vaccines and the convalescent subjects, the results for an 8th vaccine were announced by Bharat Biotech and their vaccine, COVAXIN. So based on the neutralization titer from the Phase II that had already been published, the model predicted that the vaccine should have 79.4% efficacy. But in fact, we observed an efficacy of 80.6%, which we felt was very close to what was expected.

So in addition to being able to predict the efficacy of the new vaccine, what would this relationship between neutralization titer and efficacy tell us about what would happen as immunity wanes after vaccination or after infection? So for example, if we have a twofold drop in neutralization titer, what would that mean about our protective level? It's important to note as well that this is not consistent across the different levels of initial neutralization level. For example, if you start with a lower initial neutralization level, a twofold drop will lead to a much greater decrease in the protective efficacy. So to do that though and understand what's happening -- going to happen over time, we also need to understand how the neutralization titer decreases over time. And unfortunately, we don't have that information for vaccine studies yet.

But what we did was to look at the literature and extract data on the decay in neutralization titer in convalescent subjects. And you can see here data from a number of studies. Some of them looked over shorter term and some are longer period. The study in red there, Wheatley et al, we were part of that study and had access to the raw data. But you can see that there's a general trend that over the short term, there's a relatively fast decay. And the longer the study goes on, the slower that decay looks. For the purposes of the modeling I'm about to describe, we used the data from Dan et al, and they studied the decline in neutralization titer over the first 8 months after infection. And they found that on average, there was a half-life of 90 days in that period.

So we can take this rate of loss of neutralization titer in the convalescent subjects, the relationship between neutralization titer and protective efficacy. And we can predict how efficacy might change over time after vaccination, assuming that the vaccine neutralization response decays at the same rate as the convalescent one.

So you can see here the different lines indicate vaccines that start with different levels of initial efficacy. So for example, a vaccine that starts at 95% initial efficacy is expected to drop to about 60% efficacy after 250 days. By contrast, a vaccine that starts with 70% efficacy is expected to have a greater drop. And again, that's because of the shape of the curve on the left, that it gets steeper at lower neutralization titers.

So the other question we wanted to address was how the vaccines might work against different viral variants. And you will no doubt be familiar in the news from different variants that have been discovered around the world. And 2 of these, in particular, often referred to as the South African or the Brazilian variant, have been shown to induce a decrease in neutralization titer by about 5 fold. So antibodies is just less effective against these variants.

So we can use the model also to predict how effective or how much protective efficacy we'd see against different variants by considering how the decrease in neutralization titer would translate into a decrease in protective efficacy.

So everything I've talked about up to now is about protection from detectable SARS-CoV-2 infection. And so this is my sort of schematic representation of how I think about the viral levels and severity of illness in a patient population. So a small number of people have very high viral loads and severe infection. The majority of individuals have intermediate viral loads and mild to moderate infection, and some patients have very low viral levels and no clinical symptoms.

So in this sort of schematic representation, vaccination is expected to push the average viral level down. So some proportion of people will have undetectable infection in the gray on the left. And some people will just have very mild illness. So in the Phase III trial, generally, it's looking at symptomatic detectable SARS-CoV-2 infection. And so we're mainly measuring people in the middle of that because there's relatively few severe cases in these studies.

But what we might expect is that the decrease in severe cases might actually be greater than the decrease in mild to moderate cases. So can we use our model to predict how many antibodies you need or what neutralization titer you need to protect against severe infection? So when we do that, we estimate there is indeed a lower titer required for protection against severe infection, 3% of the convalescent titer as opposed to 20% of the convalescent titer to protect against mild or any infection. You can see at the bottom there, there's a caveat that there have been less than 100 severe cases seen across all of the vaccine studies. So we have relatively little data to estimate this, although we're confident that the level of protection against severe infection is lower than that against any or mild infection.

So how might the loss of immunity play out over time against both severe and mild infection? So this is extrapolating forward from the data we have. So for example, up to 250 days, we're using the half-life of neutralization that was measured by Dan et al in their study. That's 90 days, half-life of 90 days over the first 8 months. So then we're extrapolating forward from that and assuming that the half-life will become very long, for a few years. And that's because there are a number of studies that are booked at the half-life of antibodies to other vaccines after decades after vaccination or infection and found this long half-life. So we're assuming that the decay of antibodies will slow down and extrapolating forward.

So in this case, thinking about someone who has been infected, and so they are a convalescent subject. They start off with an average convalescent titer. So the ratio to convalescence is 1, and then that will decrease over time. Now we predict that sometime within the first 250 days, their protection will drop below the 50% level. However, if it stabilizes in the long term, it's likely that they'll maintain 50% protection from severe infection for a long period.

You can use the same approach to think about how different vaccine responses might play out over time. Again, I'll emphasize that we're extrapolating beyond 250 days, and we're also assuming that the decay of neutralization titer after vaccination will be the same as that observed in the convalescent subjects. But with those caveats, you can see that going forward, obviously, if you start with a much higher initial convalescent titer, you might maintain your protection much better and, in fact, maintain above 50% protection for a prolonged period. By contrast, if you start with a very low titer, you may even drop below the 50% protection against severe infection.

So I hope I've made clear the number of caveats for this modeling study as we've gone through. So for example, in the vaccination studies, there were a variety of different tests in neutralization and different definitions of protection and relatively little data available on severe infection.

Similarly, when predicting future efficacy, we've relied on data from convalescent subjects because we don't have sufficient data going forward on vaccinated subjects yet.

But the implications of this, for example, are, if you think about protection from any SARS-CoV-2 infection, for example, we may need to vaccinate -- revaccinate within a year in order to maintain greater than 50% protection in subjects. Similarly, many of these variants may significantly undermine the efficacy of vaccines, and we may need variant-specific vaccination.

However, if we think about protection against severe SARS-CoV-2 infection, because a smaller level of antibodies are required, we predict that protection against severe infection will be considerably more robust over time.

So I'll thank you again and take questions in a question session later.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Thank you, Professor Davenport, for the fascinating look at mathematical models for vaccine efficacy. We're now going to shift gears and discuss another vaccine candidate currently in development for protection against another respiratory pathogen, respiratory syncytial virus, or RSV. And specifically, we're going to speak about our third generation candidate vaccine, mRNA-1345.

Next slide. So RSV is a respiratory pathogen that repeatedly infects us throughout life, with nearly all children being infected by the age of 2 years. This virus causes lower respiratory complications, including wheezing, bronchiolitis, pneumonia and respiratory distress, with nearly all of the morbidity and mortality occurring at the extremes of age. So in young children as well as older adults over 65 years of age. Children under 5 are hospitalized in the U.S. at a rate of approximately 3 per 1,000, resulting in annual hospitalizations numbering over 86,000 per year. There are even more hospitalizations in the U.S. amongst adults 65 years of age and older, with approximately 177,000 hospitalizations and 44,000 deaths -- or 14,000 deaths, excuse me, each year. Taken together, treatment for the complications of RSV in young children and older adults accounts for over \$5 billion in annual U.S. health care costs.

Next slide, please. RSV has a surface glycoprotein called prefusion protein or F protein, which mediates viral entry and cell-to-cell spread by membrane fusion. Because of the importance of this protein to the virus, the F protein is highly conserved and is the target antigen of mRNA-1345. After fusion with cell membranes, this protein undergoes a conformational change from the prefusion to the postfusion form. And similar to the spike protein of the SARS-CoV-2, the prefusion conformation is observed to be much more immunogenic. And therefore, the F protein in mRNA-1345 is also stabilized in the prefusion conformation.

Next slide. So now let's review the design of our Phase I study of mRNA-1345. This is a randomized, placebo-controlled dose-ranging study being conducted in healthy younger adults, older adults and seropositive children. The primary objective of the study is safety, and we will be assessing for the adverse reaction profile as well as the potential for vaccine-associated enhanced disease in the seropositive children. Immunogenicity is also being evaluated to allow us to investigate dose selection in our various target populations. Today, we will be sharing interim data for younger adults, 18 to 49 years of age, who received a single dose of 50 micrograms, 100 micrograms or placebo.

Next slide. So this slide summarizes the local adverse reactions reported in adults 18 to 49 years of age. The most common local solicited reaction was injection site pain, which is really comparable to the safety data that we've observed across our platform. The majority of reactions were mild to moderate in severity and occurred within 1 to 3 days of vaccination resolving after 1 to 4 days. Reported rates tended to be lower in the 50-microgram as compared to the 100-microgram group.

Next slide, please. So now let's move to the systemic adverse reactions. The most common systemic solicited reactions were headache, fatigue and myalgia. And as with the injection site reactions, the majority of reactions were mild to moderate in severity and short-lived in duration. In addition, no deaths, serious adverse events, events leading to subject discontinuation or adverse events leading to study pauses were reported. So overall, the mRNA-1345 vaccine was well tolerated at doses up to 100 micrograms.

Next slide. So now let's turn to the immunogenicity of 1345. There are 2 main serotypes of RSV called RSV-A and RSV-B. The F protein is important to the biology of all RSV strains, and the F protein is highly conserved. So our vaccine will target both of those types. On this slide, we show neutralizing antibodies to RSV-A in the top panel and RSV-B in the bottom. And increases were observed to be at least 20-fold for RSV-A and 11-fold for RSV-B with comparable titers observed between the 50 and 100-microgram groups. So this indicates that the mRNA-1345 vaccine can induce robust immune responses even in subjects with preexisting antibodies and is very reassuring for the older adult segment, which is currently enrolling and vaccinating now.

Next slide, please. The immunogenicity results of mRNA-1345 are improved over our previous mRNA candidates. How are we able to achieve this, given that both mRNA-1345 and the previous candidate, mRNA-1777, encode for the same antigen? The answer is through continuous improvement of the platform, including the lipid nanoparticle. Changes in mRNA-1345 have included optimization of the protein sequence and code on usage for the antigen and importantly, utilizing the same lipid nanoparticle technology as has been used for mRNA-1273 or Moderna's COVID-19 vaccine.

The next slide, please. Now continuing our discussion of the development of vaccine candidates against the respiratory pathogens, let's move to our pediatric combination vaccine for human metapneumovirus, or hMPV, and parainfluenza virus type 3, or PIV3.

Next slide. Similar to RSV, hMPV and PIV3 typically cause upper respiratory symptoms in adults but can cause lower respiratory tract symptoms, particularly in young children. And these symptoms include: croup, bronchiolitis, pneumonia and respiratory distress. Most hospitalizations for hMPV and PIV3 occur in children under 2 years of age at rates of 1.2 and 0.5 per 1,000, respectively.

Next slide, please. Again, like RSV, hMPV and PIV3 express fusion or F glycoproteins on their surface, important for viral entry and cell-to-cell transmission. mRNA-1653 includes 2 mRNA sequences expressing these proteins stabilized in the prefusion conformation, which are then separately translated and expressed independently on the antigen-presenting cell surface. This surface expression then activates the adaptive immune response.

Next slide, please. Moderna currently has a Phase Ib safety and dose-ranging trial ongoing in healthy adults and in young children seropositive to both viruses. In this trial, the adult cohort and the youngest dose cohort in children have been enrolled.

Next slide, please. So although we do not have data from this trial to present today, I would like to share an interesting finding. Because this trial is being conducted in seropositive children, children are prescreened prior to enrollment. And we have noted a decrease in the percentage of children who are baseline seropositive for these 2 viruses since the onset of the COVID-19 pandemic. In February to March of 2020, before the implementation of social distancing measures in the U.S., children were observed to be 63% to 93% seropositive at screening. After approximately 5 months of social distancing in August of 2020, those rates have dropped to 35% to 50%. So why is this important? Social distancing has clearly prevented other infections than COVID-19 during this pandemic. And while that is positive, it will leave us more vulnerable to these respiratory viruses when social distancing restrictions ease.

An important caveat is that this analysis was not prespecified and is not an outcome of a study. But it nevertheless supports our strategy to continue to develop vaccines against respiratory viruses.

So now I'd like to introduce Professor Benjamin Cowling who is the Head of the Division of Epidemiology and Biostatistics in the School of Public Health at the University of Hong Kong. Dr. Cowling is going to speak to us about the epidemiology of influenza and the need for improved flu vaccines. Dr. Cowling, please go ahead.

Benjamin Cowling

Good morning, everybody. Thank you for the opportunity to present on the topic of epidemiology and control of influenza and particularly on the need for next-generation influenza vaccines. I'm Ben Cowling. I'm a Professor in Infectious Disease Epidemiology at the University of Hong Kong.

Influenza is a very common acute respiratory infection. Many people will get influenza every year. And there's a common misperception that flu is the kind of illness you get with a headache, a fever, you're in bed even for a few days, severe symptoms. Actually, flu can often be mild, and the

picture on the right-hand side of this slide is a little bit of a misconception, the distinction between the common cold and the flu. Because actually, influenza virus infections can sometimes present like common colds with relatively -- relatively milder symptoms, sorry, maybe no fever. And I think one of the ways that flu is able to spread so easily every year is that it does have this milder spectrum. If everybody with flu was so sick that they stayed in bed for a few days, they wouldn't have a chance to pass an infection to other people around them. I think it's the milder cases who are maybe responsible in some cases for transmission.

Now having said that influenza is sometimes mild, it can also be, in some cases, very, very serious. I think it's a minority of infections that are serious. But when you have 10% or more of a population getting infected every single year, year-on-year, then even a small fraction being severe will still lead to a considerable health burden. On the right-hand side of this slide is estimates of the burden of flu in the United States. More than 10,000 -- 12,000 to 60,000 deaths per year from seasonal flu, hundreds of thousands of hospitalizations and millions of illnesses. And of course, the flu vaccines can prevent infections and illnesses and hospitalizations and death, and that's the potential to prevent a considerable amount of disease burden.

In the past year, influenza seems to have disappeared from the world. We really haven't seen an awful lot of flu. This particular slide is on the World Health Organization's regular surveillance update. This was in March, but the map has been pretty pale, indicating hardly any flu activity. It's been pretty pale for most of the last year across most of the world. There's been hotspots here and there with relatively smaller epidemics but no widespread transmission, which is very, very unusual. And I think the reason that flu has gone away is because of all the social distancing measures that have been in place for COVID, face masks being worn around the world. And also, travel restrictions so that people don't travel. And then flu can't easily -- so easily spread from one country to another.

So there's quite a number of reasons why we've been able to stop flu from spreading. And these will be noted down for use in future influenza pandemics. It's interesting, but I don't think flu will stay away.

We've also seen the disappearance of a lot of other respiratory viruses. The data on this slide is from Texas in the past year. And most respiratory viruses are seasonal coronaviruses, of course, common colds, flu, metapneumovirus, parainfluenza and RSV have mostly disappeared. The levels of infections have come down to a very low level. Exceptions, though, are adenovirus and rhinovirus, where there have been still some circulation of these viruses. These are non-enveloped viruses, where they're a little bit more robust in the environment, survive a little bit better. For rhinoviruses, maybe more transmission in children, maybe a higher level of transmissibility as well. So more difficult to stop with the measures that we have in place for COVID. It's interesting to think about why some viruses have been able to spread when others like influenza have not. But certainly, it's a number of underlying reasons most likely.

Now influenza will be back. That's clear. So the slide -- the picture on the right-hand side of this slide is from nextflu.org -- nextstrain.org, sorry. It's a website that tracks information from surveillance so from around the world, from the GISAID database and tabulate it very nicely so we can see how flu viruses are changing over time. The different colors in this picture represent different clades of H3N2. The black Xs represent vaccine strains that were chosen in different years. And what we can see on the right-hand side, the top right of this slide, of this figure on the right-hand side of this slide, in 2021, there are still some strains being detected in some parts of the world, which are H3N2, similar to what's come before, but quite a substantial narrowing of the variability of the diversity in circulating flu strains. I would imagine within a year, there's going to be a big expansion again in flu activity, a big expansion in diversity of H3N2 and other flu strains because of the relaxation of public health measures.

And one thing I'm particularly concerned about is because we haven't had flu for the past year, there's been a drop -- there must have been a drop in population immunity to flu. And I think that means we are at risk of having an even bigger flu season next winter. So the biggest flu season in recent years, I think, was 2017, '18, if I remember correctly. That was a big flu season. It was a lot of media attention, a lot of public attention on flu that winter. I think next winter could be an even bigger flu season than that because there will be a lot of susceptibility. We may still have some social distancing measures in place, basically wearing masks to some extent. But I think across the U.S. and also in Europe and some other parts of the world, a lot of those measures would have been relaxed. People will be looking to get back to normal life.

What can we do to slow down or to stop the spread of flu? We can think about seasonal flu that comes every year. We can also think about pandemic flu that comes once in a while. The most recent influenza pandemic was in 2009. Before that, we had 3 pandemics in the 20th century. Pandemics occur less frequently but can be more serious when they do come from about -- maybe from an animal flu virus that jumps into humans and then

is able to spread. As we see with COVID-19, when there's a bad pandemic, it can be very bad, particularly when there's not much immunity in the population to slow down transmission.

There are 3 basic classes or types of tools that we have available to deal with seasonal flu and pandemic flu. The first one is vaccines. And flu vaccines are the most used vaccines in the world. About 500 million doses a year have been administered in recent years. That's more than any of the childhood vaccines that we use. So that's really the cornerstone of our control of seasonal flu in the United States and in quite a number of other high-income locations.

In middle-income and low-income locations, vaccine availability, maybe the cost isn't -- makes them a little bit less accessible. Vaccines are still sometimes used. In addition to vaccines, we also have, on the right-hand side, medications like antiviral drugs, Tamiflu, more recently, Baloxavir, Xofluza, and a few other antiviral drugs and supportive medications as well, maybe antibiotics to treat secondary infections. Those can help to treat people with the infection, but they don't necessarily prevent transmission or reduce the spread of infection in the community. They just deal with infections as they occur.

And then in the middle of this slide are the other types of measures, the public health measures. We can use such a lot around the world for COVID-19, things like social distancing, like face masks, hand hygiene, school closures, working-at-home policies, travel reductions or restrictions and so on. There's a lot of different non-pharmaceutical interventions available that can be used for flu. A lot of them have been used in previous pandemics. They're not used so much in flu seasons. Although maybe after the influence of COVID, maybe face masks will be more commonly worn in heavy flu seasons. Maybe there'll be more working at home if companies think that it's good for their workforce and so on. So we have to see.

But by and large, vaccines are really the tool that we rely on the most to control influenza. They don't rely on behavioral changes, on people doing social distancing. And vaccines really can prevent infections and prevent almost transmission of infections.

Most of the vaccines that are used worldwide are made in chicken eggs, grown in embryonated eggs and they're inactivated, split-virion vaccines, shown in the red box on this slide. And so those make up the bulk of the 500 million doses that are administered every year. There are also a number of other technologies. There's a nasal spray vaccine called FluMist, which is a live attenuated vaccine. And there are some more recent additions to the toolbox for vaccines. There's vaccines that are grown in tissue cultures rather than embryonated eggs. There are vaccines that are adjuvanted. There are vaccines also that are made in insect cells. And one other way to enhance the effect of a flu vaccine that is used by Sanofi Pasteur is to increase the amount of adjuvant. So they have a high-dose vaccine, which has 4x as much. So you increase the amount of antigen, which has -- the high-dose vaccine from Sanofi Pasteur has 4x the antigen of a standard vaccine. So it gives a lot more antigen in the vaccine, and it's called a high-dose vaccine.

One of the issues though with growing vaccines in embryonated hen eggs is the possibility that the virus will slightly change. Now we'd like the virus that we use to create a vaccine to end up as the virus, which will be circulated which people will face the risk of infection with. So that when we vaccinate people with that -- against that virus, they're protected against the thing that's going to be circulating in the future.

However, because of the differences maybe between chickens and humans and also chicken eggs and how influenza viruses grow in eggs, something can happen called egg adaptation, where the virus changes slightly so that it grows better in eggs, but maybe can be a little bit different to the virus that was created at the start or detected at the start of this process, that the vaccine is supposed to be protecting against. And sometimes, that's no major problem that the egg adaptations are very minor. But in some years, this has been suspected to be one of the reasons behind relatively lower vaccine effectiveness. To put it in a simple way, the vaccine was protecting against a slightly different virus. There was a virus that grew well in chicken egg, but wasn't the same as the virus that was circulating in the community.

How do we judge how well vaccines work? We have a number of laboratory assays that can be used. And what would typically happen, we have a person, we take their blood to see what's in it already. They will then have received a vaccination, and maybe a month later, we'll get another blood sample to look at the convalescent level of antibodies. And those can be measured on the slide here, the hemagglutination inhibition assay at the top, then a neutralization assay, single radial hemolysis and some ELISA assays at the bottom as well.

These are different ways to measure the amount of antibodies in blood and we can see if someone receives a vaccine, that antibody should generally increase. And actually, for the hemagglutination inhibition assay specifically, that's been relatively more standardized in different laboratories across the world. And so regulatory agencies will now allow new vaccines, I think inactivated vaccines, particularly, to be licensed just based on what kind of boost they generate in the hemagglutination inhibition assay.

So for example, if people who get vaccinated with a new vaccine, if their blood in convalescence shows a particular rise in HI titers above a threshold and then some proportion of vaccine recipients has that kind of rise to above that threshold, then the vaccine can already be considered for licensing without needing to go into a placebo-controlled trial against laboratory-confirmed influenza virus infection, which can be a much larger study that needs a lot more time.

So that's a real advantage. And every year, it's possible to track vaccine responses in people on the HI assay. If that's of interest, maybe in some years, particularly if there's a fear about poorer vaccine effectiveness. The other assays I mention on this slide, some of them are a little bit less standardized, a little bit more variable between laboratories, so they're not yet used for regulatory purposes, but they may be in the future. And actually, one of the issues with hemagglutination inhibition assays in recent years, we've discovered that some influenza viruses don't work very well in that assay. The blood doesn't hemagglutinate for some reason.

Or if you use the virus that's grown in hen's eggs with the egg adaptations, then that doesn't quite work properly or -- and with the Flublok vaccine, the insect cell-grown vaccine now marketed by Sanofi Pasteur, initially, there was a problem when their antibody titers in people who received that vaccine were tested against egg-adapted viruses in an HI assay, and it didn't look that good. But then when they switched over to cell-grown viruses in the HI assay, then the responses looked much better because there, the responses were to something more like the virus that grow in cell cultures and less like viruses that grew in eggs with egg adaptations.

Now influenza vaccines save lives every year. They are effective. But they are only moderately effective. There's room for improvement, actually. And so for different strains in different years, the effectiveness can vary. But a meta-analysis by Belongia et al a few years ago estimated that vaccine effectiveness can vary from maybe 33% for H3N2 on average, up to 73% for the monovalent H1N1 vaccine and often somewhere in between -- in that range of 30% to 70%. Occasionally, the vaccine effectiveness could be even lower than that, if their sort of vaccine effectiveness should go beyond 70% in my experience.

So that's a moderate level of effectiveness. And there's room for improvement in some enhanced flu vaccines like the high-dose vaccine with extra antigen or the Flublok vaccine grown in insect cells or the adjuvanted vaccines, which have an extra compound to boost immunes. Those vaccines can improve on this vaccine effectiveness to some extent. But in the elderly, where these enhanced vaccines are targeted, the effectiveness may be starting from a slightly lower level anyway than the averages shown on this slide. So we're still facing a situation where a lot of the vaccines that are available have relatively moderate effectiveness, and there's still quite substantial room for improvement.

What are the reasons for limited effectiveness? One of them is that the vaccine strains are often a little bit different to what's circulating. The flu virus is an RNA virus, and it's not very good at copying itself. So when it replicates inside human cells, it makes a lot of copies of itself, which then come out and maybe be transmitted onto the next person.

But it's not very good at copying. It makes a lot of mistakes. Mostly, those mistakes end up with a virus that doesn't work anymore. It's inactive or it can't replicate any further. But occasionally, some of those mistakes work out really well for the virus and allow it to get around population immunity that may have built up, allow it to get around individual immunity that might have come from their prior infections or from the vaccines they've received even recently.

And so that's a problem, this antigenic drift that occurs over time. And for flu, it occurs relatively faster than with some other viruses. And that's one of the reasons why we have annual flu vaccination. It's because the vaccines got to be updated to keep up with what's circulating. And any protection that people might have from vaccination they've had years earlier, that protection may have been lost, not necessarily because the antibodies have gone but because they're the wrong kind of antibodies that don't protect against the newer virus that's shown in the bottom right of this slide, the virus speed that's antigenically drifted.

On this slide is a picture of how often vaccine strains have been changed in the years between 1999 and 2017. And in the fiscal year 2018, '19, '20, '21, there's been obviously even more changes as well. So what's shown here is 26 changes in strains in 19 years. And a lot of those changes have come maybe a little bit too late. So in some sense, the vaccine can be one step behind the virus. So we've got virus A, and then it changes to virus B in the community. The vaccine is against virus A because that's what was circulating last year. And then now we update the vaccine to be against virus B, but the virus is already changing and next year, it's virus C. So again, it's one step behind. And part of the reason for that is the long development cycle, the long production cycle for flu vaccines that I'm going to show in a moment. But the flu virus really does change quite rapidly. And it's difficult to keep up with it.

Another issue that's more of a concern where I live and work in Hong Kong than maybe it is in the United States is the vaccine effectiveness. That's the antibodies and the immunity you get from vaccination. It's probably at peak levels, maybe 1 or 2 months, maybe even 3 months after vaccination. But then as time goes on, 6 months, 9 months down the line, the immunity levels come down somewhat. So the waning over time that's shown on this slide is going to be a combination of that decline in immunity in the longer term as well as maybe changes in the circulating viruses as time goes on. That means maybe the virus is later in time, after 6 months or so, they could be a little bit different to what was circulating at the beginning around the time of vaccination and maybe the vaccine would lose some of its effectiveness that way.

Now in flu pandemics, as shown on this slide, there's a long lead cycle of when vaccines can be produced. And as Klaus Stohr noted in his letter to Nature, vaccines really came late in 2009 because by the time vaccines were widely available in October, the pandemic first wave had already been and gone. And so vaccines weren't as useful as they could have been. And that's because there's a 6- to 9-month delay in getting vaccines out after a new strain like 2009 pandemic influenza has been detected.

More generally, every year with seasonal flu, the World Health Organization has strain selection meetings. For Northern Hemisphere vaccines, the meeting is in February. And that's when they decide what strains they're going to recommend for the vaccine for H1N1, for H3N2 and for influenza B. And then the companies will go away and do their -- generate their seeds and then start to mass produce the viruses, purify formula and so on and ship. And so the whole process shown in this slide from February, March, April, May, June, July, August, September, October, that's approaching 9 months between when the strains are selected and when people are eventually vaccinated. And of course, the protection that we're hoping for from these vaccines will be in November, December, January, February in the winter flu season, whenever that occurs.

Now some companies are now taking the approach of maybe guessing or gambling. And so they may be picking what strains they think might come out. Maybe they'll pick a couple of H3N2 viruses that they think are likely to be selected by the WHO as vaccine strains. And they'll start testing those in January or February in advance of the strain selection meeting so that they can get a little bit ahead of their competition and get their vaccines out. Instead of getting them out in October, they can get them out in September or even August. And I think we've heard about some seasonal flu vaccines being available in July. That must clearly be a company that's been gambling maybe on what strains are going to be chosen. The vaccine, if they choose right, if they gamble right, if they pick a winner, then really they could get that jump on the competition. But at the same time, if they pick a strain that doesn't get chosen for the vaccine, then that's a lot of wasted effort, a lot of wasted resources.

At the bottom of this slide is the recombinant vaccine that can be produced a little bit quicker in insect cells. So that brings forward the time to vaccine availability to less than 6 months. I would imagine with an mRNA vaccine, there will be a similarly short development or production cycle so that vaccines could also be available soon after the strain selection announcement.

For now, the World Health Organization is issuing announcements of strain selections for the Northern Hemisphere in February. And for the Southern Hemisphere, I think it's in July or August. In the future, it's possible to envisage having later strain selections, maybe with updated information, maybe for companies that could make vaccines with a shorter time line to make sure that the strains that are chosen are the most likely to match whatever comes in the following winter.

Maybe there'd even be a continuous process at some point in the future of strain selection and strain updates, so that just information is continually coming in. And if necessary, if there's information to suggest that vaccine should be updated, if possible, then that may happen. And then there may be competition between different companies about getting their vaccines updated sooner. But I don't think any of that's going to happen for a little while because, as I said, the 500 million vaccines -- flu vaccines produced every year, almost all of those are in hens eggs. And so that's the long lead time that's required, strains will need to still be selected in February.

Now I'm coming to the end of my presentation. I think I've highlighted a number of limitations of existing vaccines. Of course, the flu vaccines that we have are saving lives every year. They're saving lives in the United States. They're saving lives around the world. But at the same time, they could do better. We could do better if we had better -- if we had improved flu vaccines.

So what are some of the limitations of the existing vaccines? Firstly, we have the problem of being one step behind a virus quite often because of the antigenic changes in circulating strains.

Secondly, we have this long lead time of maybe up to 9 months before vaccines are needed or before the protection is needed, where the strain selection meeting happens in February, and that's a long time before the following flu season. And by that time, the strains could have changed. So for example, today World Health Organization could choose some strains in February. And then when it gets to June, July, August, the Southern Hemisphere could have a new strain coming out, that's really a little bit different to what's been seen before. And we know, in the Northern Hemisphere that, that strain is going to be coming in our winter in December and then January, February, but the vaccines have already been manufactured. They're already being grown up and produced and filled, and so it's too late to change that. And that's really not an ideal situation to be in. It'll be much better if we could shorten that whole process, maybe with some new technologies.

The third bullet on the left is the problem of producing vaccines in eggs where some viruses will change, some strains will change and adapt to growing in eggs better, but then will be a little bit different to the virus that we're trying to provide immunity against. And also, in recent years, there have been some strains that really don't grow very well in eggs at all. So that's another problem that if a strain doesn't really grow in eggs, it's difficult to grow it up to high titers, to then be able to make a lot of vaccines. So that's another separate issue with growing vaccines in eggs. And the summary would just be the inactivated vaccines resulting relatively weak. And then, as I said, sometimes misdirected immune responses, so they give moderate protection because of those maybe weak and sometimes misdirected immune responses.

So on the right hand side of this slide, there are opportunities for new vaccines that do better, that provide better efficacy, maybe longer protection, maybe it can be manufactured more quickly, so we don't need such a long lead time for strain selection from February of a year all the way through to the following winter. It will be ideal, if that time line can be shortened so that we could have better matching of vaccine strains and circulating strains. And then thinking particularly about influenza pandemics, if we could have a vaccine technologies available that don't rely on growing vaccines in eggs, that would be really, really useful, particularly for pandemic preparedness. Because for the next flu pandemic, what if it's a strain that really doesn't grow very well in eggs. We'll be in trouble if we're going to rely on pandemic flu vaccines that grow in eggs.

So I think having new technologies: mRNA for sure, maybe other technologies as well, if we have other technologies available, to make better flu vaccines, I think there's a fantastic opportunity to improve public health, to reduce morbidity and to reduce mortality from seasonal and pandemic influenza. And I'll stop there. And thank you very much.

Jacqueline Miller - Moderna, Inc. - SVP of Infectious Disease Development

Thank you, Professor Cowling, for that excellent overview of the current landscape of influenza vaccines. So now I'd like to pivot to discuss Moderna's plans in terms of influenza vaccine development. So next slide, please.

Although multiple influenza vaccines are available, prevention of influenza infection remains an underserved medical need, as we just heard in the previous presentation. The WHO estimates that there are still 3 million to 5 million cases of influenza infection annually with approximately 290,000 to 650,000 flu-related deaths each year. Prevention of influenza is complicated by the virus' tendency towards antigenic drift, which Professor Cowling explained so clearly. And that means that the antigens that we're trying to target against flu potentially vary year-on-year, and we're really limited by the speed with which we're able to detect those changes.

This contributes to yearly effectiveness estimates of only 40% to 60% and represents a potential opportunity for mRNA technology. And why is that? So not only can we include additional antigens from hemagglutinin antigen that's the primary antigen in current flu vaccines; but given our speed of manufacture, there's a potential opportunity to select the strains in the vaccine much closer to the actual flu season, which would hopefully lead to a better vaccine and circulating flu strain match. And this could be particularly important in the case of a pre-pandemic as we were just discussing. So Moderna intends to start a Phase I influenza vaccine study with at least 1 candidate vaccine later this year.

And with that, it's time for our coffee break. So we are now going to take a 10-minute break. So please plan to be back about 10:42 in the morning. Thank you.

(Break)

Jacqueline Miller - Moderna, Inc. - SVP of Infectious Disease Development

Okay. Welcome back, everyone. And now we're going to shift gears and begin to speak about the second pillar of our vaccine strategy, which is vaccines targeted against infections important for public health and particularly pandemic preparedness. So next slide, please.

First, we're going to speak about our development efforts for vaccines that are targeting Zika virus and Nipah virus. Next slide, please. Before discussing these proposed vaccine candidates, I'd like to take a moment to recognize and also say thanks for our involvement in public-private partnerships to our partners. The Moderna COVID-19 vaccine development program would not have been possible without such partnerships, and Moderna hopes to continue to make important impacts to global public health in collaboration. Our Zika virus vaccine is a collaboration with BARDA and our Nipah virus vaccine candidate is in collaboration with the NIH. Both Zika and Nipah are on the WHO's prioritization list for the development of vaccines in an emergency context, meaning for epidemics and pandemics.

Next slide, please. Zika and Nipah viruses are both zoonotic, meaning that in addition to human-to-human transmission, they are spread from animals to humans. Mosquitoes in the case of Zika virus and fruit bats in the case of Nipah. Zika was last involved in local epidemics, including in the Southern U.S. in 2016, where the virus quickly gained notoriety for its ability to cause severe neurologic birth defects, for which the WHO declared a public health emergency. Nipah virus has a range of symptoms from asymptomatic infection to severe respiratory distress syndrome and acute encephalitis with a case fatality rate ranging from 40% to 75%. So these severe outcomes have led to the prioritization by WHO for proactive and preventative measures such as vaccines.

So now on Slide 158, we are summarizing our Phase I clinical trial results from our Zika virus vaccine candidate. mRNA-1893 has had -- has been investigated in a Phase I clinical trial, which was a safety and dose-ranging immunogenicity study conducted at 4-dose levels in initially seronegative and seropositive individuals. Shown on the right-hand side of the slide are the antibody titers in the initially seronegative subjects according to their dose groups. The vaccine was generally well-tolerated in both cohorts of participants, neutralizing antibodies increased in a dose-dependent manner at dose levels down to 10-microgram after a 2-dose schedule. And notably, doses greater than 100 micrograms were sufficient to seroconvert seronegative participants in a single dose.

Next slide, please. Our next step in the Zika vaccine development program is to initiate our Phase II clinical trial later this summer, which is being funded by BARDA. This will be a randomized placebo-controlled trial, which is being conducted in the U.S., including Puerto Rico, and each treatment group will evaluate 100 seronegative and 100 seropositive individuals. Doses of 30 and 100 micrograms will be investigated, including a group that will receive a single injection of 100-microgram dose.

Next slide, please. We also intend to initiate a Phase I clinical trial with our Nipah candidate vaccine later this year, and this study will be sponsored by the NIH. It's intended to evaluate the safety and immunogenicity of mRNA-1215, while also investigating whether there are other lessons that can be learned about the immune responses to Henda viruses in general.

Next slide. So another virus, critically important to global public health is human immunodeficiency virus or HIV. We have 2 ongoing collaborations that we intend to take into the clinic later this year that I would like to describe to you.

Next slide, please. The first is mRNA-1644, a collaboration with the International AIDS Vaccine Initiative, or IAVI, and the Bill and Melinda Gates Foundation. It's been known for some time that really humans exposed to HIV can elaborate broadly neutralizing antibodies, protecting that individual from infection against natural disease. This vaccine candidate will utilize multiple antigens for Germline targeting and immuno-focusing in an iterative human testing plan. The second clinical trial to start next year involves mRNA-1574. This is a candidate that is evaluating some promising HIV vaccine antigens, including multiple native trimeric antigens for the virus.

So now I'd like to introduce Dr. William Schief, a Professor of Immunology and Microbiological Science at The Scripps Research Institute. He's also the Director of Vaccine Design at IAVI and is an Associate Member of the Ragon Institute. Dr. Schief will be speaking to us about mRNA-1644. and Dr. Schief, the floor is yours.

William Schief

Well, thanks a lot for having me. It's great to be here and talk about our work on HIV vaccine design and, in particular, we're going to highlight our collaborations with Moderna in the latter part of the talk. I'm just going to give you some background and some data on a protein clinical trial that we conducted over the last couple of years that makes us excited about expanding to use mRNA in this space.

And so I just want to say just the stuff I'm going to talk about, in particular, the clinical studies that we're going to talk about, involve a large number of institutions as shown on this slide. So I just wanted to give a shout-out to everybody. Obviously, we can't really go through them all right now. So we're focused on HIV vaccine designed here in this talk, and there's a lot of attention to many other pathogens. In the developed world, we've got antiretrovirals that make HIV a tolerable, if you will, disease. But globally, it still continues to devastate human population. There are 1.7 million new infections per year.

There's 38 million people living with HIV around the world right now, but only -- but 33% of those are not receiving antiretroviral treatment. And so their viral loads are unsuppressed. That means they can get very sick, and that also means they can transmit the virus to other people. There, in 2019, were 690,000 deaths per year due to HIV, and overall 33 million people have died due to this virus. And finally, antiretrovirals and other treatments are very expensive. And global funding for the age response, which was \$18.6 billion, in constant 2016 dollars, in 2019 is lower than what we need is what estimate -- from what we estimated to need, and it's going down rather than up. So we really need a vaccine to protect against this pathogen in a sustainable way.

Just a brief summary here. You've heard a lot about SARS-CoV-2 to spike. HIV has a spike that operates very similarly, as depicted on this slide. It binds to CD4 as the primary receptor and then undergoes conformational changes and binds to CCR5 as a co-receptor in order to infect human cells. And as you know, neutralizing antibodies as they're being heavily focused on and beautiful talks you've seen earlier today, neutralizing antibody neutralized the spike of coronaviruses. And similarly, neutralizing antibodies to block HIV entry -- sorry, let me go back. Successful vaccines induce neutralizing antibodies.

But the problem in the next couple of slides I want to show you is that the surface -- you heard about the variance of the SARS-CoV-2 spike in the earlier talk by Stephen Hoge in beautiful diagrams of showing those mutations that are being selected by human immune response and to improve the fitness of virus. HIV has a lot more variance. It's basically millions and millions of different viruses that have different mutations -- many different mutations on the surface of the spike protein. And so for HIV, we need to induce what are called broadly neutralizing antibodies that can neutralize diverse HIV viruses.

And this movie is a cartoon or a model of an HIV spike. The blue structures flickering around our glycan molecules that are attached to the surface of the spike. And the surface of the spike is colored by surface conservation. So red are positions that are extremely variable from one strain to the next. And yellow were positions that were less than 80% conserved. So it's really difficult to induce antibodies that can broadly protect against this virus. And you know from seeing in the literature that there are many different variants now of the SARS-CoV-2 spike. And our friends and colleagues, Bethany Dearlove and Morgane Rolland at the Walter Reed Army Institute made this graph for me about 2 weeks ago, and they took all of the -- basically all of the known spike sequences and computationally analyzed them in their diversity.

And that dot on the left-hand side that the blue arrow is pointing to is a representation of the sequence diversity of nearly 43,000 spike sequences standing by entire pandemic across -- by week, by date and by continent and also by different ranges of spikes. And plotted of on the same scale on the right-hand side of the slide, they've shown the HIV envelope spike, if you will. A 1,000 different sequences that were sampled in 2010. You can see how the diversity of HIV spike really dwarfs that from SARS-CoV-2. And Bethany and Morgane made this nice graph showing that if you zoom in and you magnify the SARS-CoV-2 diversity by a factor of 75, you can see the diversity now is approaching the diversity of HIV, and so it's almost 100x more diverse.

And you were just hearing about flu vaccines. Morgane and Bethany also made this figure. And on the far left is the same SARS-CoV-2 spike graph, and on the far right is the HIV envelope diversity graph. And in the middle is shown 3,000 -- about 3,000 influenza hemagglutinin sequences and their sequence diversity from the 2018, 2019 flu season. So we're having trouble making flu vaccines that protect against all of the variants in one season. We're certainly -- it's certainly a holy grail in flu vaccine designed to develop a universal flu vaccine, as you can see from this slide that making HIV vaccine is considerably more difficult.

Having said all that, there's been a lot of work in the field to study human immune responses to HIV infection. And in that, broadly neutralizing antibodies have been discovered. And this slide is showing, in the pictures, is showing a model of the HIV spike sitting on a viral membrane. And in the pictures different broad neutralizing antibodies are depicted as bound to the spike. And some of the bNAbs, well, these broadly neutralizing antibodies or bNAbs neutralize diverse isolates, and some of them up to 99% of all isolates. Lots of different studies in nonhuman primate challenge models have been conducted to have shown that bNAbs can provide sterilizing immunity. And that indicates that if we could develop a human vaccine to elicit broadly neutralizing antibodies, it could potentially prevent HIV infection and solve this problem or at least contribute to solving the problem of HIV AIDS.

And so we're basically, we and most of the field is pursuing a reverse vaccinology 2.0 approach that was originally proposed by my colleague, Dennis Burton at Scripps in 2002, and this figure is taken really from his paper -- from his review paper. And the idea is that for vaccines that are really difficult to make, if you look at infected individuals and you look at their immune response, in some cases, and for HIV, it's rare, but you can find the rare individuals that make a broadly neutralizing antibody and if the suggestion was, well, maybe we should study those antibodies and how they interact with the envelope or spike protein and use that information to try to design vaccines that would re-elicited such antibodies. It's a very high level concept, but it really doesn't animate everything we're doing.

And so to make an HIV vaccine, our goal is to develop a vaccine that elicits sustained protective levels of broadly neutralizing antibodies in humans. And you saw the nice talk about the durability of neutralization and the durability of protection that one would need to be maintained against coronaviruses and that same problem is faced here. That's why we've included this word, sustain. But we have the additional problem that I showed you that we have to elicit these special antibodies that are broadly neutralizing, and that's very difficult.

And furthermore, we think that we need to elicit 2 or 3 different kinds of broadly neutralizing antibodies that binds at different sites on the HIV envelope protein in order to get adequate coverage against the huge diversity of global isolate. So how are we thinking about trying to do that? Well, human antibody responses to pathogens and to vaccines generally start from naive B cells. About 2/3 of the B cells in your blood are naive B cells, and each of them has an anti-biotic surface that is a random combination of human antibody genes, and they're just waiting around, generally speaking, to bind to a foreign pathogen, and then undergo a germinal center reaction and gain mutations and gain affinity and ultimately turn into a plasma cell that secretes the protective antibody. And we need to do that same thing for HIV.

It's really important for us to end up with plasma cells that are secreting broadly neutralizing antibodies and that are maintained. The very -- aside from the huge diversity of HIV that I talked to you about, HIV has some other tricks up its sleeve. There are only very rare naive human B cells that have the right combinations of genes that have potential actually to mature into a broadly neutralizing antibody. And they're not just one easily definable population of naive B cells that have potential to turn into broadly neutralizing antibodies. They're quite diverse, which makes them hard to characterize and hard to target by vaccine design.

And finally, they do have this property -- they seem to have this property that they're difficult to activate with sort of off-the-shelf HIV proteins. So we don't believe that you could take an HIV spike from any particular isolate in immunized humans and trigger the right naive B cells to get this process started. And there's a lot of evidence that, that wouldn't work. And so what is our strategy for inducing broadly neutralizing antibody? A strategy called Germline targeting vaccine design. And it all -- it really keys off this first step, where we believe you have to engineer a protein that has affinity for the rare diverse naive B cells that do have potential to turn and to mature into broadly neutralizing antibodies. You design a vaccine prime, a first shot in the vaccine that can activate those where naive B cells get them to go into germinal centers and mutate a little bit in the right direction as depicted in this first set.

So they would -- that first vaccination would create a pool of memory in germinal center B cells that would have expanded the targeted precursors and gave them a little bit of somatic mutation in the right direction. And then we think we need to have one or more booster immunizations of

different proteins that are strategically designed to bind and activate the pool of memory B cells that was produced by the prior vaccination and kick them further in the right direction. And we call this process, we refer to this colloquially as shepherding.

And then finally, we think that the last step needs to be -- of the vaccine needs to be an immunogenic optimized to trigger the most mature version -- most mature pool of memory B cells and convert them very strongly into long-live plasma cells that will secrete bNAbs for a very long time. So I'm going to focus most of my talk on the very first step because if we can't get that to work, then the whole strategy doesn't have a chance. And we showed back in 2013, as an example of this Germline targeting strategy that we made a nanoparticle with an engineered outer domain, which is very analogous to the SARS-CoV-2 receptor binding domain. And we showed in cell culture that if we added mutations to that immunogen that gave it affinity for Germline B cells, that could activate those B cells in culture as shown in the red line. But if we left the immunogen with a native HIV sequence on its surface, even though it was a nice nanoparticle, it couldn't trigger -- it couldn't activate those B cells. And so this was our thinking that the HIV vaccines that have been tried in human so far were based on native HIV sequences. And they just wouldn't be able to trigger the right naive B cells, and they wouldn't be able to get the process started for inducing broadly neutralizing antibodies.

And we showed in another paper in 2019, how to generalized its approach. I don't want to go through the details on this slide. But we do think that in order to induce 2 or 3 different classes above neutralizing antibody that binds at different sites in the envelope protein that the methods that we provided in this paper provide a roadmap for how to -- at least to design the priming immunogens to get those -- to make that strategy work.

We've also shown in collaboration with our colleague, Michel Nussenzweig, a couple of years ago, we really wanted to find out -- we said to ourselves, look, what we're proposing in this germline-targeting vaccine strategy is a very complicated vaccine regimen. You're going to give multiple shots, multiple -- with multiple different antigens in each shot. And you're trying to basically direct the immune system on a path that you've predefined, and no other vaccine has ever been made to do that, and is that even possible? And we showed in a mouse model that Michel built that, in my lab, we designed a sequence -- a vaccine sequence intended to elicit a certain kind of broadly neutralizing antibody, and Michel built a very clever mouse model and tested out the vaccine sequence and multiple different vaccine sequences and showed that one of our favorite sequences actually could induce broadly neutralizing antibody.

Now -- and so that gave us a lot of comfort that at least there is -- it's possible to do this kind of thing. That was a -- there were some caveats in that study. I mean, some people were very excited and said, well, why don't you just go do this in humans now and solve the problem. And unlike everything in research, you can't solve everything overnight. And we did prove the principle, but that mouse model was too easy basically, and we didn't think the vaccine regimen was ready for human testing. We needed a better priming immunogen and, in fact, we're still working on priming immunogens related to this project.

So I'm going to go back to this -- the importance of priming these naive B cells because, as I mentioned, that is the key first step. If you can't get that to work, the whole thing isn't going to work. So consistent planning of broadly neutralizing antibody precursors or bNAb precursors is a vaccine requirement. You've got to get it to work very, very efficiently. Otherwise, the person who you vaccinated is not going to make a bNAb later on. And consistent priming will likely require a priming immunogen that can target a diverse precursor pool for any one class of broadly neutralizing antibody, and this is due to human genetic diversity into the random nature of antibody B-cell development. And so the priming immunogen needs -- you need a primary management with appreciable affinity and avidity for diverse precursors that can all develop into one kind of bNAb, and you need do that over again for several different bNAbs.

And so the lead project, and I'll spend the rest of the talk on this project, the lead project for testing out that idea is focused on BRCA1 class broadly neutralizing antibodies. These antibodies engage with gp120 CD4 binding site. They directly compete for the same patch on gp120 that is primary receptor CD4 binds too. So when they bind and CD4 cannot bind, therefore, HIV cannot set human cells basically. In order to bind at that site, it's a really difficult site to find. It's like an narrow cave and an antibody can barely fit in there. And these antibodies require a specific gene in their heavy chain and a specific feature of their light chain, a very short CDR 3 loop on the light chain in order to squeeze in there and not clash with anything. But they do -- they are diverse in other ways. They have diverse CDR 3s on their heavy chain, and they have diverse light chains, for example, and they have different sequences. So we need a priming imaging with appreciable affinity and avidity for diverse BRCA1 class human naive precursors.

And over the last almost 10 years, we've developed a Germline targeting immunogen called the eOD-GT8-60mer. It's a self-assembling nanoparticle that presents 60 copies of an engineered gp120 outer domain. And we've shown in a lot of collaborations with a lot of people that this nanoparticle has appreciable affinity and avidity for diverse precursors. It can prime BRCA1 class responses in stringent mouse models and can induce BRCA1 class memory responses that can mainly be boosted toward development of bNAbs in mouse models. And so the question is, will this priming agent -- can it do its job in humans? And so we have carried out a clinical trial, IAVI G001 to test this molecule, eOD-GT8-60mer, as a protein, adjuvant with the GSK adjuvant AS01B, it was the first-in-human test of germline targeting. It's a self assembling nanoparticle with strong adjuvant, as I mentioned.

The first vaccination occurred in September 2018 and the last March 2020. We got -- we finished just before the pandemic shutdown basically. It was conducted at the Fred Hutch Cancer Research Center in Seattle and George Washington University in Washington, D.C. The primary end point is safety. This molecule had never been in humans before, but the major immunological end point was to determine if the vaccine induces BRCA1 class IgG B cells. And by BRCA1 class, I simply mean they meet the basic requirements of having that particular gene on the heavy chain of the H1-2 gene and having a short CDR3 on the light chain. And in order to find out if the vaccine induces such responses, you actually have to sequence the B cell receptors on B cells that were produced by the vaccine. And that kind of thing really hasn't been done in the human clinical trials, at least not for the critical readout before.

And so our colleagues at the VRC and the Fred Hutch did a lot of work to develop an assay, the first-in-human use of this assay is the bottom line at end point and we got to give a lot of credit to Adrian McDermott, VRC, and (inaudible) teams. And so this clinical trial shown at the bottom had 2 groups, a low dose and a high dose. There are 18 vaccine recipients in each -- at each dose and 6 placebo recipients. The low dose was 20 micrograms and the high dose was 100. And every vaccine recipient received 2 shots. The first shot at week 0 and the second shot at week 8.

And this slide just covers the safety and the enrollment. We lost 1 volunteer to follow-up. They stopped pursuing the study, but 47 out of 48 completed the study. The safety data are actually still blinded and not clean, but there weren't any serious adverse events and no adverse event patterns were noted. So in order to determine if the vaccine did its job, if it induced BRCA1 class responses, we took B cell samples from vaccine and placebo recipients at 7 different time points after vaccination, so -- and one time point before vaccination. You get a vaccine at week 0. We got 3 different time points after that at weeks 3, 4 and 8. You get a second shot at week 8. Now you got 4 different points, different kinds of samples after that second shot. So because this has never been done before, and we really didn't know if we would see the response in one type of tissue or another, we did a lot of sampling here to find out the answer.

And our colleagues that I mentioned at the VRC and Fred Hutch built up a pipeline to analyze these responses. And basically, they had to sort these cells that's bound to our vaccine and in fact it's bound to a specific epitope on our vaccine basically for binding site on our vaccine. They sort out those B cells and then they did PCR and PCR sequencing to figure out what were the B cell receptors on those B cells. And that was how we -- that was the only way we could tell if we induced BRCA1 class responses or not. And so we've analyzed all the sequences that they provided, and I don't want to go through the details. But the bottom 2 points are just what I want to say here. We had about 11,000 antibody heavy light pair sequences that passed all of our bioinformatic filters. And that was a median of about 300 antibody sequences per vaccine recipient and about 9 antibody sequences per placebo.

So the first really big results is shown on this slide. And that is that in both the low dose and a high dose group, we saw a robust induction of BRCA1 class responses. Overall, it's a 97% reduction of the BRCA1 class responses. And in contrast in the placebo groups, the response is very weak and in fact in both the low dose and the high dose were 1 of 6 placebos had a BRCA1 class response detected post vaccination. In those same individuals, we detected BRCA1 Class IgG B cells pre-vaccination. So there was no evidence that giving the placebo turned on that response. So for the bottom line, does the vaccine consistently induce detectable BRCA1 class responses? The answer was, yes. And that was a huge -- that was very gratifying and very exciting.

And this slide is going a little more deep into that finding and asking, well, okay, so you induced BRCA1 class responses in nearly everybody in the trial, 36 out of -- 35 out of 36 vaccine recipients. But how strong was a response? How frequent are those B cells in the blood? You've got a -- in your strategy, you've got to come back with a different antigen. They need to find those memory B cells and trigger them to mature further. If you only to 1 or 2 per person, is that going to be feasible? And so what we've plotted here, I mean, it took a lot of work to make this graph from a lot

of beautiful experimental assay make this graph, and I don't want to go into the details. But I'm showing you on the y-axis, the frequency of BRCA1 class IgG B cells in the blood of vaccine recipients.

And on the x-axis, it's samples taken at different time points from PBMC from different vaccine recipients. So -- and you see at the bottom of the graph, syringes indicate when the people got the vaccine. So at day 0, the first vaccinations given. And you can see at week 4 in the low dose group on the left side that every dot represents the frequency of BRCA1 Class IgG B cells in the blood of that particular vaccine recipients. You so there's a distribution and there's a number at the top. It's about 1 in 10,000, 1 in every 10,000 of probably those people's IgG B cells or BRCA1 class. And then we can see -- which is the -- a really fantastic number and a high number that already, you'd be happy with that.

But you get the second shot at week 8 and you see that at week 8, the frequency has died down a little bit. You get the second shot at week 8. And then the frequency jumps up at week 10 to about 1 in 1,000, which is I find a remarkable high number. And that week 16, it died down to about 1 in 4,000. And then if you look over to the high dose, the pattern -- overall pattern is similar. We just got a basically a stronger response. So by week 16 on the far right, BRCA1 class is about 1 in every 2,000 IgG B cells. And so can I put a number on that? Well, we -- with our colleagues, we've measured the frequency of naive B cell precursors that actually bind to our vaccine at approximately 1 in 300,000 IgM naive B cells. So that was kind of the starting point.

And we feel pretty confident that every -- most humans have a precursor frequency of 1 in 300,000. And then you -- after we gave this vaccine, the data indicates that 2 shots of our vaccine, just about 100-fold expansion from IgM to IgG because we're [overthrowing] our class with IgG B cells and 1 shot gives about a 15-fold expansion. And certainly, after 2 shots, it seems like we ought to be able to boost these responses. And quite possibly after one, we might be able to boost. So this brings it more into practical reality. Not only did we get it to work in every -- nearly every individual, but it worked really strong. So it looks like it's something you could build on.

And I just wanted to show this one other finding that we're -- there's a lot of findings we're excited about. I just wanted to show this other one because we've talked about our sequential vaccination strategy and that requires that every shot of the vaccine is able to select or drive additional maturation in the B cell pool. We need more mutations to accumulate every time we give another shot of the vaccine. And what this slide is showing is the present mutation in the VH gene of BRCA1 class antibodies. Basically, for all the BRCA1 class antibodies in the trial, the low dose is on the left and the high dose is on the right. And every blue dot is another antibody. And you get the first vaccine, let's look at the low dose data on the left. You get the first vaccination at week 0, and then you see the day of week 3, week 4 and week 8. You see the average mutation is a little bit less than 1%.

You get the second shot at week 8, and then at week 9, 10, 11 and 16, you see the mutation levels have jumped. They rise up to more than 1.5%. And you get the same pattern in the high dose data. And we see this as direct evidence to second vaccination did induce increased mutation from BRCA1 class B cell receptors. And we're happy with that because, as I said, that underlies our entire strategy. We need each shot to be able to select for increased mutation of specific class of B cells. And finally, we made -- we've made a whole bunch of the BRCA1 class antibodies that were detected in the trial and measured their affinities for the eOD-GT8 monomer biosurface plasma (inaudible). And this slide is just showing that the synergies are quite high, 80 nanomolar on average at week 4 and the increase to around 5 nanomolar by week 16. So we're seeing, formally speaking, antibodies (inaudible) GT8 and they increased this time.

So major conclusions in this clinical trial. The vaccine has an acceptable safety profile in humans. It induced BRCA1 class response of 97%, 35 or 36 vaccine recipients. The results established proof or principle for germline targeting in humans. That's probably the most important feature of the trial. Supports extending this strategy to other targets in HIV and other pathogens. It looks like something you could work with. And in fact, we didn't really even dream that the responses would be this good. We figured maybe we'll get proof of principle. But we'll have to -- it won't look superefficient and we'll figure who want to build a vaccine on this particular molecule will have to go back and improve it. But while we still could probably improve this molecule, we feel like the responses are sufficiently robust, that we can keep working on developing a sequential vaccination regimen, while maybe in the background, we work on improving it because the responses are already pretty darn good.

The results provide evidence that boosting induced maturation can be achieved in humans, as I showed you. And it provides -- the antibodies that (inaudible) candidates. They help us determine what should be the next antigen in our step. Because that next antigen should at least have some

affinity for the antibodies that are induced by the prime. Otherwise, it won't be able to -- in order to be able to activate those B cells and to have some affinity.

And finally, this is the first human vaccine trial to confirm its intended mechanistic hypothesis. And so that -- we feel like that's a pretty big success, and it validates the reduction of philosophy. It's a big step forward. But it's not solving the entire -- we're not trying to solve the entire problem in one fell swoop. So big steps, but one that at a time is what we're going for. So where does Moderna fit in? It's going to be -- it's really important for us, this collaboration with Moderna and I would like to explain to you how, why and what we're doing with them. So in order to develop a highly effective HIV vaccine, we will need to carry out many iterative human clinical trials. But if we rely, as we did in IAVI G001 on producing a protein by GMP manufacturing, our progress will be limited by the relatively slow pace and the high cost of manufacture. It took us years just to do that 1 trial, many years. And we're hopeful that Moderna mRNA will provide a rapid economical and highly immunogenic vaccine platform to enable expeditious iterative human vaccine optimization. So a really hard problem. We're not going to figure out only in animal models. We need to do a lot of human clinical trials, and we think that Moderna mRNA is the technology that will let us do that.

And I would say the rapid development and high efficacy of the Moderna mRNA-1273 COVID vaccine bodes really well for our work together on HIV. So we have this very broad Moderna collaboration with Scripps, IAVI, Gates Foundation, or (inaudible) NIAID and PEPFAR, USAID to develop an mRNA-based HIV vaccine. And the overall vaccine strategy is the one I outlined to you. We call it germline-targeting vaccine design. It involves a priming immunogen that can trigger the right naive B cells. Shepherding immunogens to get the maturation to go further in the right direction. And then finally, polishing immunogen to produce high levels of plasma cells that secrete broad neutralizing antibody. And just sort of a picture of the iterative vaccine design and testing cycle, we have immunogen design, and we'll do a lot of protein design and a lot of preclinical testing of proteins in my lab down to the last ones if we were testing by mRNA.

Moderna formulates the mRNA that we collaborate on vaccine testing and engineered mice in nonhuman primates. There's an iteration loop there. If things don't look so good, we go back and design new immunogens. If they look really good, then we can go to human clinical trials. And there's another iteration loop there, iterative human clinical trials. And finally, we hope to converge on a protective vaccine. And I mentioned that we need to try to -- we think we need to succeed at inducing 2 or 3 different types of broadly neutralizing antibodies, and we're focusing on 4 different classes that probably neutralizing antibodies, figuring that 1 or 2 of them might not work. But if 2 of them do, maybe we're doing pretty darn well. And there's -- we're doing animal experiments in these -- in this collaboration with a lot of different labs, if at all, from Howard to kind of the Ragon Institute, Shane Crotty from La Jolla Institute; immunology, Bart Haynes; David Nemazee at Scripps; Guido Silvestri at Emory; (inaudible) at San Diego Paramedical Research Institute. And so it's a major collaboration with a lot of partners, and very exciting.

So I'm just going to pivot now and show you some preclinical data that we've collected in collaboration with Moderna, and then we go over the clinical trials that we're planning on carrying out. And so what this is showing is 3 different mRNA vaccines. All including variants of eOD-GT8 60mer. In each case, we immunize at day 0 and the -- and just 1 shot and the day 42 readout. (inaudible) and sequencing. And we're asking what percent of epitope specific B cells are BRCA1 class and they're comparing -- sorry, mRNA vaccine to protein plus adjuvant vaccine are the same immunogen.

And on the right-hand side of the graph, of the slide, is the percent BRCA1 response to an mRNA vaccine. So higher -- the higher percent of the B cells are the right class, BRCA1 class. And on the X-axis is the percent BRCA1 class response to the protein plus adjuvant vaccines, so further to the right is a higher percent. And the diagonal line at least would be if the mRNA and protein plus adjuvant vaccines perform the same and aligning the mRNA did slightly better. And so this is literally was the data that we got from the first 3 groups who ran with Moderna mRNA, an exclusive mouse model that we've been focusing on. Fred Hutch gave us a lot of encouragement. We made antibodies, BRCA1 class antibodies induced by mRNA launch GT8-60mer and protein plus adjuvant launched GT8-60mer and worth sharing this graph or just the affinity of those antibodies for eOD-GT8. And you can see that mRNA is producing antibody responses that are basically equivalent to protein plus adjuvant in the stringent mouse model.

Now I'm going to show you, I mentioned that we have a strategy that we have to give sequential vaccination with different antigens in order to mature the population of antibody. And so this slide is going to just show you one experiment where in the red data, we only gave an mRNA prime of eOD-GT8-60mer. And then at day 42, we interrogated the B cells. And in the blue data, we gave an mRNA launched eOD-GT8-60mer prime, and then we gave a different immunogen that we call core (inaudible) G28-V260mer also launched by RNA. It is that boost at day 42, and we analyzed the B cells at day 84, hoping for more maturation due to the boost. And so in this first graph, I'm just plotting what fraction of the sort of B cells

were BRCA1 class. And you can see that after the prime, it's a rest between 10% and 20%. And after the boost, it's also between 10% and 20%. So boosting maintain a certain amount of BRCA1 class response.

And then in the bottom graph on the right, I'm plotting the percent amino acid mutation in the VH gene. And you can see after the prime we were getting around between 0% and 4% mutation, average of 2%. And then after the boost in the blue data, the percent mutation went up. So that is a direct indication that the boost was selecting for more mutations. And we know if you give a placebo boost in this model, you really don't get more mutations. I don't have that shown. We also can measure something about the quality of the mutations. We can ask well, how many of the mutations are ones that we've seen in the BRCA1 class broadly neutralizing antibody or in human broadly neutralizing antibodies. And so that's what -- in this slide, we're plotting -- we're counting BRCA1 class mutations on the Y axis and counting total VH mutations on the X axis. And it's a 2-dimensional histogram.

So after the prime, you can actually see that most of the antibodies don't have any mutations in the VH seen. 77 of the antibodies don't have any. But after the boost, most of the antibodies have mutation, and they're gaining a lot of BRCA1 classification so we've tested actually in preclinical models, a whole bunch of different boost candidates and this one is the best or equal to other ones that are just as good. So we're quite excited about it.

So we're carrying forward with IAVI G002 Phase I trial to launch in August 2021 in the United States, a Phase I randomized first-in-human study of eOD-GT8 60mer mRNA and this core (inaudible) mRNA boost in healthy adults. And the key aims of the trial are certainly to evaluate the safety and reactogenicity of the vaccine. And then, number two, would be to test eOD-GT8 60mer RNA priming. The question is, will mRNA generate similar BRCA1 class responses as in G001 with protein plus adjuvant. And then the third question -- key question is, if we give this boost, will a heterologous boost generate increased maturation toward bNAbs in humans. And just the diagram of the trial, probably don't want to go through the details. But we are testing. The first group is just the same as G001 in its design. Second group to give 1 priming shot of GT8-60mer and then you give the core boost. And the third group to give 2 shots of GT8-60mer and then the core group. And then, the fourth group is a control. And I would like to say that the (inaudible) the cost advantages that Moderna mRNA have really enabled us to develop this trial rapidly, and we're extremely excited to be able to get started this trial very soon.

We're also carrying forward with IAVI G003 Phase I clinical trial to launch in September in Africa. And this is a Phase I randomized open-label study of just eOD-GT8 60mer priming immunogen delivered by RNA (inaudible) testing responses in Rwanda and South Africa, in populations where we need this vaccine to work the most. And so we think this is really exciting. Again, we want to take -- test the safety and reactogenicity of the vaccine. And for the priming, the question is, will mRNA generate similar BRCA1 class responses as with G001, and now in an African population where HIV vaccine is most needed.

And finally, in this clinical trial, we're increasing the capacity for cutting immunological assays in Africa. And so the analysis will be conducted by African Sciences (inaudible) country. And so that's just a single group with 2 shots. And again, the speed and cost advantages with Moderna mRNA has really -- it's been great to be able to move this rapidly and get this trial done sooner.

And the last concept that I want to talk about is mRNA delivery of HIV trimers. And we've been collaborating with people at Moderna for several years now looking at this concept. The key problem is that if we're going to do the sequential vaccination strategy, a lot of the antigens are going to have to be native-like trimers, sort of analogous to the Moderna spike vaccine. But in the HIV vaccine world, there are some complications with delivering these trimers by mRNA. You can't purify them. They don't necessarily assemble that well. You can't guarantee they'll be cleaved by native curing. And in our -- in the HIV vaccine design world, many people have been doing experiments with soluble trimers that are not anchored to a membrane. But using mRNA affords the ability to try delivery of trimers that are anchored to the membrane in a native manner.

And so we've been working with Moderna test these ideas preclinically. IAVI, Scripps, The Gates Foundation in collaboration with Moderna to test HIV vaccine concepts preclinically led to an NIAID-sponsored Phase I trial called HVTN 302. And the idea is to test these 3 different formulations of HIV trimers launched by RNA One, a soluble trimer shown on the left. And then the one in the middle is a membrane anchored trimer. And then the one on the right is the membrane anchor trimer with a mutation that will lock out binding to CD4, the human CD4 protein to test the idea that if the vaccine antigen binds to CD4, it might actually screw up the structure and make immune responses worse to the vaccine. So we want to see if we can avoid that problem. Or if knocking out the binding improves responses to the vaccine.

So that's HVTN 302 Phase I clinical trial, also scheduled to launch in September 2021. It's a Phase I randomized first-in-human clinical trial to evaluate the safety and immunogenicity of these 3 different HIV trimers that were designed in my lab. I'm sorry for the -- that the text is a little bit messed up here, but I think you can still read it. Obviously, we want to evaluate the safety and reactogenicity of the vaccines. We want to test RNA delivery of HIV-native trimers and [side wall] versus membrane-bound versus membrane-bound with CD4 knockout.

And some of the key questions are which platform elicits the most robust autologous neutralizing response. Do membrane-bound trimers suppress induction of base-directed responses? When you have a soluble trimer, you expose the very bottom of the trimer that is not normally exposed on the virus. And a lot of different labs have shown that animals make strong response to that base that are non-neutralizing. And so we're wondering that -- we're hoping that membrane-bound trimers will avoid that problem. And finally, does the C4 knockout mutation improve responses to the trimer? And in this clinical trial, we're also testing 2 different dose levels to find out which dose level is better for immunogenicity versus reactogenicity. So we're hoping that this trial will really be a great test of a platform and help us and other people in this field decide which of these 3 general platforms to use for mRNA and nucleic acid launched trimers in the future.

So in summary, I would just say IAVI G001 establishes proof of principle for germline-targeting vaccine design in humans. We believe this strategy is necessary to develop an HIV vaccine, but doing so will require multiple iterative human clinical trials. Moderna mRNA technology has great promise to assist HIV vaccine development, as I've described. We have 3 Phase I trials testing HIV concept delivered by Moderna mRNA to launch in 2021, and we envision multiple trials over the next 5 or 10 years until we converge on a protected vaccine.

And I really have to acknowledge, just from the clinical data, the G001 that involves many different institutions shown here for funding and for carrying out the study. And obviously, there are tons of people involved in the G001 clinical trial for many different institutions. G002 and G003 likewise involve multiple different institutions, and we're really adding a whole cluster of them from PEPFAR, USAID and African institutions to allow vaccine concepts in Africa. That's really exciting and really important to get going and obviously, a whole another step and expanded set of people involved in those trials.

I also covered HVTN 302, and I didn't really go through all the preclinical work, but that's a long story involving a lot of people and a lot of different institutions doing the preclinical work and then leading to development of this HVTN 302 and got to thank NIAID and HVTN for funding and clearing out that trial that's very exciting. And a lot of the other data in the introduction I showed is from many different collaboration, [you can tell], in the HIV vaccine world. We're very interlinked. We have a lot of different funders and a lot of different collaborators, and I don't think we would make -- we don't -- we wouldn't have a chance of making a vaccine if we didn't have it that way. It's really important to acknowledge all these people were involved.

And I'll stop there, and so thank you.

Lori Panther - Moderna, Inc. - Director of Clinical Development, Infectious Diseases

Thanks very much, Dr. Schief. Good morning, good afternoon, everyone. I'm Lori Panther. And as the clinical lead for our cytomegalovirus vaccine program, I can certainly attest that it's been an exciting year for us, and I'm speaking today to update you on our progress.

Next slide, please. So from a clinical standpoint, we are currently conducting our Phase II trial. And today, I'll be sharing a quick update on our Phase I trial. And then I'll take a deep dive into our latest interim analysis from our Phase II trial, and it's this data that's allowed us to achieve the major milestone of selecting a dose level to implement in our Phase III efficacy trial.

Next slide, please. So a brief but important reminder of why we're talking about CMV today. CMV is a common infection in most populations in the world. It's spread from person to person, mainly by contact with infected secretions and most commonly contact with saliva. Now the major impact of CMV infection is in children, specifically infants who become infected in utero, and this is called congenital CMV infection.

So how does congenital CMV infection happen? Well, a mom who has a CMV infection during pregnancy can transmit that virus to the placenta, which then infects the developing infant. And obviously, this happens at a time that's crucial in the development of that child's brain, vision and hearing. And so the effects of CMV can be devastating. Now the highest risk for congenital CMV infection is when mom gets her first or primary

CMV infection just before or during that pregnancy. But keep in mind that congenital CMV infection can also happen in infants born to moms who had a CMV infection in the years prior to becoming pregnant.

Now to 20% of kids with congenital CMV infection will suffer its most devastating effects from the day they are born, and most trouble their entire lives with neurological visibilities, including deafness, blindness, seizures, cognitive impairment. But even infants with congenital CMV infection who pass all of the tests and who are healthy in the delivery room, even these kids carry a higher risk for being diagnosed with disabilities such as hearing loss and developmental delays in their infancy and childhood.

Now given all this, keep in mind these 2 things about congenital CMV. It's the most common congenital infection worldwide, and it's the most common nongenetic cause of childhood hearing loss. So imagine what we could do with a safe and effective vaccine to prevent CMV infection, and what we see here is the potential to improve the health of kids all over the world.

Next slide. So CMV is clinically complex. And as Dr. Hoge mentioned earlier this morning, our CMV vaccine is also complex. And I'm going to remind you here of why that is. The key proteins on the surface of the CMV virus are crucial for establishment of infection, and they are the pentamer and glycoprotein B or gB. So of course, our mRNA vaccine was designed to contain both of these antigens. However, given that the pentamer is a 5-part protein, our CMV vaccine needed to contain a total of 6 mRNA components. Now it takes 1 of those mRNAs to encode the full-length, functional gB antigen, and the other 5 mRNAs encode those 5 subunits of the pentamer antigen. And these 5 mRNAs are translated then self-assemble to form the pentamer, which appears to our immune system as a functional, highly immunogenic, key CMV antigen in its native confirmation.

Next slide, please. So here on the top bar is our Phase I trial, and it's almost buttoned up. We're looking forward to completing that clinical study report in the coming months, and a manuscript is currently in preparation.

Next slide, please. And the quick update on Phase I is that we've received the interim analysis showing safety and immunogenicity through all 4 dose levels through the entire vaccination schedule. And also, the analysis gave us an initial picture of longer-term immune persistence at the 3 lower dose levels. And from the safety side, vaccine was generally well tolerated and no treatment-related SAEs were reported.

And to summarize the immunogenicity in the CMV-seronegative group, we saw neutralizing antibody responses against the pentamer antigen of up to 17x higher than benchmark level of our CMV-seropositive group at baseline, which is how we measure immune response in our seronegative group. And we saw neutralizing antibody GMTs to the gB antigen that were at or above that benchmark level. And in the seropositive group, we saw a continued robust boosting response at all dose levels. Also, this interim analysis included some longer-term immunogenicity data at the 3 lower dose levels, and we are able to see immune persistence up to 6 months after that last vaccination. So the interim data from this Phase I trial remains encouraging, and the final clinical study report will include immune persistence through 12 months after that last vaccination.

Next slide, please. So between our Phase I and Phase II trials, some process changes were made to this vaccine in that the ratio of the 6 mRNAs were optimized with the aim of further improving immunogenicity. And the presentation of the vaccine was changed from the liquid form, which was used in the Phase I trial, to a lyophilized form for the Phase II trial. And this is -- so in this presentation, the lyophilized presentation is what we will be taking forward into Phase III.

Next slide, please. So on to the Phase II trial. This trial is assessing safety and immunogenicity of a narrower range of doses, so 50, 100 and 150 micrograms in both CMV-seronegative and CMV-seropositive groups with the same 3-dose vaccine schedule as was implemented in the Phase I trial. And the operational update here is that dosing has completed for these participants. They're now on a follow-up period. And today, I'll show you some data from a planned interim analysis looking at safety and immunogenicity through 1 month after that last vaccination, so through the whole vaccination period.

Next slide, please. First, looking at the safety profile. And this is the safety profile in our CMV-seronegative group. The vaccine was generally well tolerated. There have been no SAEs related to the study product, and the study pause rules have been met for either of the sero-status groups. And this graphic shows the most commonly reported solicited adverse reactions following each vaccination. Now injection site pain was the most frequently reported solicited local adverse reaction, and the most common solicited systemic adverse reactions were headache, fatigue, myalgia, arthralgia and chills. And one notable observation is that the frequency of solicited fever and chills in this Phase II trial was lower compared to that,

that was observed in the Phase I trial. And after the second and third vaccinations, you see the rates of adverse reactions were generally similar, and the rates of severe adverse reactions were either comparable to or slightly less than after the third vaccination compared to after the second vaccination.

Next slide, please. And this graphic is in the same layout and shows us the solicited adverse reaction profile for the seropositive group. So in general, the frequency of solicited adverse reactions for this group trended somewhat higher compared to the CMV-seronegative group in the previous slides. And again, we see here that in general, the frequency and severity of solicited events after that third vaccination were either comparable to or slightly lower than after the second vaccination. So we saw a similar pattern to what we saw in the CMV-seronegative group on the previous slide between the second and third vaccinations.

Next slide, please. So moving on to immune response for the Phase II trial thus far. We'll start with the neutralizing antibody response to the pentamer component of mRNA-1647, which is what you see here, and this is the neutralizing antibody response in both CMV-seronegative and CMV-seropositive groups through 7 months, so 1 month after that third vaccination. Now just to orient you to this graphic because it's similar for the next slide, the dotted lines represent the seropositive group; the solid lines represent the seronegative group; the red, blue and gold lines, the 50-, 100- and 150-microgram dose levels, respectively. And also, please note the Y-axis is on a logarithmic scale. And lastly, that black horizontal line across that graph is the average antibody level or GMT value of our seropositive group at the start of the study. So that line is representative of what a previously infected population looks like immunologically, and this is a benchmark against which we can compare the immune response of our vaccine.

So we see here in the seronegative group, so the solid lines. The neutralizing antibody responses were above benchmark levels starting at month 3, so 1 month after that second vaccination. And by month 7, which is 1 month after that third vaccination, these neutralizing antibody levels exceeded the benchmark value by at least twentyfold at all dose levels. And also note that this cluster of data points on the very right-hand side of the graph is showing the GMTs in both the seronegative and seropositive groups overlying each other. So vaccination of that seronegative group, a group that's never seen CMV infection before, turned it immunologically into a population that looks like a boosted seropositive group, which is very encouraging to see. We also see that in the seropositive group, so the dotted lines, they're showing a nice boost after that first vaccination, and it stays at similar levels after the second and third vaccinations.

Next slide, please. So this is the same way out here for the neutralizing antibody response to the gB antigen. And here, we see that the neutralizing antibody response in the seronegative groups, again the solid line, approximated that benchmark value starting after the second and as well after the third vaccinations. And in the seropositive group, the dotted lines, we see a boost response pattern similar to what we saw to the pentamer antigen on the previous slide.

Next slide, please. So what has this Phase II trial taught us thus far? Well, from a safety standpoint, the vaccine continues to be well tolerated, and the vaccine shows functional neutralizing antibody responses against both pentamer and gB antigens that are at or well above that seropositive benchmark value. And it shows antigen-specific boosting immunogenicity in our CMV-seropositive group. So again, very exciting data from this Phase II trial, and it continues to support taking the CMV vaccine candidate forward into Phase III.

Next slide, please. So this Phase II interim analysis is providing the data that we needed in order to choose a dose to take forward, and we'll be implementing the 100-microgram dose level in our Phase III efficacy trial. The primary objective of this upcoming efficacy trial is to demonstrate the efficacy of this vaccine to prevent CMV infection in CMV-seronegative females of childbearing age, and we're also including a CMV-seropositive safety group for this trial.

So that concludes my update. It's been a real privilege to share this update with you today, and thank you so much for your attention. So I'll hand it over now to Dr. Melanie Ivarsson, who will share more about the Phase III trial. Thanks so much.

Melanie Ivarsson - Moderna, Inc. - Chief Development Officer

Thanks, Lori. My name is Melanie Ivarsson, and I'm the Chief Development Officer at Moderna. It is with real pleasure that today, I'm going to talk about some of our learnings from running our Phase III COVID-19 vaccine trial called the COVE trial, how we're building the capabilities of our clinical development organization, and how we will be applying this to the delivery of our upcoming Phase III CMV trial.

2020 was an unprecedented year for Moderna as we embarked on the clinical development of our COVID-19 vaccine. The world looked to our industry to conduct these studies not only to the highest levels of safety and quality but also as quickly as possible in the face of the pandemic. Our Phase I study started enrolling in March, our Phase II in May and our Phase III in July, with a target to enroll 30,000 participants at over 100 sites.

However, speed and quality were not the only considerations for our vaccine program. At Moderna, we were committed to developing a vaccine for everyone. In setting up the COVE study, we focus not only on identifying sites that can conduct high-quality clinical research but also where we would expect to see cases of COVID-19 infection as the trial progressed. Most importantly, we chose sites that would be able to reach out to a diverse population of participants, those most impacted by the pandemic, whether that be due to occupation, living with comorbidities or other social determinants of health. As the trial progressed, we monitored progress daily and, in September, made the decision to slow down our enrollment in order to ensure that communities of color will have the opportunity to be represented in our trial. Our trial completed enrollment in October and included more than 11,000 participants from communities of color, representing 37% of the study population.

But why do we think that diversity and inclusion is so important at Moderna? The primary goal of diversity in clinical research is to understand the influence of age, sex, race, ethnicity and non-demographic factors in treatment response. Diversity is multifaceted and exists across many dimensions but is also context-specific. As we're all aware, COVID-19 infection had a disproportionate impact on communities of color. And therefore, it was essential that at Moderna, we did everything we could to ensure that our clinical trial was representative of the U.S. population.

We understood that achieving diversity in clinical trials poses even more scientific complexity and practical barriers. In our COVE study, it was critical that we took into account barriers such as mistrust, limited awareness of trials, time and resource constraints, lack of information or language/literacy barriers and conflict with one's ethnic and cultural belief, to name just a few. It is therefore important that as we plan and set off our clinical trials at Moderna, we consider these factors in our design and execution plans. Each program needs to be considered individually and a careful participant recruitment plan developed. However, as we discovered during the running of the COVE study, this also requires regular adjustment as the trial evolves.

Efforts to reach underrepresented communities were focused around 3 main components for the COVE study. Firstly, we educated ourselves and stakeholders around the importance of diversity and inclusion and encouraged meaningful dialogue with community leaders. We also convened neighborhood members to build an advisory board with faith-based and community groups. Bringing together diverse perspectives and voices made all of us better. The worst thing an industry can do is to sit in the room and think we have all the answers. We've continued to seek out partners and listen to the voice of the patient as they add incredible value to what we do. We were also very fortunate to have the support of Dr. Tony Fauci and other leaders who took time out of their busy schedules to talk to our investigators and site staff about the why.

We also realized that transparency would be critical as we aim to build trust. I'm incredibly proud of the fact that we were the first sponsor to publish an unredacted Phase III protocol for COVID-19 vaccine trial on our website, and we continued with our commitment to transparency by providing weekly updates on our enrollment, including diversity information about our trial. We ensured that our patient information materials were tailored to different populations and, in collaboration with our digital team, provided each site with data regarding the epidemiology of the pandemic and what was happening within their community. And we monitor this daily.

And finally, we understood that we needed help. We partnered with trusted community organizations and leading trial site and recruitment experts who could bring our expertise to help support these assets. We also spent time listening to our sites to find additional ways to help and by supporting them through motivational visits to highlight the incredibly important work they were doing.

As a result of our efforts, 37% of the individuals enrolled in the COVE study are people of color. As shown by the graphic on the right of this slide, the participants in the COVE study represent the population of the U.S. While we can always strive to do better, this was a tremendous outcome when you consider that historically, 94% of all clinical trial participants in America were white.

However, as discussed previously, diversity is about more than race and ethnicity. Diversity is context-specific. And when developing a vaccine against COVID-19, this means ensuring that your trial consider factors such as gender, age and comorbidities. This graphic shows how everyone can find themselves in the COVE trial. Our trial has enrolled people of different ages, with 29% of our participants between 25 and 44 and 25% of participants over 65 years of age. Our vaccine study also included over 8,000 participants living with chronic diseases as well as individuals in varied occupations such as health care, the retail and hospitality industry and in education. However, something that they all had in common was that due to these and other factors, they were at increased risk of COVID-19 infection.

On behalf of Moderna, I would like to acknowledge and thank every single one of the participants in the COVE study. They did an incredible thing in signing up to be in our trial and continue to contribute valuable information to our study. We could not have done this without them and the tireless efforts of all our clinical trial sites and staff. So a big thank you.

Diseases don't discriminate and neither should clinical trials. Diversity and inclusion is grounded in Moderna's core values because we believe that future mRNA medicines will be Moderna's biggest contribution to society, inclusive of racial, ethnic, minority communities and vulnerable populations. We are actively incorporating best practices from the COVE study into the Moderna operating model for trial recruitment and retention efforts moving forward.

The companies don't run clinical trials. People do. And I'm really pleased to also be able to talk about our talented people and evolving capabilities. We're investing in our clinical development organization, recruiting experienced talent and building capabilities that will help us lead across our portfolio. Our infectious diseases group is in the process of scaling up fivefold, along with the rest of our development operations organization to support our expanding portfolio. Success with our COVID-19 vaccine development effort has afforded Moderna a unique competitive advantage in hiring talent, including those with deep vaccine development experience to build on this already existing therapeutic competency. Our clinical operations team, directly accountable for the execution of the CMV Phase III program, are tenured Moderna staff with many decades of global industry vaccines experience between them. Previously, they've held significant roles leading 7 different vaccines to approval.

We're also strengthening our partnerships and engagement with vaccine clinical research centers throughout the U.S. to develop holistic planning and strategies to execute on the Moderna vaccine platform, not just single development assets. The experience of the pandemic has emboldened us to think differently about the way we do vaccine clinical trials. We've built a dedicated patient recruitment and retention team focused on innovative ways to help our sites and participants connect with each other, and we have a dedicated diversity and inclusion lead who sits with our clinical development teams and is committed to inclusivity at all levels. And we are exploring new ways to expand our digital capabilities and patient-centricity strategies to not only increase diversity on the back of the success of our COVID-19 vaccine but also expand access to our trials to a wider geographic footprint.

And so finally, I'd like to spend a few moments talking about how we're thinking about our CMV Phase III trial. We plan to conduct this trial in approximately 150 sites across the U.S., Europe and APAC in about 8,000 participants. This study will be conducted in women aged 16 to 40 at the time of enrollment. Now the majority of the participants in this trial will be from the millennial generation, which forms the most racially and ethnically diverse adult generation in America's history. Across our clinical trial site footprint, we're ensuring that we have locations in diversity-dense areas, and we are already incorporating the learnings from the COVE trial into how we plan to operationalize our Phase III CMV study.

We believe that transparency is so important, and I'm delighted to share that we're setting demographic enrollment goals for our Phase III trial. As shown here, we will be working closely with our clinical trial sites to aim to enroll 58% white participants and 52% (sic) [42%] participants who are persons of color. We will be transparent in our progress and hold ourselves accountable to meeting these objectives. At Moderna, we believe that this is the right thing to do, and I'm really proud to work for a company that values the importance of diversity and inclusion in clinical trials and is boldly leading the way in transparency in these efforts.

Thank you for your attention. I'm now going to hand you over to Dr. Jacqueline Miller, who is going to talk about our Epstein-Barr virus vaccine program.

Jacqueline Miller - Moderna, Inc. - SVP of Infectious Disease Development

Thank you so much, Mel. And as you mentioned, I'm now going to describe another vaccine candidate going into clinical trials next year. This is the mRNA-1189 vaccine which targets another very complicated virus, Epstein-Barr virus, or EBV.

Next slide, please. So like CMV, Epstein-Barr is a member of the herpes virus family which can reactivate after years of latency and is commonly spread through body fluids, infecting mostly young children and adolescents. It primarily infects B cells, which are responsible for the production of antibodies, but also can infect epithelial cells, which are widely distributed throughout the body, and this is part of the explanation as to why there can be such a diversity of longer-term sequelae. EBV is the major cause of infectious mononucleosis, more commonly known as mono, accounting for approximately 90% of the approximately 1 million cases each year. Young children who get infected with EBV are typically asymptomatic, but adolescents more commonly develop the potentially debilitating symptoms of mono, which include milder symptoms like a sore throat or fever that can progress to lymphadenopathy and extreme fatigue.

Next slide, please. Globally, the annual direct and indirect costs due to mononucleosis are estimated to exceed USD 1 billion each year. There's currently no available vaccine for the prevention of EBV, which, combined with the unmet medical need and the debilitating nature of infectious mononucleosis, implies a significant commercial opportunity.

Next slide, please. Infection with EBV can also lead to significant long-term consequences. Nearly 100% of patients with multiple sclerosis have evidence of previous infection with EBV. And as Stephen mentioned earlier in the presentation, the combination of previous EBV infection and mononucleosis raises the risk for the development of multiple sclerosis by 10- to 15-fold. This virus is also commonly associated with a range of cancers and, in particular, forms of lymphoma. We're currently focusing our clinical development plan on preventing infectious mononucleosis due to EBV, but we are also very interested in investigating whether these types of chronic and more severe longer-term conditions could be vaccine-preventable.

Next slide, please. The Phase I clinical trial against EBV is planned in the second half of 2021. This slide depicts some of our preclinical data generated in the mouse model. Neutralizing antibody titers are compared from mRNA-1189, shown in blue, to the neutralizing antibody titers from convalescent serum from people recovering from EBV, in orange. mRNA-1189 shows significantly higher neutralizing titers in these mice, which gives us confidence for the onset of our clinical trial in humans.

Thank you so much for the opportunity to present our clinical development pipeline today. And now I will hand over the floor to Corinne Le Goff, our Chief Commercial Officer. Corinne?

Corinne M. Le Goff - Moderna, Inc. - Chief Commercial Officer

Thank you, Jackie. So hello again. This morning, I gave you a commercial update on COVID-19 and a view on our commercial organization and strategy. And now I'd like to take you through our commercial vaccine business model.

Next slide, please. Our platform approach to mRNA [things] leads to an essentially very differentiated business model and translates into a disruptive go-to-market approach. I will focus on the key 3 attributes of Moderna's mRNA technology platform and their business implications as I see it.

Starting with speed. Due to our technology platform, we have demonstrated that we can rapidly design and develop vaccines and bring them to market. This speed can translate into a first-mover advantage from a commercial point of view. Also, the fact that through rapid iteration cycles, we can always be in the position of commercializing the most updated and most relevant vaccines, is an undeniable competitive advantage compared to other technologies. Of course, the commercial organization, too, then has to be at the ready.

Second, we believe our mRNA vaccine platform is de-risked. The licensure of our COVID-19 vaccine as our first product establishes mRNA vaccines are safe and effective. And because we use the same mRNA and LNP technology, the same manufacturing processes in all our commercial vaccines in our development pipeline, we believe our development candidates have a high probability of coming to market. So with already high POS,

probability of success, at an early stage of development, we can consider risk-adjusted investments in a different way and invest early for potential fast uptake post-registration.

Third, because Moderna is built for speed, we are building a lean and agile commercial organization with low fixed cost and flexible resource allocation. The key benefit of setting up a commercial book from ground zero is that you can leapfrog into the future and build, from the get-go, capabilities that will be fully digitally enabled so that we can adapt fast to changing market conditions and opportunities.

Let me now go through a few examples of each of these attributes within the commercial realm on the next slide, please. So I will start with speed. As mentioned today, the development of our variant vaccines has already begun. We currently have vaccine candidates in human clinical trials. Our rapid development cycles will allow us to be fast to market and drive a competitive advantage.

As a commercial organization, we are prepared to meet demand and maintain speed to market. The commercial preparation for the endemic COVID market, bringing a boost of vaccines against various strains to market, will start with an approach that incorporates value-based cost-effectiveness analysis. As an example, during the pandemic, an incremental cost-effective ratio analysis was developed by ICER, the Institute for Clinical and Economic Review, assuming 90% vaccine efficacy and a quality threshold of \$50,000. And it found that for a 2-dose vaccine regimen to be cost effective at between \$460 and \$540 per [case]. And of course, similar analysis can inform cost-effectiveness for booster vaccination as well. So we are already incorporating all these elements in our marketing strategy, and we are refining them in real time as more data become available.

Next slide, please, regarding the de-risked attribute. So knowing that our platform is de-risked has implications on our organization. It gives us the opportunity to educate and build trust with our customers both at the vaccine technology platform level and at the disease awareness level. An example of this is the launch of our aboutmrna.com website to educate customers about our vaccine platform across many infectious diseases. We are providing information comprehensible by anyone about the biological aspects of mRNA, how our bodies can create their own defense, how the mRNA science is being used in vaccines. And I think that this type of educational programs are extremely important for people to feel comfortable and to trust this new technology.

On the next slide. So today, millions of people know who Moderna is. They know us. They trust us. Moderna has become a household name in less than a year, which is astonishing in itself but is also a great responsibility. We have the duty to educate and raise awareness about mostly unknown and silent disease like CMV, as mentioned by Lori earlier. CMV is ignored because it's a complex [infectious] disease, which has not been previously targeted. But as Lori told you, this is the leading infectious cause of growth defects in the U.S. So our ambition is high. It is simply to eliminate CMV. But our market research showed that more than 90% of women today are unaware of CMV and its effects. Well, we hope that we, as a company, can play a role in changing this because, in fact, 90% of women should know about CMV and its effects. So it is important to educate and build trust because at the end of the day, we know that people, more than providers, play an important role in vaccination decisions.

On the next slide. Let me go back to what we are doing with COVID-19. The challenge to immunize hundreds of millions of people across the U.S. cannot be understated, and we want to play our part in removing barriers to immunization and in making it easy for people to get their vaccine. But we realized that we cannot do it alone, and we are proud of having established a coalition of partners in the U.S.

Here are a few examples of what we're deploying for COVID-19. So with Uber, we are working to provide education and access to ridesharing. We are also working with at-home treatment partners, like Ro and Truepill, to solve access issues by immunizing people at home, so people who can't get out to immunization sites. With Labcorp, we provide a solution for thousands of employers that want to get their employees back to work. With IBM, we are working to better understand the need for credentialing and supporting indication. And we are also partnering with Color to support the development of community outreach and address the specific needs of underserved populations. So I'm just showing here a few examples of the types of partnerships that we are forging because I think that this is quite unique, and it reflects how we work as a company.

And finally, on the next slide, when it comes to building an agile organization, [natural] speed and efficiency, we have to adopt a digital-first mindset in everything that we do. The commercial organization at Moderna is lean. The team uses data and analytics to gain deep customer insights. We use scalable approaches to customer engagement and dedication. So we are building our commercial capabilities from the get-go as a digital organization, and we are not transforming into one, which should be easier, we think.

On the next slide. So let me conclude. At Moderna, we went from being a development company to becoming a global commercial organization from day 1. It is an unprecedented acceleration. I call that an epic adventure like no other in the history of biotech companies. What made this possible is the type of talent that we recruit into the company. People who join Moderna bring decades of experience in the area -- in their area of expertise, and I'm not afraid of challenging the status quo to build something different to find innovative solutions to complex commercialization issues. They live by the company's values of being bold and relentless. And I want to conclude on that point because at the end of the day, at Moderna, our people make all the difference.

Let me turn now to Stephane for his concluding remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thank you, Corinne. I would like to thank our guest speakers and also to thank my team and their teams for incredible work day in and day out. Their dedication to helping our world with mRNA vaccine is really humbling.

On Slide 15, we believe we could become the best vaccine company in the world. We have a large pipeline and we have a unique platform, same LNPs, same mRNA nucleotides, same manufacturing process, same commercial infrastructure. I won't go back on Slide 16 on the pipeline, but just again to emphasize the depth and the breadth of this pipeline, and more is coming.

What I think as really important about where Moderna sits today is that given our scientific conviction and our cash balance -- I'll remind you our year-end position was \$5 billion of cash, we have a large appetite to invest. We want to continue to invest in mRNA science. We don't think we are done. We believe we are still getting started. We want to increase our investment in infectious disease research, and we're actively increasing the size of the research team. We have heard a little bit from Mel. We want to really build state-of-the-art digital clinical development capability, and we're hiring really top-notch clinicians to help us lead those important studies. And we are very committed to do long-term studies that are required, and we'll hear more over the next months and quarters.

If I turn to Slide 18, our long-term vision for respiratory vaccine franchise. We want to provide a convenient annual, single-dose boost against as many respiratory virus as possible. You heard the team talk about COVID-19 and our strategy on variants and boosters. And as we said before, the company is fully committed to continue to move quickly to develop as many variants as we think is necessary to get this pandemic under control. We're very committed to do the same against flu and bring disruptive transformation to the flu vaccine market and to address an unmet medical need that hurt thousands of people around the world every year. And our vision is to combine all those things. What about a combination of high-efficacy seasonal flu shot in the same dose as the relevant COVID variant for that year? Or what about adding RSV on top of it?

We are very excited about our complex antigens, CMV and EBV, given once infected, people are infected for life, we believe carry a very high burden of disease not only short term like CMV for birth defect or EBV for mono but also long term. We don't believe it is a good thing for your immune system to be fighting those viruses for the rest of the life. As Corinne described, given our belief in our ability of those products to reach market, we want to invest heavily in education about those diseases during Phase III. And Corinne and her team are very, very active in that dimension. Our goal as a company is to eradicate these viruses in humans. I'm very pleased with the commercial team ambition to move from 91% of women who do not know about CMV today to 91% of women who know about CMV at the time of product launch. A great success for us will be that we have a lot of women in the age of bearing a child aware of the virus, aware of a vaccine and be interested in talking to their OB-GYN or their GP to get vaccinated to protect their future pregnancy.

While we build what could be the best vaccine company, we also aim to transform medicine yet again but this time with mRNA therapeutics. 2021 will be an inflection year for the company. 2020 was a historic year in what the team was able to achieve, and we are very proud and humbled by the contribution our product is making every day around the world. The number of e-mails we get of happy consumers that feel protected now is really heartwarming. But in 2021, in addition to the acceleration in the vaccine business, we could have several proof of concept in the therapeutic space.

If I go to Slide 22, let me start with oncology. We currently have 5 oncology trials ongoing. We presented some early clinical signals in the last few months, but given that most of the world is focused on COVID-19, few people notice those. We are in HPV-negative head and neck cancer, some

very interesting early clinical signal that we are chasing by expanding this cohort. AstraZeneca recently presented some new data on the IL-12 mRNA program, so-called MEDI1191, in monotherapy efficacy in refractory melanoma patients. And the Phase I is ongoing, it is dose-escalating, and we will continue to keep you updated as we learn more.

Localized regenerative therapeutics. The AZD8601 program is in Phase II now. I remind you that the preclinical data published in Nature, in pig, shows a very good proof of concept in animals. And then like in our therapeutic area where preclinical model is not always predictive of humans, as many of you know, the cardiology, the peak model is a good predictor in terms of translation to human. And on the right, you see the positive Phase I data showing increase in blood flow. So we're very eager to see the Phase II data where AZ is injected with people [to help] therapeutics as a onetime injection as a regenerative treatment.

This year is going to be very exciting as we expand in the clinic in autoimmune disease. Our team believes that autoimmune disease is a great area for Moderna to invest in. And we have already 2 programs, and the team is working in preclinical studies in expanding in a material way our autoimmune disease portfolio. I remind you that this is using the same technologies in terms of LNP that has been used for the chikungunya antibody program, mRNA-1944, for which we have shown a very nice dose response as well as the ability in human to safely repeat those with this technology. We have the exciting PD-L1 program and the IL-2 program. The IL-2, I want to point out, is going to be our first use of subcutaneous injection into human. As you know, the vaccine are injected intramuscular. We have already tested intratumoral in oncology and also intracardiac, of course, and IV with the chikungunya program. So that's yet again us trying to continue to expand the possibility of what we can do with mRNA technology by going for first-time subcu.

And on Slide 25, 4 rare disease program for systemic intracellular therapeutics. The PA program, we have Phase I/II sites being initiated as we speak to enter into the clinic, and we are working to file an IND and the CTA around MMA.

As many of you know, we are always focusing and investing to expand what we can do with our science to translate into new application to help patients. We call those new applications or new modalities or new verticals. We have been working with Vertex and making some good progress to deliver mRNA into the lungs. Our first Vertex partnership was to apply mRNA to code in the mRNA the instruction for CFTR, the key protein responsible for the disease.

Recently, in September 2020, we announced a second partnership with Vertex, where we asked ourselves with Vertex the following question: could we use Moderna's mRNA and LNP technology to do gene anything? Well, here, the idea will be to code in the message an instruction for gene editing protein. We use an example, purely illustrative in this case obviously, in Cas9 to basically go and do gene editing. That will again extend the possibility of what we can do with mRNA.

On Slide 28, we have the full pipeline of the company. I won't go into detail into it, but it gives you a sense of what's coming. And as I said, our research teams are very actively working to bring new candidates to complement this pipeline while our development teams are working to accelerate given what we know now, given our funding position to accelerate development of our clinical programs. A lot of people believe that Moderna equals COVID vaccine, but we have this amazing platform and we believe this is just the beginning.

With this, I would like to thank again our teams and our guest speakers, and I would like to turn to the operator for us to take questions. Thank you.

QUESTIONS AND ANSWERS

Matthew Kelsey Harrison - Morgan Stanley, Research Division - Executive Director

Great. I guess 2 from me. The first one, could you maybe help us think a little bit about flu? And I guess the ultimate question here is, obviously, you've talked about combination approaches with COVID. How much work do you think you need to do with flu before you might think about an actual combination vaccine as we think about boosters and how that market develops over time?

And then the second question is really around the efforts in HIV, and just given historically how difficult that's been to produce anything that's reasonable. What would you consider sort of good data from a first effort? Or what would give you encouragement for the first effort that you're actually headed down the right path?

Stephen Hoge - Moderna, Inc. - President

Matthew, it's Stephen. I'll take the first question, the first part of it on flu. So obviously, we -- as I shared at the beginning, we've already taken 2 influenza vaccines in the clinic and showed they work. It was many, many years ago, but H10 and H7. And so we already know the platform works in generating neutralizing immunity as measured by HAI and seroconversion in -- from those studies.

And so what remains to be done is demonstrate that we can do that with 4 -- at least 4 strains of flu like the seasonal influenza vaccine but not something that we think is a particular barrier, given we've already put many, many more mRNAs than that into a vaccine.

Your question at the core of it is when do we expect to do combination. So assuming we relatively quickly demonstrate that we can achieve against seasonal strains the same types of protection that we demonstrated against the pandemic strains, then the question becomes, do we develop a flu vaccine as a stand-alone first or combine it relatively rapidly with coronavirus, which is another vaccine that we think will need a seasonal booster.

The answer is we're still working on those decisions and ultimately, it's subject to conversation with regulators about how to do that. But we do think that there's value in advancing a stand-alone flu vaccine all the way to licensure, in part, because of the reasons described today in terms of the deficiencies with current approaches to influenza vaccine.

And so at a minimum, the answer will probably be both. But we don't have more guidance yet on when we're going to be combining those. Certainly though, with an authorized COVID vaccine and hopefully soon thereafter, a licensed influenza vaccine, we'd have an opportunity to do combination relatively quickly, given our technology and given that we're not making one of those vaccines, for instance, in eggs and another in some other way. In fact, it will be the same.

So on the HIV vaccine, I think maybe I'll take that as a first step and then invite colleagues to pile in. But I'm not sure. Is Bill on the line still?

William Schief

Yes, I'm here.

Stephen Hoge - Moderna, Inc. - President

Oh, Bill, then maybe I'll let you go first on that and then I'll follow on it for you.

William Schief

Okay, thanks. Yes, it's a very good question. It's going to be a complicated vaccine to make. And I think we're going to be -- we're far off from setting goals as far as, like, protective efficacy. I think the vaccine strategy is a very stepwise one and is a reductionist strategy at kind of an engineering approach where each vaccine, each stage of the vaccine has an intended output.

And so I think what we're going to be looking for is every time we do a trial, we have a certain goal. Do we achieve that goal in terms of the responses that were elicited? And is it consistent across the vaccine recipients? And I think as long as we can keep marching toward the ultimate goal with success each step of the way, that's what -- at least that's what I'm going to be looking for.

We'll know if we're on the right track, and we'll know if we've just failed in our recent trial because we didn't get the output we wanted. But it is going to take a number of years until we have anything like broad protection against HIV in humans. But I do think, and many of my colleagues think, it is plausible and technically feasible, and in doing so, I think we're going to inform a lot of other vaccine efforts.

Stephen Hoge - Moderna, Inc. - President

Thanks, Bill. Well the only thing I guess I'd add to that from the company side is, we will always be looking to demonstrate that the technology that effectively translates from preclinical experiments into the clinic. And we're hoping to see, even though as Bill said, there will be many years of work ahead, that this concept of heterologous serial vaccination might provide a benefit because we would love to use the benefits of investing in RNA technology to try and do things like shepherding against horrible diseases like HIV and AIDS.

Operator

Our next question comes from Salveen Richter with Goldman Sachs.

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

So one around what might need to structurally be changed, such as with the WHO, around the current process for flu to enable better processes as you look to what we've seen with mRNA technology with COVID-19.

And then secondly, if you could just help us understand how you're thinking about manufacturing on the forward given the demand for COVID-19 but then also all these other programs that you're looking to bring onto the market.

Stephen Hoge - Moderna, Inc. - President

Thanks for the question, Salveen. So I think first on the flu vaccine, what we hope to demonstrate very, very quickly, as I said a minute ago, is that our mRNA technology can do at least as good or better in developing an mRNA-based vaccine against the seasonal strains. And until we've shown that, to be fair, we can't expect the WHO and everybody to change their process and approach.

But once we've shown that, as I think the speaker said today, we think we're going to -- given the advantages of mRNA that we've demonstrated, for instance, with COVID-19, be able to respond very quickly to changes in influenza strains and perhaps to selecting strains later in the season based on what's most prevalent. And that's in addition to the benefits of avoiding things like egg adaptation and antigenic drift associated with it.

And so we hope to first demonstrate that we have a vaccine that works with the existing paradigm. And then once we've done that, we would hope to show that we can adapt that paradigm and more rapidly respond to the seasonal flu epidemics and even future pandemics as they merge.

Now the one thing that was noted was that there's several hundred million, 500 million doses of flu vaccine a year. And traditionally, sort of changes to the paradigm, whether it's by the WHO or otherwise, have probably been held back by the fact that it's hard to change a paradigm when you maybe wouldn't be able to get all 500 million doses into that new world. But fortunately for us this year, what we're already demonstrating, for instance in the COVID response, is the ability to vaccinate or generate over 1 billion doses of vaccine as our target this year and even more next year.

And that would start to substantially dwarf that's what's needed in the flu market. And so we hope we'll be able to provide both a better vaccine but also a platform that could be expanded into a very large portion of that market so that others would have the incentive to start adapting the approach to selecting strains in the future.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thanks, Stephen. And Salveen, this is Stephane maybe taking the manufacturing question. Well, we are continuing to scale up the process. What we use now, I don't think, is at all the last scale we're going to be using. We are not done in terms of increasing the reactor size. Being a cell-free manufacturing process, so far, the processor scales very nicely in terms of volume of reactors. One is technical development team have a lot of ideas that they are implementing and testing as we speak.

Our goal is to stay ahead of the demand. As you know, the great thing with mRNA is we have a platform. There is no dedicated manufacturing for COVID that is different from flu, that's different from therapeutics. It is all the same manufacturing process. So we're managing a portfolio, allowing us to think about investment for the portfolio.

Given the public health impact of what we do, we, of course, would rather be on the side of having a bit too much capacity than not enough just from a patient impact standpoint. And then, of course, from a financial impact, as we've said on COVID vaccine, which as you know has a relatively low price, we anticipate around an 80% gross margin. As we said in the past, from products like CMV, where we think the market forces will be more typical, will be more in the 90% gross margin.

And so when you have that type of human impact on public health, that type of financial impact and you're managing your portfolio, I think you'll agree with us that we'd rather have 1- or 2-year capacity ahead of the game than behind. That's exactly what we are doing. We're also going to be looking at vertical integration where we believe it makes sense in terms of controlling the quality of the raw materials, controlling the supply. And so we are actively looking at our current capacity, especially in light of what has happened in the last few weeks with our vaccines platform and looking at the entire portfolio of the company.

Another thing I've mentioned in the past is not to forget the different mass requirements, MR, between vaccinating 1 human being and doing repeat dosing for treatment like in rare disease or like to immune disease and so on. And so we continue to look at the whole portfolio to make sure that we continue to scale, and we will not be shy of investing like we've done a couple of months ago, as required.

Operator

Our next question comes from Michael Yee with Jefferies.

Michael Jonathan Yee - Jefferies LLC, Research Division - Equity Analyst

A question on COVID variant 2.0 vaccines and a question on flu. On COVID, do you have a view as to when you would be able to make a call on which variant or which program to move forward and actually start manufacturing and preparing for 2022? And is there a view that there's no data for anyone to use a different platform afterwards, after getting injected with mRNA? This is kind of an interesting question there as you think about 2022.

And then on flu, I don't know if it's a question for Dr. Cowling or for you guys. You seem to be emphasizing that strain selection and time of the strain selection is most important. Is your advantage much more the platform immunogenicity? Or is it more the timing of the picking the strain to add advantage?

Stephen Hoge - Moderna, Inc. - President

Thank you for the questions. So I'll start with the first one on COVID variant selection. So as I said, we've already completed dosing the initial Phase II portion of the 3 different strategies. And so reminding you, the 351-specific booster, a multivalent booster which combines 351 and 1273, and then just 1273, our ancestral vaccine by itself. And we expect to have that clinical data in the near term, obviously, in the second quarter.

And that will probably inform very much the vaccines we take forward. If we see a situation unlike the mouse, where a multivalent approach is providing the broadest boosting immunity, then I think we would very likely make that choice unless there was some other data at that moment that cause us to suggest a different approach. But if, of course, you see the 351 or the industrial strains are equally good or better, then we would make that choice. And so we'll really be guided by that second data -- second quarter data that we hope to have here in the near term.

I think what would then happen would be we would move that into a quick, following the FDA's guidance, a larger study that would confirm that in a larger number of folks that we had the right boosting of that immunity and obviously, a tolerable profile. And then we'd follow regulatory guidance on updating our associated filings and conditional approvals.

But we wouldn't stop there. I mean the most important part of this question is that -- is maybe the part you didn't ask, which is -- and would we be done? And the answer is no. We're committed to making sure that we update our vaccine with any variant of concern that we think our current vaccine or booster don't provide protection to. And so as we continue to look at what happens in the southern hemisphere or the rest of the world as there are continued infections globally, as Dr. Farrar mentioned. We will keep looking at every variant. And if we need to add additional variants to our vaccine, we, of course, will do so. And so this will be the update for now, but we'll continue to watch this space and make changes in the future.

I think the other part of your question there, as you look forward to next year, we are -- we feel very confident in the safety data that's been generated to date with our vaccine, particularly, I think, the large amount of real-world data and very confident on the real-world efficacy with the mRNA vaccine platform. And so we do believe that from 2022 forward, if we can scale to continue to meet supply expectations into the billions of doses that really mRNA should be the primary approach that people take to boosting in the future, both because of the facility with which we can update the vaccine but also the, perhaps, leading efficacy on safety data to date.

In terms of influenza, your question there, so we continue to look at a range of different reasons why we think mRNA will be differentiated generally in respiratory vaccines. I think first and foremost, I don't want to lose it, is as we said in our strategy, it is combination vaccines. And so we do expect that over time, the best answer is 1 needle, 1 injection that provides you the broadest protection against all of these respiratory pathogens, particularly in the high-risk population, 65-plus, where we think there's a very strong case for that protection. But over time, other at-risk populations, even children.

Now likely it's going to be fastest in the boosting environment with the 65-plus. And of course, flu is the platform where that is done most regularly. As was you've heard today, there's 500 million doses a year being administered already in that market. And so our expectations for the base of the differentiation are -- obviously, we believe our platform has great immunogenicity and a tremendous amount of data to support it based on COVID experience.

But we really believe it's going to be the ability to add those other pathogens over time into that vaccine, including and perhaps even starting with COVID at the right time. So that will be the principal feature. There are other advantages that we're talking about that you referenced, and we do believe in them, the ability to perhaps make strain selections more continuous in the future or at least 9 months in advance and the ability to make sure that we're expressing the protein in the most native confirmation in-vivo, which mRNA allows you to do, but obviously is not something you can accomplish in egg-based or other expression systems. So Mike, I hope that answered your questions.

Operator

Our next question comes from Gena Wang with Barclays.

Huidong Wang - Barclays Bank PLC, Research Division - Research Analyst

I have 2 questions. The first one is regarding the vaccine, the booster shot that is more maybe for doctors, Dr. Davenport and to Dr. Farrar. So a low level of efficacy rate, do you think it's necessary to take the booster shot? Are we looking at below 50% or is that the bar? And also based on the 6 months data seen so far, do you expect boosters at 12 months?

My second question is regarding the pipeline vaccine candidates. So are the lipid nanoparticle largely sustained across different CoV? What additional modification do you plan to do for both lipid nanoparticle and mRNA?

Stephen Hoge - Moderna, Inc. - President

Great. So let me -- I'll take the first -- the second question first. It's actually pretty straightforward. We do use the same lipid nanoparticle and technologies across our -- all of our vaccines programs to date. In some cases, as in the CMV vaccine, as I noted in 2019, that went forward as a lyophilized formulation, so refrigerator-stable lyophilized formulation. In other cases, we do other small tweaks. In the pandemic, obviously, we moved as fast as we could and wanted to be conservative and so we kept things frozen. But those are small tweaks really to formulation technology. The core of the lipid nanoparticle and the underlying platform technology is not changing.

Now I'll speak briefly to my perspective on sort of the evolving epidemic but then invite Tal to come in and just give his perspective on what level of efficacy would likely be relevant from a regulatory perspective. So in terms of the evolving picture with the variants, I think we are concerned anytime -- it's sort of obvious, but anytime you start lower on neutralizing titers, those neutralizing titers will decline over time. And if you look at the modeling data presented today, you might conclude that at some point, maybe 20% of a convalescent serum level, there starts to be a real impact on breakthrough infections.

Now those first infections, as they break through, are likely to be asymptomatic. People won't know and/or mild. But the problem is, as you go into a population basis, some people passing around asymptomatic SARS-CoV-2 variants really puts anybody who's got a low titer, perhaps somebody who is immunosuppressed because they've had an organ transplant or they're older or did not have a substantial immune protection response or a less effective vaccine, and all of those would be circumstances where somebody might -- an asymptomatic person might pass an infection to that at-risk person and you could obviously have a more severe outcome.

I think our view is during the pandemic, while there is still this risk of ongoing viral evolution, and we do see these variant waves that are seeing neutralizing titers that are substantially less effective against them, we think the right answer is going to be to be bringing forward a vaccine booster on a pretty regular basis. And I think a relatively conservative assumption would be annually, probably seasonally, even though the pandemic is raging in a nonseasonal way.

The truth is that as we come in and out of the indoors or closed environments and as -- particularly, as we get into the winter in the northern hemisphere or the winter in the southern hemisphere, we would expect to see increase in respiratory virus transmission, just like you see for endemic coronaviruses. And so our baseline assumption is probably seasonally, from a conservative perspective, doing that boosting.

Now Tal, do you want to say anything from a regulatory perspective to add to that?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Yes. Thanks, Stephen. So I think what you've seen this morning is sort of an outline of the science. I think the science then has to interject with 2 other elements that ultimately the regulators will have to take into account. The first is the population-based assessment of our people generally protected or not, in light of the emerging course of the pandemic, right? Because I think that's going to matter as well.

And the second element is going to be the individual variability. And I think while it's great to note that certainly in the first 6 to 12 months, we see a pretty consistent effect with tight error bars, you would expect that the individual's level, over time, there's going to be some variability in everybody's immune response and people's individual risk factor, not just for getting the disease but actually getting severe disease once infected, is also going to be highly variable. And I think regulators are going to have to take that into account as well when they consider what is the threshold of protection.

So I think you're going to see an approval here that's not necessarily based on, like in the beginning of last year, some are 50% number on a Phase III trial, but rather a more nuanced approach that says, "Look, here's an approximation of a correlative protection. This is the immunogenicity that

we know correlates with very high effectiveness. Therefore, it makes sense to give people a boost, whether it's everybody, whether it's people at high risk, whether it's within a window of the primary series." All that is going to then be colored by the actual epidemiology that we see in the months ahead of us.

Operator

Our next question comes from Ted Tenthoff from Piper Sandler.

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

So I had 2 quick questions, if I may. Firstly, is there any reason to believe that a virus-delivered vaccine such as J&J or AstraZeneca's could actually induce immunogenicity that would impair or even prevent use as a booster?

And the second question is, and I just missed what you said, but would the EBV vaccine candidate enter the clinic next year?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

So let me jump in, Ted, to take the first question. This is Tal. I think it's a really good question. Our presumption has always been that mRNA vaccines are uniquely suited to be booster vaccines. And I think if you look at the underlying technology, the fact that we focus the immune response specifically on just that protein and the fact that the immune system actually doesn't see our vaccine per se like it does a vector vaccine, it really only sees that protein once made.

As you will have seen from the CMV data, you come in with a boost, you come in with a third dose, you continue to raise the antibody levels and you do that with a pretty consistent safety and tolerability profile. So we expect that that is an underlying strength of this platform, and you will see that translated into the use of booster vaccines. I'd rather not comment on the other technologies but I think the differences are obvious. Let me hand it off to Jackie to talk about EBV.

Jacqueline Miller - *Moderna, Inc. - SVP of Infectious Disease Development*

Thanks, Tal. I think the question was around when we're intending to start our Phase I program. And we are intending to start the Phase I program later this year in 2021.

Operator

Our next question comes from Cory Kasimov with JPMorgan.

Cory William Kasimov - *JPMorgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Two for me as well. First, as a follow-up on that booster question. I realize this is a moving target. But over time, do you anticipate the need for boosters will be driven more by emerging variants or waning immunity?

And then the second one is I'm just curious if there are, like, complicated steps or risks when thinking about future heterologous booster. So again, when starting with vaccination, when a person is vaccinated from 1 platform and then moves to another down the road.

Stephen Hoge - Moderna, Inc. - President

Great. Thank you, Cory, for both of those questions. So first on the booster, I think -- we think it's both, right? So variants and waning immunity will determine when you're at risk of reinfection. And the more you have variants, the sooner that that risk will go up. But inevitably, as you see with the seasonal coronaviruses, there is a rate of reinfection even without that concern of rapid evolution of variance that's going on right now in SARS-CoV-2.

So our expectation is that, particularly for the next 2 years perhaps, as we're dealing with these highly -- sort of highly evolutionary environment for the virus, you're starting to see the emergence in adaptation of even better versions of the virus that have not yet infected probably the world's population, that we're going to need to be boosting relatively regularly, perhaps seasonally as I answered just a minute ago.

At some point, that will slow down as a pace of evolution and then you'll be left with just waning immunity. And that's where if you look to the endemic human coronaviruses, there is disease in the 65-plus population every year. And that waning immunity probably is in that 1- to 3-year range. And that becomes the primary driver as opposed to variance in the future, the long-term future.

In terms of the second question on heterologous priming and boosting with our boosters, one of the advantages of a messenger RNA LNP approach is that you don't really get anti-vector immunity. But antivector, so immunity against the viral vector, is something that's really well characterized, there's extensive literature on, in the case of adenoviral vector vaccines.

And one of the challenges, of course, is the more you boost with a vaccine that might be vector-based, the more you might start to distract the immune system towards that vector and get less and less of your antigen that you're interested in and therefore, less and less effective boosting,

Certainly not a concern for mRNA and LNP. And certainly, from our perspective, we don't see any reason why mRNA-based -- mRNA LNP-based vaccine boosters aren't going to be useful with all populations, regardless of what your primary series was. That's also something that we're going to be looking at, both ourselves and with external partners, in the months ahead.

Operator

Our next question comes from Geoff Meacham with Bank of America.

Geoffrey Christopher Meacham - BofA Securities, Research Division - Research Analyst

I just had a couple. When you think about 1273 and the experience in populations that are penetrated, is there any evidence of breakthrough? I know it's pretty early. What does that mean to the booster probability? I'm just trying to think of the Pfizer vaccine and the utilization of that one and the breakthrough seen in that in Israel. I just wanted to kind of look at that.

And then the second question is just as you think about BD and when you use pharma companies to help collaborate for commercial, is that a strategy down the road that you could use across the board and more in infected disease?

Stephen Hoge - Moderna, Inc. - President

So I'll -- maybe I'll start there and invite on the first question as it relates to when do we start to see the breakthroughs. So as we shared in our update on the data today, we can still consider -- continue to see very high efficacy in our clinical trials. And that's now out to a median follow-up of about 6 months, and it's entirely consistent with what we reported earlier on, which is encouraging.

It's important to note that there's no 100% prevention of COVID-19 infections on any of the vaccines reported to date. Obviously, we're preventing severe disease and things like that. But there is some level of infection that already happened. And that's probably just baseline. Some people get exposed to very high levels so they're at risk where they don't develop good immune responses for whatever reason.

And so you would expect that there's going to be some "breakthrough infections" in vaccinated populations. And I think that's what you see in the real-world evidence data that's coming out more generally. But hopefully, it remains very, very low. I mean in the case of ourselves and Pfizer, a very small percentage of that.

Obviously, it gets more concerning with some of the other vaccines that maybe have lower efficacy to date because you will see more rates of -- you would expect to see, based on the vaccine efficacy, higher rates of breakthrough infections. And then over time, which is maybe the core of your question, you just would expect that number to go up. The further you get out from your primary vaccination series, 6 months, 1 year, 2 to 3 years, you would expect to see an increase in the rates of reinfections with these coronaviruses and perhaps even breakthrough symptomatic and maybe even severe disease.

What we don't know yet, we don't have the data on yet is how long is that over time? Is it 12 months? Or is it 2 to 3 years? And I think in the face of an evolving pandemic, that's why we expect that for the most part, public health will recommend that we continue to boost people and maintain broad population-wide immunity against the widest number of strains possible.

I might now hand to Corinne to answer the second question.

Stephane Bancel - Moderna, Inc. - CEO & Director

So was the second question on BD or on commercial? It wasn't clear?

Stephen Hoge - Moderna, Inc. - President

BD. It wasn't BD.

Stephane Bancel - Moderna, Inc. - CEO & Director

And so just maybe to jump in, and Corinne, to add if I'm missing something. I think on BD, I think it's important to really appreciate that the company today is in a very different place than it was 3, 4, 5 years ago. As Corinne explained very well, we are building a commercial network around the world made of subsidiaries and distributors.

If you look at the existing subsidiaries, which we've already created, plus the ones that are planned to be created this year that the team is currently working on Japan, Australia and South Korea, those geographies represent around 80%, 8-0, of the EBIT margin of the global market. So that's, on the one hand, is we are leveraging the COVID vaccine to create, as Corinne said, something that would have been unthinkable a few years ago, a global network very quickly.

The second piece is around capital. As you know, a lot of the deals we've done in the past were because Moderna was a cash flow-negative company, and we did some of those partnerships to help provide capital. And the other piece we tried to provide at that time was development capability. Well, here again, we have been hiring amazing talent that has late-stage development experience, very successful launches in vaccines, in autoimmune disease, in oncology, in rare disease.

And so if you look at where the company is now, I think that at a high level, it's important to remember that our strategy is really to keep most of the medicines that we're going to be developing with this platform and I would say, especially in vaccine. There might be cases where we will be practical, like, for example, the partnership we've done with Vertex a few years ago. Vertex is the undisputed leader in cystic fibrosis, and to go and reinvent preclinical/clinical capabilities in cystic fibrosis, especially for a new modality that has technology risk, doesn't make so much sense for us and so partnering with Vertex makes a lot of sense.

So I think we should expect that most of the medicines we are bringing to the clinic, we're going to develop the whole way and commercialize ourselves, that will be practical on a very few case-by-case basis. I don't know, Corinne, if you want to add anything?

Corinne M. Le Goff - Moderna, Inc. - Chief Commercial Officer

Yes. Thank you, Stephane. I will just add one comment on the commercial partnerships. As Stephane mentioned, our ambition is to develop a direct presence in key strategic markets, and we have already started doing so. But there are markets where we might establish a presence in the future, but what we need is first to establish a distribution partnership so that we can -- in this COVID-19 pandemic, so that we can distribute our vaccine around the world, partnering with a distributor who will ensure the pharmacovigilance, all the regulatory aspects, medical information aspects.

So that's also very important for us to establish a strong commercial network. And as I said, the ambition is really to develop Moderna as a vaccine company that will have all the capabilities to commercialize the variable portfolio vaccines that we currently have in development.

Operator

Our next question comes from Hartaj Singh with Oppenheimer Company.

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

I just got a couple of general questions for Sir Jeremy Farrar and Professor Davenport, they're still around. One is just the presentation on infectious diseases. And so Jeremy Farrar touched on being proactive versus being reactive. With the COVID-19 sort of pandemic kind of -- I won't go on it's under our belt now but getting close to it, what are some of the specific things that he feeds between governments and nongovernmental organizations being implemented over the next sort of 1 to 3 years being proactive as opposed to being reactive?

And then for Professor Davenport, it was great to see how you can model efficacy in infectious diseases. How about safety? I mean I know that, generally, you've got to run clinical trials for that, but are there ways to model safety also as you're running -- as you're thinking about vaccine trials? And I just got a couple of specific follow-ups after that.

Stephen Hoge - Moderna, Inc. - President

So Hartaj, thank you for the questions. I apologize that both Professor Davenport and Jeremy are not on, given the time zone differences, I'm sure you understand. They do not stay on for the Q&A section. But let me quickly try and answer the first part of your question and then hand it over to Tal to offer his perspective on the safety one.

So in terms of adaptability, we really do think messenger RNA has already demonstrated that it's a platform that could be very proactive and very quick in responding to public health threats. And one of the things we would look to do is partner with governments for broadly in thinking about how to use that platform, use our platform technology to anticipate and stay ahead of the next epidemic and pandemic threats.

Moving broadly in the respiratory viruses is actually a big part of that strategy. As you can imagine, most of this concern really is around respiratory pandemics. And establishing -- using the COVID infrastructure capabilities to establish that respiratory annual seasonal booster opportunity is one way that we hope to address that, but we'll ultimately need to partner with public institutions, governments to do even more investment to make sure that in the situation in the future, which we know will arise, when we need to respond to an additional pandemic that we're able to do it even faster than we did last time.

Tal, do you want any comment on the safety side?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Yes. It's an interesting question but I think it's very hard because of the way to model safety. I think you can model tolerability, which is primarily a function of the near-term reactogenicity. And I think as you've seen from our platform, it's pretty consistent and you start with small numbers in Phase I, you repeat them in Phase II and Phase III holds it up and then what you see in the post-marketing world is very similar.

I think when we think about safety, we really worry about the more serious but, thankfully, rare adverse events that, of course, matter when you're immunizing people who are otherwise healthy. And that is very hard, I think, to model our priority, as you can see with some of the stories unfolding for some of the other vaccines these days. I think that requires very proactive diligence at looking for early signals.

I have to say that if you kind of step back and look at the last few months, I think the pharmacovigilance signal detection system, by and large, is working. It's global. There's a lot of moving parts but the signals that are in 1 in a million are being picked up and they are being appropriately evaluated. So I think the answer to that is careful and diligent and ongoing monitoring as opposed to trying to think that we can model what will be the reality.

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

Great. That really helps. And just my specific questions were for the flu vaccine, so has Moderna already participated, I guess, in the Northern Hemisphere strain selection meeting in February? Or would you kind of aim for the July Southern Hemisphere meeting in terms of if you're going to start trial in 2021? And then the CMV Phase III, is there a possibility or probability of a potential interim look also in that trial?

Stephen Hoge - Moderna, Inc. - President

So I'll invite Jackie to answer the second question on CMV. I'll start with a little bit of a nuance in how we think -- how you think about flu vaccine development. So early on, you will often want to -- for instance, if you were starting off-cycle with the season, for instance, this summer in the Northern Hemisphere as a hypothetical, you would likely go forward with the -- you'd want a comparable vaccine, and you'd likely go forward with a variant like the Southern Hemisphere, even in the Northern Hemisphere so that you could then offer a Northern Hemisphere vaccine for people going into that season. And that's kind of the principle of how these studies are usually conducted.

And so -- but then one of the things our platform would allow us to do, which is the other part of your question, is we would pretty quickly in that process, if we were interested in doing it, be able to switch over and actually do the Northern Hemisphere strains even -- perhaps, even intra-year as we move forward.

And so one of the advantages of the fact that mRNA manufacturing is really the same ingredients and pretty much the same process is that we would -- we think we would have an opportunity in the development here of both Northern and Southern Hemisphere alternatives relatively quickly to demonstrate the flexibility and adaptability of that platform and actually participate in both Northern and Southern Hemisphere seasons without having to have been at the altar in February because we are able to move quicker.

Jacqueline Miller - Moderna, Inc. - SVP of Infectious Disease Development

Thanks, Stephen. And so then it's Jackie to speak about the design of the CMV trial. And the question was whether we intend to build in an interim analysis in the Phase III efficacy trial. And the answer is yes. So building on the successful clinical trial methodology of our COVID-19 vaccine, we've designed the trial to be case driven in the sense that we will have an interim analysis at a point when a prespecified number of cases have been accrued. And the trial is designed that if we are not successful with that initial look because the sample size simply wasn't large enough, we will continue to follow the subjects in the trial and then have a final analysis. So very similar to what was done with mRNA-1273.

Operator

Our next question comes from Simon Baker with Redburn.

Simon P. Baker - Redburn (Europe) Limited, Research Division - Head of Pharmaceutical Research

A couple, if I may, please. Firstly, on COVID, the historic perspective on OC43 was very interesting because the S gene evolution rate of OC43 and SARS-CoV-2 are similar. So I'm just wondering if you had any details on how infection severity and frequency has varied over time, and what that potentially tells us about SARS-CoV-2 going forward?

And on the mutations, B117 and B135 (sic) [B1351], we've seen in 2021 that the global frequency of B135 has stayed pretty constant around 6% or 7%. B117 has gone from 7% to nearly 40%. And even in Africa, it's catching up with 135. What would you read into that about the long-term viability of the B135 variant?

And then a more general question. You said that you're using the same LNP formulation across your vaccines. That encompasses quite significantly different mRNA payloads. So I'm wondering if you could give us some thoughts on what is the limitation of that formulation in terms of how much you can incorporate within it.

Stephen Hoge - Moderna, Inc. - President

Great. I will try and answer all 3 questions as best I can. So first, on the OC43, what can we learn from it? Well, it's a difficult question to answer because we've only really been getting molecular diagnostics and monitoring of OC43 as an infection, really, in the last decade. And there have been a number of publications more recently, a group out of Belgian paper but also the CDC paper I referenced, that have been capturing the rates of those infections.

And so I think what's hard to know is if you look back beyond 10 years from now or even 20, 30 years from in the past, what the rates of infections were and how it related to spike protein evolution of OC43, clearly, as you pointed out, the spike protein has continued to evolve as have the other proteins in OC43 for 130 years. But we've only really been tracking it for the last couple of decades intensely.

And so I'm not sure that there's too much we can say yet about it other than the observation that it's still here. It still infects us and it still -- kills some people every year. And so that's something that we can at least anticipate will happen in the future with SARS-CoV-2, unfortunately.

Now in terms of the different variants that you referenced, so 117 and 351 (sic) [1351] in particular, I think it's important to note, and I think Jeremy -- Dr. Farrar said this very well, we have not yet seen the contribution of immune pressure, immune selective pressure really on these viruses. What you see is you see nonpharmaceutical interventions. Very recently, we're starting to see the value of vaccination, but it's really vaccination -- acute vaccination. So it's the 3 to 6 months right after you receive your vaccine when your immunity should be boosted to the highest level.

And what we haven't yet seen is the real sort of immune pressure and some competition between the viruses afterwards. And so it's -- I think you point out quite rightly that the 351 variant seems to have sort of maybe plateaued or peaked. But I don't think we really know yet what the competition will look like between these variants as they continue to evolve. What we can clearly see is that 351 was reinfecting, particularly I think the reports out of South Africa were most concerning, and it did seem to correlate with lower neutralizing immunity.

And so as we get to immune selection between the virus and you start to see breakthrough infections that are really based on waning immunity, I think you might start to see a little bit of a difference there with 351 and 117, but that's speculation. We'll have to wait and see. Fortunately, the ancestral vaccine, 1273, covers 117 quite well. And obviously, we'll be looking to make sure that all the boosters do that as well.

And then I apologize, I actually forgot the third part of your question.

Simon P. Baker - Redburn (Europe) Limited, Research Division - Head of Pharmaceutical Research

Yes. It was on LNP formulation that you're seeing the same formulation, yes, across -- what's the -- how far can you push it essentially?

Stephen Hoge - Moderna, Inc. - President

Yes. Thank you very much. So we have -- we used that LNP formulation, that's the technology we used to put mRNA in there across all of our existing vaccines. That is we've done many generations of other technologies. If you look back in our history, there's lots of other things. But we've really landed on what we think is our best-in-class delivery vehicle.

In terms of the number of complex things we put in there, preclinically, we've pushed that very far and quite excited by the power of the diversity of that payload we can bring in. It sometimes feels like there's not many limits, although I'm sure there will be, as we continue to test things we'll eventually discover a limit. Clinically, the largest number of mRNAs we've put in and had clinical data is the cyto megalovirus vaccine, where we have 6 mRNAs and they generate 6 different proteins and generate the 2 different antigens that Dr. Panther presented, pentamer and gB.

We have also done a combination for 2 respiratory viruses, hMPV/PIV3. And so far, all that critical data support that there's really not a limit that we're obviously were in terms of the technology's ability to bring in multiple mRNAs. So we're optimistic. We're not -- are we talking about jumping into 100 mRNA combinations? No, not anytime soon. I think if you look at the diseases that I highlighted in terms of the virus combination opportunity, many of those are single antigens like RSV, the F protein or SARS-CoV-2, COVID the spike protein. In a few cases, there are multiple antigens like in the different strains in influenza, but something that could easily be accomplished with 10 or under mRNAs if you need to, and we feel like that's in well within the demonstrated capability of the platform today. Maybe in the future, we'll dream of going much higher than that, but not probably in the near term.

Operator

Our next question comes from Nick Abbott with Wells Fargo Securities.

Joseph William Poen - Wells Fargo Securities, LLC, Research Division - Associate Equity Analyst

It's Joe on for Nick. I really appreciate the update. And with respect to the broader platform, the data is obviously suggestive that the technology can induce robust antibody generation, not only with COVID but CMV and RSV and others. So maybe how do you think about optimizing T cell responses, both with respect to coverage for potential future emerging COVID variants as well as the broader application within your oncology portfolio?

Stephen Hoge - Moderna, Inc. - President

Yes. Great. Thank you for the question. So I think as Dr. Panther presented today and as we've updated in the past, we generally see very good T cell responses. So we shared some CMV data today, but we shared CD4 and CD8 data that's been published against SARS-CoV-2. And more importantly, and this is kind of the root of your question, we had previously presented at conferences data on our T cell data in the cancer vaccine space, showing that we get very strong, and frankly, I think as good as anybody has seen, T cell responses in humans with neoantigens in those vaccination -- the cancer vaccine, the personalized cancer vaccine context.

And so at this point, we feel very confident about the strength of the T cell responses. It's often very hard to compare T cell responses because the assays themselves are not as well standardized. And I would just come back to a fundamental principle of immunology more generally that we've talked about, including, I spoke about last year at our Vaccines Day, which is that really long-term high-affinity B-cell responses of the kind that we're seeing are really only possible if you're getting strong T cell help.

And so at some level, memory is -- T cell memory is baked into every time we look at these neutralizing titers because ultimately, you can't get there without it. And so we'll continue to sort of look at ways whether we can improve that or tweak it one way or the other. We do use some differences in process and differences in our technology between the cancer vaccine space, where we really do want to focus on the T cell responses exclusively, and the more generalized immune responses we want to see in infectious disease vaccines, where you really want cell-mediated immunity, but you really also want humoral immunity.

And that is something we'll always be looking to adapt to the needs of any disease we're going after. But we're actually quite confident and pleased with the data that we have today.

Operator

Our next question comes from Mani Foroohar with SVB Leerink.

Mani Foroohar - SVB Leerink LLC, Research Division - MD of Genetic Medicines & Senior Research Analyst

A quick manufacturing scale-up and timing question. With the disruption, however temporary or perhaps longer lived in supply for the adenoviral vaccines, is there an opportunity for you guys to scale up manufacturing capacity and supply more quickly than anticipated, both in the U.S. and OUS, on the one quarterly that you mentioned? And how quickly could we start to see that show up in doses delivered additional contracts, et cetera?

Stephane Bancel - Moderna, Inc. - CEO & Director

So this Stephane. So I think for 2021, we are still on track to our plan to deliver between 700 million and 1 billion doses. As the year goes by, we'll give you updates. As we discussed previously, by adding capacity, which we announced around a month ago, that will increase very materially the output in '22.

As you know, adding big sort of capacity takes time because you need to buy the machine, have them installed, find a GMP suite and do other qualifications and so on and so forth. I think the biggest leverage we're going to have is really around those. As you know, and it was presented today, the boosters are being tested in the clinic at 50 microgram and less. And so if you go from a world where you use 100 microgram per dose to a world where you could be at 50 microgram per dose for a booster, assuming most of the world moves to booster, that will have a very material impact in terms of our dose output in 2022.

So we're going to reassess, as I said before, what should we do with our manufacturing capacity based on what's happening in the marketplace and based on what's happening on over vaccines. But I don't think it is reasonable to believe there could be an impact in the next few months.

Operator

And I'm currently showing no further questions at this time. I will turn the call back over to Stephane Bancel for closing remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Well, I would like to thank you very much for participating in this important Vaccines Day. I would like to thank our speakers. I look forward to speaking to many of you soon when we'll do our Q1 reporting and also what to put in your calendars that as usual, we will do a Science Day in late May, where Stephen and his team will basically get you a peek for all the new things that they are working on in the platform to keep pushing the boundary of science and to expand the impact we can have with mRNA in terms of human health.

And in September for our traditional R&D Day to review pipeline updates with a big focus on therapeutic and of course, updating any important data on the vaccine front. So with this, I wish you a great day or a nice evening if you're calling from Europe. And please, everybody, stay safe. Bye.

Operator

This concludes today's conference call. Thank you for participating. You may now disconnect.

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