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PRESENTATION

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

Good morning, and welcome to Moderna's Third Annual Vaccines Day. Today, you will be hearing from our scientists and program leaders present data from our mRNA vaccines programs. You will also hear from distinguished key opinion leaders in Immunology and Vaccinology as it relates to SARS-CoV-2, influenza and latent viruses, including the association of EBV and multiple sclerosis.

Following the formal presentations, we will take your questions during the Q&A section. You can access the press release issued this morning as well as the presentation slides by going to the Investors section of our website. On today's call are Stephane Bancel, our Chief Executive Officer; Stephen Hoge, our President; Jacqueline Miller, Senior Vice President and Head of Infectious Diseases at Moderna; Raffael Nachbagauer, Program Leader for influenza vaccines; and Sumana Chandramouli, Program Lead for EBV vaccines.

Before we begin, please note that today's presentation 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 me now turn the call over to Stephane Bancel to open the remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thank you, Lavina. Good morning or good afternoon, everybody, and thank you so much for joining our Vaccine Day. Some of you, it's your first Vaccine Day, but welcome back to all of you that have watched the Vaccine Day last year or the year before.

Before the pandemic, too many people forgot the profound impact of vaccination. First, on health, preventing disease, some vaccine preventive cancer and having a huge societal impact in terms of ability to afford vaccines and access, the empowerment of women and mothers, and of course, the huge economic impact on which I'll come back in a few slides.

If you just look at the impact of vaccination on health over the last, let's say, 20 years, it has been really profound. What you can see on the left graph here is that over the last 20 years, the reduction of disease around the world has been really profound. And as you can see for this WHO data, for example, on rubella in green line, you have a very massive reduction of children being affected by this virus. And if you look on the right side, what you can see is that the vaccine has been a key contributor in the global reduction of under 5 years of age mortality since 2000, as you can see.

And as many of you know, from an economic standpoint, if you look at the data, the return on investment on health care dollar on vaccine is actually the best use of health care dollars. The data shows that you have a return on investment of about 44x in low income and middle telecom country, and that is despite the cost of the vaccine being actually very low compared to high income country.

If you look at the U.S., between 1994 and 2013, the CDC has estimated around \$1.3 trillion that have been saved because of vaccines. And you can see some examples of returns on the economic benefit of those vaccines around the world.

Despite all that, what is very interesting to observe is that there are around 220-ish of viruses that are known today to infect humans around the world. And what is remarkable since 1918, in the last 40 years, more than 18 new viruses have been identified, thanks to new technology like PCR sequencing and so on. And if you look at the data of actually how many vaccines are available against those viruses, it's actually quite a low number. It's around 10% on the entire population, around kind of 25 vaccines have been made available.

And so that gives us a lot of hope of the impact we believe Moderna should have on this space and what we all should expect from vaccines in our public health. So if you think about now the Moderna solution, the Moderna platform, we really believe it is a unique opportunity to truly transform and disrupt the traditional vaccine market.

If you look first at mRNA technology, as you know, we have the ability to move really fast. We have the ability to combine different mRNAs in a single dose to do very complex biology, and like this going after either combination or after very complicated or difficult to target pathogens.

So now if you look at Moderna and the platform we have built over the last 10 years and the lead we have taken in infectious disease vaccine, it's quite remarkable to see what the team has been able to do in terms of high biological fidelity through this technology. The other piece too that I think is going to surprise most observers of the company is that the probability of technical success, we believe, is going to be really high on our vaccines. And why is that? Because for every vaccine we bring to humans and eventually to the market, it is exactly the same technology that is being used at the chemical level.

It's the same chemistry used to make the mRNA molecule, the same manufacturing process, the same chemistry for the lipid. So what your body sees when you get an intramuscular injection is exactly the same lipid that you got, many of you, in the Spikevax vaccine. And that's what is really the unique benefit of this technology.

And as we've shown in 2020, the ability to go from sequence to approval in a record time. We have a few dataset on this slide that I won't go into detail. But it's just a very different time frame, total disruption compared to traditional vaccine making.

So we talked about speed, but now let's talk about manufacturing, which is another extraordinary competitive advantage of this technology versus what the industry is using. We actioned first the ability to scale in a way that few people could think was possible. In 2019, the year before the pandemic, Moderna made less than 100,000 vaccines in the entire year.

In 2021, Moderna made more than 800 million doses in the fiscal year. And how is it possible that a team of maybe 1,000 or 1,500 people in manufacturing could do so much. Well, if you think about it, it is the same process for all of our products. And by the way, not only vaccine, also therapeutics. The same process in the same physical equipment, in the same room, by the same people, using almost all the exact same raw materials. That is an extraordinary platform and that has never really happened in the pharmaceutical industry. And that is going to give us great benefit and advantage to serve patients and to compete in the years to come.

Now let's look at the pipeline. We are extremely proud and excited about the work our team has realized in the lab, in the clinic, and now in the commercial world. The company today, just in vaccines, has 31 development programs, 19 of which are in the clinic, 4 are in Phase III, and we have, as you all know, 1 approved product.

If you look at the massive advantage of technology, we have 9 viruses for which there is unmet medical need, where there is no vaccine available on the market. We have 8 combination vaccines and 7 vaccines against latent viruses. So today, we are very excited about a lot of new data that we're going to be sharing and also a lot of news that have come in, in the last 48 hours.

As you know, we have announced a new development candidate that we're very excited about, the COVID + Flu + RSV, mRNA-1230. And also, we are very happy about, and for those of you who attended Vaccine Day last year, we talked a lot about one of the human coronavirus that circulates in the community pre the pandemic, which is OC43.

And so what the team has done is develop a new candidate, mRNA-1287, that is a combination of several human coronaviruses into a single vaccine. Those viruses help human and the team will give you more detail in a minute. We are so very pleased to have finalized the partnership with Australia, which I will come back to in my conclusion. In terms of new clinical data that have been released in the last 48 hours, we are very excited to have met primary endpoint for pediatrics vaccine after 2 doses, and the team will share the data with you in a minute.

We're also very happy today to share with you for the first time the mRNA-1283, which is, as you might recall, the next-generation COVID-19 vaccine with up to 2 years of storage in a regular fridge, and that data will be shared with you today by the team.

And then we are very excited today to share with you our flu vaccine Phase II data for mRNA-1010. And as you can see on the slide, the team will provide you some update with a bit more clinical data. So it's going to be a really exciting and very impacting. So I'm very pleased to welcome the team in the following hour or so to present the data. Stephen, obviously; Jacque who, as you know, leads development for infectious disease; and Raffael and Sumana, who work in vaccines.

Now let me share with you quickly the agenda before handing over to Stephen. So Stephen is going to walk you through the development strategy of our vaccines before turning over to Jacque, who's going to be the master of ceremony for the vaccine against respiratory viruses, and she will introduce our guests. We'll take a quick coffee break. And then when we come back, Jacque, again, will introduce our guests and talk to us about vaccines against latent viruses.

Before Stephen will explain our global health vaccine and mRNA access platform, and as you can imagine, and I'll talk about it in my closing, this mRNA access platform is quite a unique way that has never really been done in the industry. That's why I'm extremely proud and excited to enable scientists in labs around the world, academic labs, government labs, to just put Moderna technology and platform on steroids. And then I'll come back to close the day before, of course, opening to Q&A.

With this, thank you very much for your attention. Have a great day, and I'm turning now over to Stephen.

Stephen Hoge - Moderna, Inc. - President

Good morning and good afternoon, everyone, and welcome to our Vaccines Day. I'd like to take a few minutes now to briefly frame our vaccine development strategy.

Now I'd like to take first a step back and say what have we learned in the past year about our mRNA platform and its potential? First, we've learned that it's highly effective. In fact, mRNA vaccines have demonstrated the highest efficacy in published Phase III clinical trials, and the highest effectiveness in the real world. We've also demonstrated the broadest immunity, including for Spikevax, where mRNA-1273 has induced significant antibody-mediated immunity and neutralized antibodies against variants of concern and demonstrated that it can generate very significant cellular responses, including CD4 and CD8 responses against the SARS-CoV-2 virus.

But third, we've demonstrated the unique agility of our mRNA platform. In fact, we've updated and rapidly advanced variant-containing vaccine candidates on multiple occasions. Today, we have 3 variant-specific vaccines against Beta, Delta and Omicron, and 3 bivalent vaccines, including combinations of Beta wild-type, Beta and Delta, and most recently, our 214 vaccine, the Omicron wild-type bivalent.

We've also advanced a next-generation vaccine, mRNA-1283, into its Phase II studies. All of that demonstrates the incredible power of our mRNA platform in infectious disease vaccines.

Now as we've talked about before, we think there is significant unmet need looking forward. And our strategy is to pursue that unmet need in 3 big areas. First, in respiratory vaccines. Respiratory disease has the highest burden in the young and the old and those that are immune-compromised or immune-suppressed. Infections with respiratory diseases are a top cause of death globally. And we think there's incredible opportunity, as I said, in the moment, to address that unmet need.

Second, latent viruses. These are viruses that often cause a disease immediately upon infection, for instance, birth defects with cytomegalovirus or mononucleosis with EBV. But the long-term sequela from those latent infections, including things like cancer and autoimmunity are the real burden of those diseases over time, and we think an important opportunity for us to address the vaccines.

And then third, global public health threats. There are a number of persistent threats causing epidemics globally, including malaria, Zika. Often, those have been identified by WHO and CEPI. But there's also inevitable need to prepare for the next pandemic, because there will be another emerging pandemic at some point in the future, and we believe there is an opportunity for us to continue to play a leading role in that space.

I'd like to first double-click now on that respiratory vaccine need. The disease burden from acute respiratory viral infections is not limited to hospitalization and death, as illustrated here. In fact, hospitalization and death usually represents a minority of the overall burden associated with that disease. There is moderate disease, and there is even inapparent societal burdens associated with these respiratory infections.

So while we will tend to focus on clinical development, on the mortality, hospitalization or infections captured, there are a number of things related to disability, a loss of productivity economically and the quality of life that we do think represent unmet needs we can address with our vaccines. Prevention through vaccination has had a large impact historically in this space, and we think there are an incredibly large number of unmet need viruses that Jacque and others will speak through in the coming slides.

But if you look at just the quantity of that, it is almost unrivaled in terms of opportunity for impact. So COVID, as we unfortunately know, in the pandemic setting, has caused over 6 million deaths globally. And the global population of older adults is only expected to increase. In fact, it is going to double between now and 2050.

If you just look at the projected deaths, mortality rate and disability-adjusted life years associated with respiratory infections in 2016 and extrapolate into that larger population, it will become 1 of the larger dramatic drivers of cost and disability globally over the next few decades. This opportunity is large today, and we think it will only get larger, unfortunately, as populations age and those at risk of respiratory viruses increase in number.

Our second focus area, which we'll also talk about today, is latent viruses, which have short-term and long-term health impacts. And many of these are viruses that we already know well. Cytomegalovirus, which we're addressing with our mRNA-1647 program, is a leading infectious cause of

birth defects in the United States and in developed economies. It's also a major driver of immune dysfunction with aging, often leading to increases in cancer and other diseases.

EBV, as we've talked about extensively, and we'll speak more about today, is also a major driver of cancer, accounting for over 160,000 deaths attributable to malignancies annually. But it is an incredibly important driver of multiple sclerosis risk as well, which we will cover today and is responsible for a greater than 30-fold increase in that disease.

Third, HIV, which we all know well, is on our pipeline with 2 different programs, and is a major cause of AIDS, resulting in approximately 700,000 deaths worldwide each year. And we're proud to be developing potential vaccines or early-stage programs against that with a number of global public health partners as well.

HSV, the herpes simplex virus, HSV-2, establishes life-long infections, which have debilitating effects, including upon reactivation with general herpes. About 5% of the population in 18-49 is HSV seropositive.

And lastly, VZV in our pipeline, a recently announced program, which as a result of declining immunity in older adults, leads to reactivation of the virus from latently infected neurons causing pain and itchy lesions. Herpes zoster occurs in 1 out of 3 adults in the United States in their lifetime. And because of a limited availability of vaccines, it's an important unmet need that we hope to address. The third part of our strategy is to address global public health needs.

Now we have 2 development programs that are in the clinic and are approaching very quickly. The first is our Zika virus vaccine, mRNA-1893, which is against a virus which is borne by mosquitoes and drove a global epidemic in 2016. That program is in Phase II, which is ongoing. We also have a Nipah virus vaccine mRNA-1215, which has a dramatic outbreak potential. In fact, mortality associated with Nipah virus can approach 75%. That program is expected to enter a Phase I study later this year.

Now we've also recently committed ourselves to expand this pipeline dramatically. In fact, we've committed to advancing vaccines against 15 priority public health pathogens into clinical trials by 2025. These pathogens have been identified by WHO and CEPI as specifically concerning public health threats.

Now that I've covered that overview of our strategy, I'd like to pass the presentation on to Jacque Miller, who will walk you through some further details.

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

Thank you, Dr. Hoge. Good morning. My name is Jacqueline Miller, and I am the therapeutic area head for infectious diseases at Moderna. It gives me great pleasure today to shepherd you through the vaccine portfolio that we currently have in development.

As Dr. Hoge mentioned to you, we have a large portfolio of respiratory vaccines, and we'll be discussing many of these candidates with you today. Spikevax is our licensed vaccine against SARS CoV-2, and we now have multiple booster candidates, both monovalent and multivalent, in the clinic.

In addition, we'll be sharing Phase I data from mRNA-1283, which is a next-generation formulation intended to increase stability in the refrigerator and preserve longer shelf life. We also will be discussing our influenza portfolio, starting with mRNA-1010, our seasonal influenza vaccine. We also have a vaccine candidate, mRNA-1345, against respiratory syncytial virus or RSV. And we will be discussing data from that vaccine and programs for that vaccine in both older adults and the pediatric population. We'll be sharing a new vaccine program with you today, a trivalent influenza, SARS COV-2, and RSV combination vaccine, as well as a new candidate against other human corona viruses.

And then finally, we'll be discussing an update of our pediatric portfolio, including a new vaccine candidate against RSV and human metapneumovirus. We'll also be discussing our latent virus portfolio, including our CMV vaccine, which entered Phase III this year, as well as EBV in 2 formulations, 1 intended to be prophylactic and 1 intended to be therapeutic.

We also will be announcing our new herpes simplex virus vaccine, as well as our Varicella zoster virus vaccine candidates. And we'll be giving you an update on our collaborations to develop HIV vaccines.

And then finally, I'll hand the floor back over to Dr. Hoge to talk through the Zika vaccine candidate as well as our Nipah virus vaccine candidate. So first, I have the pleasure to introduce to you Dr. Shane Crotty from the La Jolla Institute for Immunology. Dr. Crotty is an immunobiology expert and has published in T follicular helper cells as well as CD4 cells; he's looked at viral immunology against SARS CoV-2; and also investigated B-cell immunodominance and the central role of germinal centers and memory B cells. So he is the perfect person to speak to us about the immunobiology of SARS CoV-2 infections. Dr. Crotty?

Shane Crotty, Ph.D.

Thanks to Moderna for the invitation. The COVID vaccines have clearly been world-changing medicine, and it continues to be important to understand how those vaccines work and what is protective immunity against COVID-19. And so those will be topics that I'll be speaking on today, understanding immune responses to the vaccines and to the virus and understanding immune memory, and how your immune system remembers these things to be able to provide protection.

I am at the La Jolla Institute for Immunology, which is a nonprofit Research Institute on the University of San Diego campus. And my disclosures are that I wasn't paid for this presentation, but I do have other consulting disclosures shown here. And with that, we can get on to the science.

Early in the pandemic, there were a lot of fears about many aspects of this disease and this virus. And one of those was that maybe you didn't make immune responses to this virus or developed immunity. And so we endeavored to help understand that better. And almost everything I'll show you today was in close collaboration with Alessandro Sette, also a professor at LJL. And throughout the talk, I'll be showing photos of the scientists in our labs who did the experiments and did all this hard work to generate this knowledge.

And our first study, and the front page that is shown here, or if you prefer a live-action version, here's a copy of it being held up to try to explain immunology of this disease to congressmen and women. In that study, we took the perspective that one way to try and understand what kind of immunity is important against COVID-19 would be to measure all 3 major parts of the adaptive immune system, okay?

And the immune system is complicated and understanding, demonstrating immunity in humans can take a decade or more in terms of proving multiple different mechanisms. But we felt a good first way to get a sense of this was to ask in average cases of COVID-19, what do the immune responses look like? Because these are cases where people get infected, they had significant viral loads, but then they cleared the viral infection. And so what immune responses were associated with the clearance of the viral infection, what was present afterwards.

And so we measured antibody responses, CD4 T cell responses and CD8 T cell responses because, again, these are the 3 major branches of the adaptive immune system. And they contribute to different degrees in different kinds of infections, including different viral infections. And antibodies are known to be important in almost all currently licensed human vaccines.

CD4 T-cells are critical for most neutralizing antibody responses, i.e., in general, you don't get neutralizing antibodies unless you get help from the CD4 T cells. But these T cells can have actually multiple different kinds or subsets of these cells with different functionalities, including direct antiviral activities. And then third are the CD8 T cells, also known as killer T cells. And these are known to be important in many viral infections.

And in an oversimplified view of immunology, antibodies stop viruses outside of cells, and CD8 T cell stop viruses inside of cells. Once cells are infected, it's difficult for antibodies to have function, and that really the specialized functionality of CD8 T cells is to recognize those cells.

And so we measured all 3 of those in previously infected individuals, and we saw that 100% of them made antibody responses against spike. But also 100% of them made CD4 T cell responses, including many of them make good CD4 T cell responses against spike. And most of them made detectable CD8 T cell responses. And the magnitude and qualities of all of these responses were largely interpreted as good news that this was antiviral immunity that largely matched expectations and that these responses were not particularly large, but they were particularly broad against

different viral proteins, including recognition of spike. And this was considered a positive sign in April, May 2020, that it would be plausible to potentially develop a vaccine against this disease, okay?

And then the next question we turned to in terms of protective immunity was immune memory. Immune memory is how your immune system remembers a disease, whether that's from an infection or a vaccine and protective immunity is fundamentally based on the presence of immunological memory. And to do that, we again looked at infected individuals and asked whether each major component of immunological memory might be there.

And so I said before that there were 3 major branches of adaptive immunity, right? First, the CD8 T cell, the CD4 T cells, and then essentially the antibody responses, which the products of which are antibodies, but they come from B cells. And so there are also quiescent memory B cells that aren't actively producing antibodies, but can produce antibodies upon a reinfection or re-exposure.

And so you can really think of memory B cells as essentially being antibody factories with the lights turned out, and that if you get infected, then only B cells turn on and start making more of those antibodies. And so we measured all of those in previously infected individuals and did so in a large cohort. This is the largest study ever of its kind.

And another key parameter for us was that it can be challenging to predict immunological memory. And we felt like the best way to assess immune memory was to wait at least 6 months and then look at the immune memory to get a sense of the kinetics. And in fact, that worked out quite well, and we ended up having 8 months' worth of data.

Here's all of that data. I just thought I would like to show at least a little bit of raw data, so you can get a sense of what it looks like. And we measured neutralizing antibodies, memory B cells, CD8 T cells, and CD4 T cells. And the take-home message here was that previously infected people had neutralizing antibodies and that they were present in most people for at least 8 months. And in fact, other labs have now shown that they get sustained for a year or more, but they're relatively low levels of neutralizing antibodies.

And interestingly, people do make a memory B cell response. Virtually, 100% of people make memory B cells, and they made them with different kinetics than the antibody response. And then CD8 T cells and CD4 T cells were also made and about 50% of people had CD8 memory and about 100% of people have CD4 memory out of 8 months, but of different magnitudes and each of these with different kinetics. And one of the ways we interpreted all of this was that, well, the presence of this memory at 8 months meant that there was probably going to be memory for years into the future, at least at some level. And that of the parameters we measured, we considered that these were probably relevant for protective immunity at some level, at least protection from severe disease.

And so we asked if we take all those components and see, amongst all the people we studied at 1 month versus 6 months post infection, how much immune memory was there? And we could see that there is variation in the population, but the take-home message was that 6 months post COVID, about 95% of people still were positive for at least 3 out of 5 of these immune memory responses. And again, given the kinetics that we saw, this suggested that people with previous infections would likely be protected for years into the future, at least from severe reinfection, okay?

And this is, again, tri-negative sense of the behavior of immune memory in the context of protective immunity. And indeed, those predictions have widely held up in epidemiological studies, which is notable because, again, previously infected individuals generally have relatively low levels of neutralizing antibodies, but they have other components of immune memory suggesting that those other components are contributing to a protective immunity in some ways.

We then shifted to try to understand immune memory to the COVID vaccines, again, with the same perspective that antibodies are great. It's very valuable to measure antibodies, but there are multiple different components of the immune system that may be contributing to protective immunity.

And so we wanted to measure antibodies, memory CD4 T cells and memory CD8 T cells. And we did so in this study led by Professor Daniela Weiskopf, who did a fantastic job, and it was published a few months ago. And in particular, through the NIH, we got access to low-dose Moderna vaccine clinical trial samples, which were incredibly helpful. And what we could show with that was that indeed there was, between the peak

response after 2 doses of the vaccine and 6 months later, there was approximately a seven to tenfold decline in circulating antibodies, which has been widely reported in other studies, too, for example, the full-dose Moderna or to the Pfizer vaccine.

But we were particularly keen on whether does the Moderna vaccine elicit memory CD4 T cells. And indeed, it does with only a twofold decline in the 6 months after the second dose. We interpreted that as really quite a positive sign because most likely, but not proven, most likely, though, the greatest decline would occur in the first 6 months, and then most likely there would be a stabilization thereafter, okay. And so we suspect that there will be T cell memory detectable for years in the future.

And then for CD8, we also found that something like 80% to 90% of people had a detectable CD8 response. They then declined to about 67% over 6 months, but only a twofold decline in the quantitation. If we compare those immune responses to the vaccine to immune memory after infection, specifically looking at spike, we observed that they were really pretty comparable out of 6 months, which again, we consider really a positive sign for RNA vaccines that they were able to elicit memory CD4 T cells and memory CD8 T cells similarly to that of natural immunity.

It was a little bit lower than what the full dose elicited. And then obviously, age is a very important topic in COVID with age being the biggest risk factor for hospitalization and death, and different vaccines in the past have been known to have differential immune responses across age groups, but nicely this clinical trial was structured such that there were people above age 50 or above age 70 included. And what we found was that the T cell memory in all of those age groups was equivalent, which again is a positive sign for this vaccine, and I don't have time for this particular topic today.

So I talked about measuring each of these different parts of the immune system and that they are present at different levels. And so what does that tell us about protective immunity? Well, in this one slide, I have a summary of my perspective on mechanisms of protective immunity against COVID-19, and I'll talk through these in the subsequent slides. I do want to point out that these aren't definitive, that there's still plenty to learn and that immunology is complicated. But based on what we know about other diseases and about immunology as well as what we have learned -- many labs have learned about COVID-19, I think these are reasonable interpretations and perspectives, okay.

And when thinking about protective immunity to a disease, I always think it's important to start with the biology of the virus, where does the virus replicate, and then what kind of disease does it cause and what are the kinetics of that disease? Because those parameters determine what types of immune responses may be protective against the disease.

And for SARS-CoV-2, this is really a virus that replicates very quickly in nasal passages and in the oral cavity such that you have transmission of the virus, right, within about 4 days. But really, it's important to consider that these are the first tissues that are involved. But the serious disease is in a different tissue. It's in the lungs, and it's really in the lungs that you have the pneumonia, which results in the hospitalizations and the ARDS and the fatalities.

And so we can think about these tissues and the disease as a spectrum and that if you're trying to protect from any infection, you have to be able to protect quite effectively in these 2 tissues. But if you're trying to protect from the more severe outcomes to hospitalizations and deaths, it's really the lungs that are involved. And also, there's different kinetics. These -- again, transmission is happening in about 4 days, but hospitalizations are normally occurring out between 10 and 15 days post infection. That's a lot more time that's available for the immune system to respond and control this disease as opposed to prevention of initial infection or preventing someone from being positive in an antigen test.

And really to phrase that in a different way, it's all a race, okay? It's a race between the virus and your immune system. And vaccines change the race, right? You then have the head start instead of a virus because you've already made an immune response. And in thinking about those different immune responses and what they might contribute, the simplest option is high-level long-lasting neutralizing antibodies.

If you can have high level of long-lasting neutralizing antibodies, that will provide outstanding protective immunity if it's a virus that's susceptible to neutralizing antibodies, which this virus clearly is. And antibodies can clearly protect. Also, it is worth noting that antibodies, if you measure antibodies, that's also a correlate of other immune responses that are present.

For example, there has to be a correlate of CD4 T cell responses because the neutralizing antibody responses that you get are dependent on the CD4 T cells. So the presence of the antibodies are also, to some degree, a surrogate marker of the presence of other parts of the immune system at the same time, okay? And one of the things that we've focused on has been, yes, this is great. And in fact, understanding the immunological principles of this is what I founded my lab to do, and so I'm definitely a big believer in this, but again, the immune system is complicated.

If you have situations where you don't have high levels of neutralizing antibody, which, for example, infection is 1 of those, or if they're not long-lasting, or if they're obviated by variants, are there additional lines of defense besides neutralizing antibodies that can provide some degree of protection? And one way to think about this is as a layered defenses kind of model.

Layered defenses is a concept that is valuable in many walks of life from various things, and it applies pretty well to immunity as well, or sometimes this would be referred to as like a Swiss cheese model, which is to say, okay, if you have one layer such as neutralizing antibodies, that's great. But if it's imperfect, additional layers can keep providing additional layers of protection, so as to provide sufficient immunity to prevent severe outcomes, i.e., the severe COVID pneumonia, and that it's plausible that memory CD4 T cells, memory CD8 T cells and B cells and non-neutralizing antibodies contribute in some degree at that serving as additional layers of protection.

So some of that data comes from work from my lab, where in this study, we looked at hospitalized versus non-hospitalized cases of COVID-19 as well as different severity of hospitalized cases. And we measured antibodies, CD4 T cells and CD8 T cell responses in all of those people and asked were those immune responses associated with better or worse outcomes. And what we observed was that coordinated immune responses were associated with positive outcomes. And in particular, there was statistically significant evidence that the presence of T cell responses in people resulted in better outcomes against disease.

And really, it was the absence of these responses that were associated with poor outcomes. And one of the notable findings of this study was that, obviously, age is a strong factor in COVID-19, and we observed with increased age, people were less likely to make a strong T cell response, either a CD4 or a CD8 response.

And one parsimonious model for explaining some of the reason for age being a COVID-19 risk factor would be that actually in aging, it's harder to make a new T cell response. And so if T cells are important for controlling an ongoing infection, older individuals are likely to have more difficulty doing so to a new virus that they've never seen before. And so we had evidence of that shown here that the older people were, the fewer the naive T cells they had, and the more association there was with disease severity.

And that's because in humans, this is data from Dana Farber at Columbia, T cells are produced in your body in an organ called the thymus. And it's known that actually birth of new T cells drops dramatically with age. And so again, to a new viral infection, if you are depending on those naive T cells to be able to recognize a new virus, that becomes harder and harder with age.

And interestingly, that's something of a positive sign for vaccines, because if we're talking about this being a race between the virus in your immune system, and we see it in the context of COVID-19, the speed of the T cell response appears to be relevant for preventing severe outcomes.

Well, vaccines change the rates, right? You then have the head start instead of a virus. And so in older individuals, it's not that they don't have any T cells, it's just that they have fewer and so it takes them longer to make that response. And indeed, from the data I showed you from that Moderna vaccine study that we published, older individuals do make those T cell responses to the vaccine. Again, it probably just takes them a little while longer.

And so various lines of evidence point to protective contributions of T cells. I'm not going to walk through all of these. But overall, it's reasonable to consider that T cells are playing a role in contributing to protection from more severe disease outcomes. And some of this comes from analysis of variants. I love this particular article in Scientific American. And in response to Omicron, people who have had previous infection have no neutralizing antibodies, but people who have been previously vaccinated with say 2 doses of RNA vaccine, have low or no neutralizing antibodies. And so there was lots of question about would people have any immunity still even if they didn't have neutralizing antibodies.

And so our groups measured recognition of Omicron by T cells generated by COVID vaccines, and we published that indeed T cell response, both CD4 and CD8, of Omicron is preserved and half a dozen other groups have now published similar findings. And so that preservation of the recognition of Omicron by T cells has been interpreted as some evidence for why people are still having generally positive outcomes against Omicron if they've been vaccinated twice.

There are other ways that T cells can contribute and T cells have to play a role at the site of infection. And so if you're circulating T cells in your blood they will contribute to protective immunity by trafficking, by moving to the infected tissues and controlling the virus in those infected tissues. But another way for this to happen is that the T cells can just reside permanently in those tissues. And these are difficult studies to do because you have to have direct access to human tissue.

And we collaborated with, again, the wonderful Dana-Farber at Columbia University, who has had a long-standing organ donor program, to ask in lungs of people who have had previous COVID-19, just unremarkable COVID-19, non-hospitalized, is there any evidence that the immune system remembers that by leaving memory cells in that tissue so that they might be able to respond faster to a re-exposure. And we did indeed see, in the lungs of these individuals, that there were CD4 T cells, CD8 T cells and memory B cells that directly reside in that organ.

And so as a result, when we think about this layered defense kind of model, it's actually that the immune system has even more opportunities because if it can generate tissue resident memory cells that are actually in the tissue, those then serve as an earlier line of defense to try and stop the virus in the first tissues that it's showing up at.

And then you additionally have your circulating memory, which is what we are normally measuring in the blood, right, that can also activate and provide additional layers of defense. And there are data suggesting that T cells in this context are indeed helpful.

So if we get back to looking at each of these, how do we think about the memory B cell part of the equation? I've talked about the T cells, what about the memory B cells. And I think they're also quite important, and here's a video of the process of generating memory B cells in the immune system. So it involves interactions over time between T cells and B cells early, and then they go and they form germinal centers shown as GC, which are just amazing immunological structures, which are essentially a classroom, an education location, literally a physical location in your body where the B cells get educated. And they literally evolve in real time in these structures in response to a vaccine or infection.

This is literally a place where the B cells undergo real-time evolution by replication and mutation and selection by the T cells, so that they can evolve better antibodies. Antibodies that can neutralize better and have higher affinity and generate memory B cells that have those properties as well as antibody-secreting cells that have those properties. And one of the aspects of B-cell memory is your immune system has really evolved knowing about variants. And your B cells will not only try and make memory B cells that are great at recognizing the virus you just got exposed to or the vaccine spike protein, right, that you just got exposed to, but also make cells that are essentially guesses about what variants might look like, so that if your primary antibodies don't stop the virus, you do still already have memory B cells that are guesses about what variants might look like.

And that's absolutely turned out to be true in the context of COVID-19, which is really an incredible demonstration of how brilliant your immune system is, because your immune system is just being shown one version of spike and what's been seen in the vaccines is that after 2 doses of vaccine, right, you have neutralizing antibodies against the ancestral strain, but also a number of variants, including Delta, but not Omicron.

But by simply getting a third dose of that same vaccine, now you make neutralizing antibodies against Omicron and those multiple labs have shown those neutralizing antibodies against Omicron are coming from memory B cells that you made to the previous vaccine exposures. And so as a result, those memory B cells would also be able to reactivate if you got infected, okay? And memory B cells probably take 5 days to reactivate.

And so if the virus gets past the initial antibodies, memory B cells can start up and make more of the same antibodies but also more antibodies that probably match the virus that you've been infected with and can help try and limit the disease severity of that infection. And so overall, again, I think there are data suggesting that each of these components of immunity can provide some degree of protective immunity at least against serious outcomes with SARS COV-2 infection.

And then we wanted to know -- and this is the most recent data that I'll show you now. Then we wanted to know, well, how do these parts of immune memory compare between different COVID vaccines, because that will also help us understand, is there evidence for each and every one of these, or some more than others, providing a degree of protection against either infection or again, against hospitalization. And so this really requires head-to-head study in the same lab because T cell assays and memory B cell assays aren't standardized enough to really compare across labs.

And so we put a lot of time and energy over the past 9 months and 12 months into completing a study where we compared immune memory to 4 different COVID-19 vaccines over the course of 6 months, okay? And we took a look -- and this was by recruiting people in the local San Diego area, who had been vaccinated with the Moderna vaccine, the Pfizer vaccine, and adenoviral vaccine like the Janssen or the Novavax, thereby representing 2 different RNA vaccines in people -- or protein vaccine in people and an adenoviral vaccine in people and look at what those outcomes were.

And what we found briefly was as follows. So we took everybody and looked at them across 6 months, so T5 is 6 months. And the average is shown in the large bar, okay? And what we saw at 6 months, here's the overall kinetics, were neutralizing antibodies in 100% of people still to the Moderna and Pfizer and to most with adeno and with Novavax. And then we also compared them. In yellow -- I'm sorry, I forgot my labels here. So Yellow here is previously infected individuals. And that the vaccines are really doing quite well out at 6 months.

And as you can see, there are some differences between the vaccines. And so we did that for neutralizing antibodies, CD4 T cell responses shown here, 100% of people being positive here. And again, comparing it at 6 months to previously infected individuals. And then CD8 T cell responses, CD8 T cell memory, shown here across all 4 of the vaccines. And finally, memory B cells. Again, measured across all 4 of the vaccines.

And we think these data are valuable for getting a sense for why it's generally been observed that at 6 months post vaccination, with RNA vaccines, for example, protection against infection has waned, but protection against hospitalizations and fatalities has largely been maintained. And because while antibody titers have dropped a substantial degree, really, there's been very little decline in the T cell memory, CD4 T cell memory or CD8 T cell memory. And if anything, there's been an increase in the memory B cells over those same time periods, which I think are generally positive signs for protective immunity against, for example, hospitalization level disease.

And that's not the answer to everything. But those are, I think, valuable pieces of information. So in sum, when we think about protection against this disease, neutralizing antibodies are fantastic. And if you can have enough to stop them at the front door, so to speak, that's wonderful. But if you can't, the vaccines probably do still provide a degree of protection against somewhere on that spectrum of disease that I was showing against symptomatic disease or very symptomatic disease or hospitalizations and deaths by maintaining these other parts of the immune system. And so really summarized schematically here.

So in considering vaccine protection against this virus, right, we can be -- if we're really talking about protection against any detectable infection, i.e., becoming positive on an antigen test, really, we're almost certainly talking about neutralizing antibodies playing the major role with some role potentially contributed by tissue resident memory T cells, if you have those.

But really, if instead, we're talking about, along the spectrum of disease, protection against the severe outcomes, then the available data indicate it's much more likely that the multiple parts of the immune system can contribute to that, including the T cells and memory B cells in the ways that I was describing. And it's absolutely worth having more research and investigation into these to see which of these are contributing, at what times, in what ways, and what we still need to know a lot more about that to better inform vaccines.

And additionally, across age groups, right? Because as noted, older individuals are much more at risk for these severe outcomes. And so one would expect that the overall magnitude of these responses then would be more important in those individuals for protecting against these outcomes.

And so with that, I tried to highlight everybody along the way, in the slides, who've done so much work to try and generate this knowledge, and I'm really thankful for the incredible collaborations and teams that we've had. I do simply want to point out that most of this work was funded and supported by the National Institutes of Health, along with several other sources. And thanks again for the opportunity to speak today.

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

Thank you, Dr. Crotty, for that excellent overview of the B cell and T cell responses against SARS CoV-2. We hope to be able to apply some of those learnings now to the data that we're generating with our SARS-CoV-2 vaccine, Spikevax.

So now I'll take you through our COVID-19 vaccine strategy. So COVID-19 has now been with us for 2 years. And while it started initially in a pandemic phase and there was heavy focus on protecting those at greatest risk, most infections were due to the ancestral virus, the Wuhan 1 strain.

We've moved now through multiple surges of variants, starting with Alpha, moving to some concern around Beta and Gamma, then having the emergence of Delta and finally and most recently, Omicron. We're moving to an area where we believe, eventually, we will begin to see more infrequent outbreaks of other variants.

And our strategy is really geared towards moving us from a place where we are vaccinating everyone in waves against a pandemic, to where we are including SARS COV-2 in seasonal respiratory vaccines as with influenza. And so let me describe for you a little more about how this will work and some of the data associated with this plan. So variants are really the result of accumulating mutations in the receptor binding domain of SARS CoV-2 virus.

Receptor binding domain is important exactly for the reason its name states. It binds to the ACE-2 receptor on human cells. And what you see in this schematic are the original spike antibodies. And the fact that they fit like a lock and key with the original Wuhan 1 spike protein. Over time, the virus has learned to evolve that lock in key mechanism to areas where the mutations now look slightly different than the original Wuhan 1 antibodies. So in the Delta spike you see in the schematic, there's actually still very good recognition. So we observed a twofold reduction in antibody titers, but after boosting, excellent vaccine effectiveness to the level we observed against Wuhan 1.

Now if you're look in green at the Omicron, more mutations have accumulated, at least 15 in the receptor binding domain and terminal domains. And we start to see now that there are fewer and fewer sites that look like that original spike protein to which we induced antibody with our Spikevax vaccine. And therefore, changing the structure of what we prime with may be necessary to keep up with the evolution of this virus.

So now let me explain to you how we will translate that biology into our booster vaccine strategy. We're currently pursuing 3 avenues of data generation. The first is we are investigating third and fourth doses of 1273, the prototype vaccine. Second, we are conducting studies with an Omicron monovalent vaccine. So that's a 50-microgram dose of an mRNA sequence that codes specifically for Omicron or 1273.529. We also are looking into a multivalent vaccine candidate containing 50% of the Wuhan 1 strain and 50% of the Omicron sequence to result in a total of 50 micrograms. So 25 micrograms of each.

And we believe this may lead to the best breadth in protection. Why? Because we are continuing to boost important epitopes shared by all of the variants by -- including 1273 -- but also introducing the Omicron variant, which has been the one so far that has been most able to evade vaccine effectiveness.

So let me tell you a bit about the 2 trials that we have ongoing, investigating these booster candidates. The first is an ongoing study, master protocol US P205. And in this study, we have enrolled successive waves of participants who have received 2 doses of 100-microgram mRNA-1273 priming and exposed them to differing doses and booster candidates looking toward the future. Right now, we are enrolling third and fourth doses of mRNA-1273.529 and mRNA-1273. That mRNA-1273 third and fourth dose is going to be really important as a comparator.

You may remember that in the past, we had consistently bridged [PA] to the results from our COVE study. But now that everyone has received boosters, we believe that third and fourth doses of 1273 is the appropriate comparator for further boosters of the variants. And finally, we've now started to enroll a cohort of mRNA-1273, followed by mRNA-214.

And now let me tell you about a study we have ongoing in the U.K. our Phase III study, mRNA-P305. This study will enroll 2,800 participants and randomized them to either receive mRNA-1273 as a fourth dose or to receive the monovalent or the bivalent candidate. This is going to be important to evaluate the regulatory criteria for licensure of booster vaccine candidates. And we are currently enrolling both cohorts.

Now let me update you on our primary series and booster vaccine submissions in adolescents and pediatrics. In the 12- to 17-year-old age group, we are now authorized in over 40 countries at the 100-microgram primary series dose, and we are preparing to submit 50-microgram booster doses worldwide. In children who are 6 to 11 years of age, we've recently been approved in Australia, the U.K. and Canada. We're evaluating the 25-microgram dose as a primary series and we will be evaluating a booster dose in this population as well. Finally, in children 6 months to less than 6 years of age, we will present our positive primary series data today at a dose of 25 micrograms.

We're also evaluating a lower dose, and we'll be evaluating booster doses in the future as well. And we are working with the U.S. FDA to update and file data across all 3 age groups.

So overall, our pediatric data in 6 months old to less than 6 year olds demonstrated that 2 doses of 25 micrograms of mRNA-1273 met both primary endpoints for infants, 6 months to 2 years of age; and young children, 2 years to less than 6 years of age. From a reactogenicity standpoint, we have seen a comparable reactogenicity profile across multiple age groups. It was acceptable for both the 6-month to 2-year of age and 2-year to 6 year of age and is consistent with what we've seen in young adults, adolescents and older children. The safety profile is favorable with over 2 months of median safety follow-up data post dose 2 in over 2,000 young children and 1,200 infants.

From an immunobridging standpoint, both primary endpoints were met, and we were able to successfully meet our immunogenicity criteria to young adults from the COVE study. And these immunobridging data are further supported by the efficacy estimates in these age groups. We are going to move forward with regulatory submissions for infants and young children in both the U.S. and outside of the U.S. for the primary series at the 25-microgram dose.

So this slide will show you the immunogenicity results from our most recent age cohort. What you see at the top of the slide, are the original immunogenicity data in adults across age groups in the COVE study.

And then in the next row, you see the results from the younger adults. And this, recall, was the comparator group for all of our pediatric trials. You see a label for the Duke lab, that's because initially, these results were all tested at Duke University. And then you also see the same results at an outside vendor, PPD. The PPD results are important because these are the results that are consistent with the same laboratory in which the adolescents, young children and infants were also tested.

Now let's go to the pediatric population. The adults -- the adolescents, excuse me, at the 100-microgram dose had a GMT ratio of 1.08, with a lower limit of the 95% confidence variable of 0.94, which was well above the lower limit of 0.66. Then in young children, who received a 25-microgram dose, we see a GMT ratio in those 2 to 5 years of age of 1.01. Again, the lower limit, 0.88, well above the 0.67 lower limit. And then finally, in infants, 6 months to 23 months of age. We see at the 25-microgram dose, a GMT ratio of 1.28 and a lower limit of 1.12. So the immuno bridging confirms that the immune responses are noninferior to those in young adults who were correlated with efficacy in the Phase III COVE trial.

And now for a summary of our safety data. The reactogenicity profile is consistent with the known profile of mRNA-1273. Solicited adverse reactions were generally mild to moderate in severity and they were more frequently reported after the second dose.

Fever, which was defined as temperatures greater than or equal to 38 degrees Celsius, after the second dose was observed to be reported at a lower rate than in the young children, 17%; and infants 14.6%; as compared to older children, 23.9%. And the fevers over 40 degrees Celsius, which were defined as Grade 4 fevers, were seen in 0.2% of children in both the young children and infant cohorts. Ten events occurred after the second dose, and 5 of these were associated with other upper respiratory tract symptoms, and therefore, likely to be due at least in part to a co-infection.

Fever after mRNA-1273 occurs predominantly on day 1 or 2 and usually resolves within 1 day. And this is important because pediatricians will be able to guide parents and allow them to anticipate when their child might be most likely to experience an adverse reaction. These rates are consistent with fever rates of other pediatric vaccines, which are routinely administered. No study pause rules were met in this trial, and the safety profile overall was favorable. There were no deaths and no cases of myo/pericarditis reported, and no MIS-C was observed. There was 1 vaccine-related SAE that was reported within 28 days of vaccination. This was an unwitnessed febrile seizure. This child recovered without sequelae. And the safety profile overall is consistent with other pediatric vaccines administered to this age group.

In terms of efficacy, which was a secondary endpoint in this study, the efficacy was shown to have a significant value, with a lower bound that excluded 0, but lower efficacy estimates against symptomatic infections were observed, and this is because the trial was conducted during the Omicron wave. If you compare the efficacy estimates from this trial to those of the adult vaccine effectiveness trial conducted in the U.S., the results were very similar at around 40%.

The milder disease in children precluded assessment against hospitalization or death in a clinical study. But we would anticipate that since 1273 has maintained its effectiveness against more severe disease, that will be borne out in effectiveness trials in children as well.

We're also developing a next-generation COVID-19 candidate, mRNA-1283. This is intended to be a refrigerator-stable mRNA vaccine that will facilitate distribution and administration by health care providers. So how are we able to get this vaccine to be refrigerator-stable? Well, part of stability relates to the length of the mRNA transcript and by shortening that transcript only to the portions that contain the most important epitopes for protection against disease, so the receptor binding domain as well as the end terminal domain, leads to a shorter transcript that contains the most important areas of that protein for presentation to the immune system.

Our Phase I study evaluated mRNA-1283 as a primary series. And we evaluated safety, reactogenicity and immunogenicity across 3 dose levels. You see those dose levels in the schematic to the right of the slide. So 10 micrograms, 30 micrograms and 100 micrograms administered in a 2-dose series. In addition, a single dose of 100 micrograms of 1283 were compared to the 2-dose 100-microgram series of mRNA-1273, the appropriate control since we would be looking to replace the 1273 vaccine.

This slide shows the safety data that were observed in that study. And you see on the top, our solicited local adverse reactions, pain, erythema, swelling and lymphadenopathy and the solicited systemic reactions on the bottom row of the slide, including fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting and chills. Grade 1 and 2 are in light and dark blue, and Grade 3 is in the peach color. So what you can see is similar to mRNA-1273. Injection site pain remains the most important local solicited symptom.

Overall, mRNA 10 micrograms -- mRNA-1283 10 micrograms and 30 micrograms was relatively comparable to the mRNA-1273 group, except for the lymphadenopathy. Now if you look at the solicited systemic symptoms, again, the safety profile is consistent with the most common reactions being headache, fatigue, myalgia and arthralgia. And again, the 10-microgram dose group is reported at similar or lower frequency as well as with similar or lower severity as the 1273 100-microgram group.

Now let's look at the antibody responses across these 3 dose levels and compare them to mRNA-1273.

These are antibody titers against the ancestral strain of the SARS-CoV-2 virus. In gray, you see the mRNA-1273 group and 2 doses of 10, 30 and 100 micrograms resulted in relatively comparable neutralizing antibody titers. So we did not observe a dose response across the range of doses. The single dose of mRNA-1283 did not result in titers as high as in the other groups, confirming the need for this vaccine to be given as a 2-dose primary series.

So the unadjusted geometric mean ratio of each of the 3 doses was 1.2 for 10 micrograms, 0.9 for 30 micrograms and 1.4 for 100 micrograms.

Now what happens if we look at a variant that was not contained in 1283 or 1273 vaccines? These are the levels of beta neutralizing antibody titers. And once again, you see a similar pattern where all of the doses and vaccines that were given on a 2-dose schedule look comparable without a dose response curve, and the placebo followed by 100 micrograms of 1283 is approximately half of the result. So this shows a GMT ratio for 10 micrograms of 1.3, for 30 micrograms of 1.1 and for 100 micrograms of 1.3 suggesting that similar to mRNA-1273, we can induce cross protection with mRNA-1283.

So the next-generation vaccine mRNA-1283 Phase I summary. These results indicated that when administered as a primary series, mRNA-1283 induces robust anti-SARS-CoV-2 neutralizing antibody titers, which are similar to that of the 100-microgram mRNA-1273 primary series. The frequency of local and solicited adverse reactions of mRNA-1283, administered at lower dose levels was overall comparable to that of mRNA-1273. And similar to what we've seen across our platform, the most commonly reported injection site reaction was pain and the most commonly reported

solicited systemic symptoms were headache, fatigue and myalgia. So based on these results, we are progressing the lower doses to a Phase II study of mRNA-1283 as a booster dose. And we will evaluate 10 micrograms as the highest dose, evaluating additional lower doses moving forward.

So this slide gives you the study design for mRNA-1283. And you can see in the first 3 cohorts, we will evaluate a 2.5 microgram dose, a 5-microgram dose and a 10-microgram dose as a booster after 2 doses of 100 micrograms of 1273. We also are evaluating 1283 as a bivalent vaccine at both the 5-microgram and 10-microgram levels. So 1283.211 contains half of the dose as Wuhan 1 sequence and half of the dose as the beta variant sequence. We are also including Cohort 6, which is an mRNA-1273 and 50-microgram comparator, important to make sure that the booster doses we're giving are comparable with the current booster dose that's in the vaccination schedule.

And then finally, with the emergence of the Omicron variant, we are evaluating 2 monovalent doses of 1283 as an Omicron vaccine. Enrollment has been completed across all age groups and all treatment groups, and we are considering moving to other variant candidate vaccines on the 1283 platform.

That concludes our summary of the current status of our COVID-19 vaccine development program. Now I'd like to move on to talk about our influenza vaccine strategy.

Seasonal influenza, which occurs as both influenza A and influenza B and varies in severity each year, causes respiratory illnesses and places a significant burden on health care systems. Worldwide, influenza leads to 3 million to 5 million severe cases a year with approximately 290,000 to 650,000 influenza-related respiratory deaths each year. To put that into context, after 2 years of the COVID-19 pandemic, there have been 6 million deaths, which means that over the last 12 years, we've had approximately as many deaths from seasonal influenza as from COVID-19, which is staggering when you think about it. About 8% of the U.S. population experience symptoms from influenza each year with 140 thousand to 710 thousand hospitalizations and 12,000 to 52,000 deaths per year. The peak influenza activity is seen in temperate climates during the fall to winter seasons. And this is reflected in an increased volume of outpatient visits, urgent care visits and hospitalizations.

So influenza A strains lead to over 95% of flu-related hospitalizations in adults. And what you see on this graph depicted in the bar chart are hospitalizations and deaths by age group for influenza A on the left as compared to influenza B on the right. And note the 2 peaks in the youngest and oldest age groups, in red, 0 to 4-year-olds and in the maroon color, adults over 75 years of age. So you can see that both hospitalization and death occur at much higher rates due to influenza A versus influenza B where there is very little hospitalization or death. So a recent study of vaccine effectiveness from 2004 to 2015 found that the average vaccine efficacy was 33% against illnesses caused by H3N2 compared with 61% against H1N1 and 54% against influenza B. And so this really indicates that there's room for improvement for all of the flu strains, but particularly for H3N2, and this may be contributing to a higher medical burden for influenza A.

So let me review our seasonal influenza vaccine strategy, which we've discussed at previous meetings. Our first vaccine, mRNA-1010, is being developed as a standard seasonal vaccine using the WHO recommended strains. The idea with this vaccine is to generate safety, immunogenicity and efficacy data to enable us to move to market with influenza and then build upon that foundational program.

Beyond that quadrivalent vaccine, as I just showed you, there's room for improvement for vaccine coverage and breadth against H3N2. And so we are intending to develop both penta and hexavalent vaccines to enable the inclusion of additional strains, particularly of H3N2. The mRNA vaccine platform would allow us to potentially add those sequences in at later stages of vaccine manufacture, allowing us to pivot when the vaccine epidemiology isn't what we anticipated earlier in the year.

Then we have mRNA-1020/1030, which is looking to increase the breadth of the immune response by adding further antigens. Neuraminidase is known to be an important virulence factor for influenza virus. And so we will be looking at our ability to contribute additional immunogenicity and ultimately, effectiveness by adding these antigens.

So now I'd like to hand the presentation over to Dr. Raffael Nachbagauer, who's going to review with you recent Phase II data from our influenza vaccine development program. Dr. Nachbagauer?

Raffael Nachbagauer

Thank you, Jackie, and I'm very excited to show our Phase II influenza data today. I'm starting out with a brief study overview. As you can see here, we had 4 different cohorts in the study testing 3 different dose levels of mRNA-1010 -- 25, 50 and 100 micrograms -- as well as Afluria, which is the standard dose influenza vaccine that is licensed in the United States, with a total of about 500 participants in our study. And we were testing the Northern Hemisphere strains with a 2021, '22 influenza season.

The primary outcome measures of the study were safety and immunogenicity on day 29. I'm briefly showing here the demographics, which were comparable across all arms. Importantly, we did stratify across 3 different age cohorts: 18 to 49 years old, 50 to 64 and 65 years and older. And as you can see here, the numbers get quite small despite our 500 participants in the overall study when we go into the subsets. Therefore, I'm going to start out by showing the overall immunogenicity across all age groups before diving deeper into the individual age groups.

And starting out here with the geometric mean titers across all ages for all strains.

And this is the HAI assay, which is the standard assay for influenza. And it has been previously correlated with protection from infection. That's the line that you can see here at the 140 mark, which is the threshold that has been associated with a 50% reduction in infection. And as you can clearly see, we're substantially exceeding those titers on day 29 after vaccination. And importantly here, for the influenza A strains on the top, H1N1, H3N2, as Jackie pointed out, are really the main drivers of disease in adults, we see really strong immune responses that are actually stronger than Afluria. On the bottom, we see the B strains, which are less of a concern in the adult group, but we still look very comparable to Afluria.

When you look at the geometric mean fold-rises, which is the increase of titers from baseline to day 29, you can also very clearly see how for the H1N1 strains and the H3N2 strains, we have very strong immune responses against all of our mRNA-1010-tested dose levels.

And for B/Yamagata and B/Victoria, we are very much comparable to Afluria. If you look on the right, you can see the geometric mean titer ratio, which is generally what is used to assess noninferior immunogenicity against the standard dose vaccine. So in this case, we're measuring the relative geometric mean titers on day 29 compared to Afluria for our mRNA vaccines. And this is really highlighting that our mRNA-1010 dose levels, particularly the 50 micrograms and 100 micrograms, are more than twofold higher for H1N1 compared to Afluria, as well as between 1.5 and twofold higher for H3N2 and similar at 50 and 100-microgram dose levels for the B strains.

The seroconversion rates are another measure that is used for noninferiority. And as you can see here, our mRNA-1010 dose levels have all similar or higher seroconversion rates compared to Afluria, which again makes us very confident moving forward into pivotal studies.

As I mentioned before, when we go into the different age strata, the confidence intervals become wider because we have fewer individuals in each of those groups. But overall, the takeaway from this is that we see a very nice consistent pattern across all age levels, which really makes us confident that mRNA-1010 can be a vaccine for all age groups.

I want to dive a little bit deeper on the 65-plus group on the very right. And the reason for that is there has been a recent study by Dr. Ben Cowling in Hong Kong that compared side-by-side 3 different enhanced vaccines, FLUAD, Fluzone HD and FluBlok against the licensed standard dose vaccine. And you can see the geometric mean titer ratios, which are a way to standardize against the standard dose vaccine. On the left side, B/Yamagata is left empty because some of those vaccines were trivalent at the time, and it wouldn't be a fair comparison to include those.

But overall, you can see that the geometric mean titer ratio of those enhanced vaccines to standard dose vaccines were pretty much comparable for the B strains and slightly higher in the range of one to twofold for the H1N1 and H3N2 strain.

Now if you look at the right side, this is our mRNA-1010 dose levels: 25, 50 and 100 micrograms. And what you can see is that there's a trend to see titers even potentially exceeding the twofold, titer ratios potentially even exceeding the twofold for mRNA-1010 of 50 micrograms, which is really exciting because that could mean that mRNA-1010 might elicit titers even higher than those enhanced efficacious vaccines.

If we look at the safety profile, we generally see that mRNA-1010 shows higher reactogenicity compared to Afluria. And we see an increase in reactogenicity in a dose-dependent manner. Here, we're looking at the local adverse reactions. And the main drivers of that were pain and axillary

swelling and tenderness. And the same patterns we're seeing for the systemic adverse reactions were -- the main drivers were myalgia, headache and fatigue. But importantly, we didn't see any serious adverse events related to study vaccine, and we did not meet any pause rules through day 29.

This is summarized here. Again, the adverse reactions were higher in the mRNA-1010 groups compared to the Afluria group, but we didn't see any significant safety concerns, which brings me to the overall summary of our Phase II interim data.

We saw really great day 29 immunogenicity data, especially against influenza A strains with mRNA-1010. And importantly, those influenza A strains are the drivers of disease in adults. The data is also consistent with the potential for noninferiority against a standard dose vaccine for the influenza B strains and again, those B strains are more of a concern in pediatric populations rather than in adults.

We saw a really nice consistent profile across ages, and the geometric mean titer ratios for the influenza A strains in the 65 and older appear in line or even higher than the -- compared to geometric mean titer ratios observed for enhanced vaccines. Importantly, we didn't see any major safety concerns or issues. And the overall reactogenicity was about 2x to 3x higher than Afluria, which appears to also mirror the immunogenicity that we've observed for the influenza A strains.

And with that, I want to circle back once more to the strategy for our influenza program. We're still at the top level here, the mRNA-1010 vaccine, which is fairly similar to what is currently being done for flu, but better in our opinion because we are delivering the same strain recommendations by WHO as an mRNA vaccine, which has not changed through pathogen eggs or cells. So it's really high fidelity and really delivering what WHO recommended.

And based on the immunogenicity data that we've seen, we believe that we can play in the same league or even better than enhanced vaccines already with mRNA-1010. But we're not planning to stop there. We're actually also investigating mRNA-1011 and 1012, which encode for additional HA antigens. And the goal here is really to expand the coverage across the antigenic spectrum of the HAs, which will allow our public health authorities to make better strain recommendations because they no longer would have to pick just one strain and might be able to pick 2 or 3 H3 strains that we know are co-circulating at the same time.

Finally, last but not least, I'm really excited about mRNA-1020 and 1030, which we're planning to test later this year. Those vaccines are going to add a neuraminidase component to our vaccines. And the neuraminidase is the second antigen of influenza viruses. And the goal here is to really target the virus at 2 stages of its life cycle, which we believe could improve influenza vaccines quite substantially over what's currently being used.

And with that, I'm really excited to introduce Dr. Ali Ellebedy. He is at WashU and an immunologist by training. He has done a lot of work on germinal center research in people, and he is doing fine needle biopsies in -- from lymph nodes in healthy adults, and he has studied the germinal center responses to influenza vaccines and SARS-CoV-2 vaccines, and he's going to provide us an overview of his findings here.

Ali Ellebedy

Thanks for the introduction, and thanks, Raffael, for the kind word.

I would like to talk to you today about enhancing B-cell responses to influenza virus vaccination in humans. So I will first start by actually showing you my disclosures, and those are not really related to the work that I'm going to describe to you today.

So first, when we look -- discuss B-cell responses, one thing that we have to realize right away that it's a -- there's a division of labor that happens very early during a B-cell response to anything, to vaccination or infection. So we start with a B-cell that's specific to the virus, to the bacteria, to the vaccine antigen. And once these B-cells gets engaged, there is a population of cells that come from this engaged B-cell -- those are the cells that are actually producing the early antibodies. We call them plasmablasts. So those are activated B-cells that have been dedicated to produce antibodies that can be protected for short term.

Another group of B-cells that actually also descend from the initial ones that got engaged do not really differentiate to become those antibody-producing machines. They instead join a reaction that you just heard about, called the germinal center reaction. And this is, as we are going to discuss in the next slide, is a very critical reaction for the success of any vaccine response.

The cells -- the B-cells that come out of this reaction are 2 important population of B-cells that we have been -- for any successful vaccination process, these 2 subset -- generation of these 2 subsets is very critical. The first one is what we call the long-lived plasma cells and those reside in our bone marrow. And the second population, called memory B-cells, and those circulate in our body.

And why these 2 subsets are important? So the bone marrow plasma cells, those are the cells that produce antibodies for a long period of time. Those antibodies are the ones that circulate in our blood, and those can be protective if they are present in sufficient quantity and if they are matching the virus or the bacteria that is being introduced to the body. In our case, if they are matching the same influenza vaccine or influenza strain that's circulating, then these antibodies can be protective.

But if those antibodies are not there in sufficient quantities, we have another population that also comes out of the germinal center, called the memory B-cells, that can quickly respond and fire up and become antibody-producing cells themselves very shortly and then supplement the antibody that can be in our circulation and provide the protection. And as I mentioned, those 2 population of cells can be -- are actually the end product of the germinal center reaction.

But another point that I haven't mentioned is actually germinal center reaction does more than just ensuring that these 2 populations are generated. Those -- during that germinal center reaction, a refinement process of those responding B-cells happens and that process is also very critical for our vaccine-related protection.

So the B-cells that comes in are not really the same as the one that comes out. It's the same specificity so that B-cell is still specific for influenza. But actually, its ability to bind to the influenza virus is much more enhanced. And that enhancement results from a process that only happens inside this reaction, we call affinity maturation. And during this process, these responding cells acquire mutations that allow them to really recognize those antigen, the vaccine antigen, whether it's the influenza HA or the SARS-CoV-2 spike, for example. It organizes it more tightly and now you have a much better binding antibody in those cells that are produced by those cells that comes out as either bone marrow plasma cells or memory cells.

And just as a simple visual explanation of what's happening in affinity maturation is actually -- it happens like that, if we have the same exact antigen, in that case, influenza HA, hemagglutinin, or SARS-CoV-2 spike, the antibodies produced early on as a very early responding B-cell -- and then it can recognize the antigen, but it's not a perfect fit. But then that the B-cells producing that antigen now participate in the germinal center reaction and start modifying its receptor, which is the antibody on its surface that recognize the antigen. And slowly, kind of changing its really binding part, the part that is binding to the protein, to the spike or to the HA, to make it almost a perfect set. And in that case, that process happened in the germinal center.

And the result of that, that antibody is now much better binders to the antigen than the early one in the early version of itself in that way. And that also happens in the germinal center. So for these 2 reasons, for the affinity maturation part and for the generation of these long-lived populations of immune memory, the germinal center is key for our immune responses, but then when we study antibody responses to influenza, either influenza virus infection or vaccination in humans, for the past 80 or 90 years since we first isolated the first influenza here in the U.S. in 1934 or even 1933 when the first virus was isolated, we have relied heavily on studying what happens in blood because it's the easiest accessible compartment that we can really look at in humans. And you can -- in blood, you can monitor, for example, the responding B cells that, for example, those early plasma plus that produced antibody, you can see them in blood, or you can see memory cells at the other end. And also, obviously, you can look at the antibody itself and measure its functionality in terms of how its ability neutralizes the virus for example.

And based on these measures, we can -- we have been able -- I mean, we have been limited in our way to really divide -- keep on responding to this influenza vaccination, for example, to either people responding strongly or nonresponders and just based on the levels of antibodies. So it's a quantitative analysis of how strong the response. And as you can imagine, from these readings from blood, we can -- we don't have any direct evidence of what's happening in the germinal center reaction because that reaction only happens in the draining of foreign structures. And this

is something that we really -- has hindered our way of learning what -- how can we improve a vaccine that's not optimal, like our current seasonal influenza vaccines. So this is where -- because if you really want to understand, to make the vaccine more potent and more durable, you really need to understand how potent or how robust the germinal center reaction is to that vaccine because of the reasons we discussed earlier.

So now I hope I convinced you that the germinal center reaction is a very critical component of immune response to vaccination. And studying it is critical to understand how we can improve in a vaccine that we think is not optimal. But now I also told you that those reaction cannot be studied easily because those cells do not circulate in humans. So that's a huge problem. So how -- this [needle] circulate in blood, so how can you see them?

So this brings us to the next point is how you can study germinal center reaction in humans. And the way we do that in our lab is to actually use a very simple approach for fine needle aspiration, and that approach is by diagnostic radiologists to really look at -- diagnostic procedures used by radiologists through sample of draining lymph nodes usually in the axilla region. And in human axilla, there's 30 to 40 lymph nodes that can be -- that are present in that region. And some of them drain the upper artery. And if you remember, our flu vaccine as well as our SARS-CoV-2 vaccines are taken intramuscularly in this upper arm deltoid muscle. So the nodes that -- the draining of those muscles rely here including the lateral nodes.

So one way to actually for us to be able to sample and study the germinal center is to actually take a fine needle aspirate from those nodes. And we focus on the part with the cortex part. This is the cortex part. This is the pectoralis down in the lymph node, and this is the cortex of the lymph node. And we sample that part. And just to give you an example here, this is an ultrasound by the fine needle aspiration in our -- one of our participants. And here you're looking at the lymph nodes by ultrasound. This is -- will be the part where the cortex is. And as you can see here, this is the part where the needle goes inside. And then we don't apply any suction, so we preserve the structure of the node. We just take the needle out quickly. And we study the cells inside -- that went inside the needle by the pressure from inside the node. And that way, we can actually sample the germinal centers that actually in the middle of those B cell follicles.

And we -- as an example to doing that with our current seasonal influenza vaccination, we have looked at multiple individuals before and after receiving our current seasonal influenza virus vaccines. As you can see here before vaccination, the lymph node is very inactive. This cortex part that I showed you earlier is relatively thin. This is just before vaccination. But this is after vaccination, you can see that, that cortex can become thicker, and that's a sign of some activity or reactivity that -- potentially, vaccine-specific.

But to confirm that this reactivity is actually vaccine-specific, we analyze the cells that we -- came from those aspirates by flow cytometry. And the way we do that is we take the cells and gate out all the cells that are not B cells. And in that case, we get, even, out naive B cells. And what you're looking at here is this population that we call germinal center B cells. And you can start see them coming in this date around week 2, and we can see them afterwards. And this work has been published 2 years ago. This has established that this technique as a way to study antigen-specific responses after vaccination in humans.

We started with influenza vaccine for the reason that we wanted to learn how we can improve this vaccine. And we know that this is vaccine-induced responses because if you take those cells and probe them, if they are binding to the main antigen influenza vaccine, which is the hemagglutinin, the answer is yes. They can -- they are recognized by -- or they look -- they recognize hemagglutinin. So that's a very strong reason as -- strong evidence that those cells are actually vaccine-specific.

So we use that approach to really look at multiple individuals who actually responded strongly to the flu vaccination, and we wanted to know, can we actually -- how many of those individuals can actually make this important reaction or can form this important reaction in the draining lymph nodes after seasonal influenza vaccination -- the current seasonal influenza vaccination. And the answer is we -- out of 7 individuals that we probed them for a long period and probed the same lymph nodes over time, we managed to -- or we were able to detect antigen vaccine-induced responses in 3 out of the 7 individuals.

And if you focus here, this is the summary of the data here in the bottom. And if you focus in the solid blue lines, you will see that we only detect the results that are binding through the hemagglutinin of the -- which is the main -- the same hemagglutinin in the vaccine. We only find them in 3 individuals out of the 7.

And this was not really very robust because you would expect, if this is a good vaccine, you would see this more. Hopefully, that's what we want to see in everyone. And I'll give you an example for the vaccine that we actually did see an antigen-specific responses in every single person that received it, and that was the SARS-CoV-2 mRNA-based vaccine that we also studied in the last 2 years. So it started actually in December in 2020, which is the time where the first vaccine, which came from Pfizer that this became available for humans or been giving the first use. And we used that vaccine in individuals who have been, either no previous -- no history of infection or with some with histories as confirmed SARS-CoV-2 infection. Then we analyze their blood lymph node and, later, bone marrow, which I'm going to discuss, before and after this vaccination.

And one thing was immediately clear from even the first participant that we looked at their axillary lymph nodes by this procedure and that the lymph nodes are really enlarged in size after this vaccination. And also, there is a huge activity as evidenced by this increased vascularity that you can also measure by ultrasound.

So this was a very early sign that this vaccination is strongly or potentially immunogenic because of this [rare] activity in lymph node. But then to really show us in a way that we, as immunologists, can really understand, I would give you the example of what happens after influenza vaccination. So here, we are looking at our flow cytometry plots of lymph node cells taken before influenza vaccination. This would be the inactivated regular or current influenza vaccine. And this is taken 12 days after the vaccine from the same lymph node, obviously, in the same individual.

And the cells that you can easily appreciate that increase their numbers or frequency, those what we call the germinal center B cells. And we recognize those cells by expression of this very key molecule, which is called BCL6. So that was, for us, was a really nice and impressive enhancement of the germinal center response after this vaccination in this individual. This is 1 of the 3 individuals that responded by having an antigen-specific germinal center response.

If you compare that particular population, which is the germinal central B cells, and the people who receive the mRNA vaccine, especially for second dose, you will see a huge difference and magnitude, obviously, which is, in a way, explains the fact that the draining lymph node was responding much more strongly with the RNA vaccine compared to influenza vaccine or the currently licensed influenza vaccine. And we see this is obviously a huge response.

And then another thing that we -- was very impressive with those individuals who received a SARS-CoV-2 mRNA vaccine that we expected that response in every person we looked at, and we looked at -- in that study, we looked at 15 individuals. We saw -- and we looked at the same lymph node for multiple times. There was only -- all the 15 responded with a strong germinal center reaction that's also specific to the spike protein. In 10 out of 15, that reaction persisted for 6 months -- at least 6 months after second immunization, which is something that we haven't nearly seen anything close to in any of our influenza participants -- influenza vaccination study participants.

So that was very impressive. But then someone can ask, well, this is great, great for SARS-CoV-2, but why do we care for -- in the case of influenza, why do we care about having that such a robust germinal center reaction? So that's -- and that's a fair point. And influenza, we have been exposed to the same antigen, same virus, maybe changed a little bit over the years, many, many times. So we have built a lot of memory cells, I guess, that virus. And maybe we don't need a stronger stimulation. And that's what our current vaccines are relying on, are relying on having that rich memory of the virus that even with a small mark, we can get detectable responses.

The question that we should ask ourselves, are these detectable responses enough to actually generate or that stimulation is enough to generate good germinal center reaction? But why should we think about having good germinal center?

So we -- in 1 of those 3 individuals I mentioned to you that responded to current influenza vaccination, we followed responding B cells that now participate in the germinal center for a long time in that individual after influenza vaccination. And then we looked at that individual and asked, did that individual have a benefit or these responding B cells did benefit from being in the germinal center reaction for a long period. And that's what I'm going to show you in the next couple of slides.

So first, this is how it looks like if you are responding to influenza vaccination. This is every single node here is basically the same B cell -- it's a B cell family. So it's the same clone that now multiplied multiple times, and now some of them detected very early on in the first week. But then some of them, as you can see, are detected first few weeks after influenza vaccination as a germinal center because it's a circle here.

So this is detected as a germinal center long period. Those cells detected in the first week or the second week were detected as either plasma plus or an early germinal center. But now we know that during that time, between 1 and 2 weeks and 13 weeks, here in green, those cells have been maturing the receptor and antibody theoretically should have been better in terms of recognizing that, hemagglutinin or fresh ones. And actually, the data suggests that this is indeed the case.

So we made the corresponding monoclonal antibodies from those represented nodes. So you can actually see here the color map. So that node and here in red were still taken from week 1, another clone taken from week 2. And those 2 clones, they do indeed recognize the hemagglutinin of influenza A Michigan, which is a H1N1 virus that's included in the vaccine. But -- and we know that it's a positive recognition because they bind to the hemagglutinin much better than the control.

But if you look at the same exact B cell receptor, same clone, but now much later in time, in this case at 13 weeks, and we picked 2 different representatives, and as you can obviously see that they bind as much stronger to the same -- actually, they only differ in a few mutations from the early responding versions. And that's exactly what happens when you participate in a germinal center, so it benefits.

So another way to say, that's great. We really have a stronger antibody, but why -- how else this could be useful. We could have -- we have a lot of strong antibodies, but can this be helpful, other than just being able to better neutralize the virus, which is indeed the case. You have a better-binding antibody, you have a better antibody at recognizing the virus.

So as you know, influenza viruses are diverse, and there is many, many subtypes, and there are up to 18 different subtypes based -- or just on the hemagglutinin virus. And the one that I'm highlighting here is the one that the -- some of the avian influenza virus that are potentially can cause a pandemic, like H5N1 viruses, which can have a really high degree of lethality, at least in the few outbreaks that we had so far over the last 20 years.

So what can we -- can those antibodies that have been matured in the germinal center also improve the breadth, the binding of those -- remember, those antibody produced through disease or influenza vaccine that only had H1N1, H3N2 and 2 influenza B viruses in terms of HA recognition. So 4 different strains, but we have a lot of other strains that were not represented in this vaccine because they are not currently circulating in humans but potentially could be circulating in humans.

So what we saw is that we -- when we looked at the antibodies, the same lens that I showed you in this last slide, early lineages as -- and here, the binding becomes stronger as the color darkens. So here, darker red means it's binding much tighter. And as I showed you earlier, those 2 early antibodies bind through the Michigan H1N1, which is the same vaccine -- same HA in the vaccine, but now the latest version of the antibody binding tighter to that H1. But not only to that particular HA but to other HAs that also were circulating earlier. So it actually brings back some additional benefit from H1.

But then if you look at some HAs, like binding to H5 HA from this H5N1 virus, as you can see here, for some of those antibodies, for example, for this particular virus, Indonesia H5N1, those early antibodies didn't bind at all. You don't have any recognition of that particular chain. But then you started to gain recognition once you have this mature version, and we have multiple examples of H5 features when you see this enhanced bind by just enhancing -- by just having the B cell responding to the vaccine persist in the germinal center for a while. So that's an added benefit that makes this person even -- potentially being able to respond to a potential H5N1 exposure by having this better antibodies against nonintentional -- unintentional, I guess, this common epitope between the H1 HA and H5 HA.

So what I've showed you so far is really something I hope to convince you that the germinal center is not only important for really generating this long-term memory B cell populations like memory B cells, long-life plasma cells, enhancing the binding capacity of responding antibodies but also potentially expanding the breadth of those antibodies, especially in the case of influenza and potentially in the case of SARS-CoV-2, which is something that we are increasing likely will be needing in terms of improving the breadth of binding because of having those potential variants of concern.

But then what -- where this leaves us? It leaves us with really a -- what can -- can we actually get a potential persistent germinal center reaction with an mRNA-based influenza vaccine that's similar to what we saw with SARS-CoV-2 vaccine? And that's something that we, I think, will be very

critical to address because -- and the points there that we can improve that germinal center in terms of magnitude to what we're currently seeing and robustness instead of having seen this in 3 out of 7 individuals. Can we see it in every single one using the vaccine. And there -- these are things that we cannot see -- easily see from just looking at the serum antibodies.

Can this improve the breadth of the antibody? And that's another point. The antibodies produced against the same HA can actually -- can we enhance the breadth of those antibodies? And obviously, a huge -- a major problem or challenge with current influenza vaccine is that the induced antibodies don't last long. And most likely, the antibody level goes to baseline, the original levels even by 6 months, not only -- not even a year. And that's something that we think that having a robust germinal center reaction will help in enhancing the duration.

And then also now thinking about other aspects of our immune response to the virus. Can we target neuraminidase, for example? And this is a molecular -- another major target of influenza virus is that not currently optimally targeted by current vaccines. And we think that potentially having that molecular target by a specific -- including and specifically in the vaccine can actually enhance the breadth of response.

And another huge unknown for us at the moment is how T cell responses can be enhanced by current mRNA vaccines compared to just subunit vaccines, for example.

And with that, I would like to thank you for your attention, and I hope you -- again, I was able to convince you about the importance of the germinal center reactions and the potential or the opportunities that we have to enhance our current seasonal vaccines with the mRNA platform. Thank you.

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

Thank you for that review of influenza vaccines. Now I'd like to pivot to talk about another one of our respiratory vaccine candidate, mRNA-1345, our vaccine against respiratory syncytial virus, or RSV.

RSV is a leading cause of respiratory illness in both young children and older adults. In pediatrics, hospitalizations occur at a rate of approximately 3 per 1,000 in those under 5 years of age. And annually, there are 2 million medically attended RSV infections in children of this age group, of whom more than 86,000 are hospitalized. This results in an estimated annual medical costs of USD 2 billion per year. Almost all children will have had an RSV infection by their second birthday, meaning that the youngest children is the best place to intervene to provide active protection.

Now let's pivot to older adults. There are approximately 177,000 hospitalizations each in adults over 65 due to RSV in the U.S. and 14,000 deaths due to this pathogen. Globally, it's estimated that there are 1.5 million episodes of acute respiratory tract infection and over 300,000 hospitalizations related to RSV each year. So it's clear that in these 2 age groups, there is an important medical burden against RSV, against which currently there is no licensed vaccine.

So our RSV vaccine, mRNA-1345, encodes for a single protein, the stabilized pre-F glycoprotein that is responsible for fusion of RSV with respiratory cell membranes.

We have an ongoing Phase I study in pediatric and adult populations. This study is evaluating the tolerability and reactogenicity of the vaccine in younger adults, older adults, children and women of childbearing age who have vaccinated could potentially transfer antibody to their young infants. We also are evaluating neutralizing RSV antibody titers in each age group.

All of these cohorts are fully enrolled, and enrollment is ongoing in the youngest RSV seropositive cohort as well as in a separate cohort of individuals of Japanese descent. This will enable RSV vaccine development in Japan.

In older adults, we have observed that mRNA-1345 boosts RSV neutralizing antibodies. As expected, because we have multiple RSV infections over life, all participants had neutralizing antibodies against RSV at baseline. A single dose of mRNA-1345 boosted antibody titers to RSV-A on the left and RSV-B on the right. And what you see are the geometric mean fold rises, or GMFRs, over baseline, which are in gray, at the top of each graph.

So the GMFR over baseline at 1 month post vaccination ranged from 9.8 to 16.9 and 5.3 to 12.3 for RSV-A and RSV-B, respectively, and a minimal dose response was seen in terms of neutralizing antibody titers.

Now let's talk about the safety data from this Phase I study in older adults. We observed that the RSV vaccine candidate was generally well tolerated in older adults at all dose levels. The local solicited reactions were primarily those of injection site pain.

In terms of systemic reactions, which were reported at rates of 50% to 78% in mRNA-1345 and 45.5% in placebo groups, included headache, fatigue, arthralgia and myalgia, similar to the adverse event profile observed with the rest of the vaccine platform.

Treatment-related unsolicited AEs were reported by 6.7% of mRNA-1345 recipients and 10.2% of placebo recipients. And we saw unsolicited severe AEs in 7 of the recipients of mRNA-1345, with none reported in the placebo group. There were no related SAEs or adverse events of special interest reported.

So now our pivotal Phase III study in adults is ongoing, and it's called ConquerRSV. We started this study in November of this year as a Phase II portion and proceeded to Phase III after a DSMB review in February of 2022. This study was placebo-controlled and has a case-driven design where we're looking at acute lower respiratory tract infections in adults.

The study is occurring in a population over the age of 60 years. We anticipate enrolling 34,000 participants who will be randomized 1:1 to receive either the vaccine or a saline placebo. And the Phase II trial comprise the first 2,000 participants. After safety had been evaluated, we will now move on to Phase III. Importantly, RSV infections that occur in the Phase II portion will also count towards the Phase III analysis. Our efficacy analysis will be triggered based on the accrual of respiratory infections that are due to RSV. This program has received Fast Track designation from the U.S. FDA.

So now pulling that all together, I'd like to talk about our strategy of combination respiratory vaccines. So I've told you a bit about our development of Spikevax. You've heard from Dr. Nachbagauer about seasonal influenza vaccine, and we just finished discussing RSV vaccine. These are all foundational pieces in a puzzle that we will put together for our combination respiratory strategy. And we're already starting moving toward that space with our flu and COVID combination vaccine, which you've heard about earlier -- in earlier calls from us.

So now we are moving our next step towards our combination vaccine goal where we will combine the 3 core respiratory pathogens into a single vaccine. So the sequences for COVID-19, or Spikevax, and flu, which is called mRNA-1073, will enter the clinic this year. We will also start a new development program for a vaccine encoding the spike protein for COVID-19, the 4 seasonal influenza hemagglutinin antigens as well as the RSV pre-F antigen into a single 3-component vaccine. Finally, we are initiating a vaccine candidate program in human coronaviruses other than mRNA-1273, or SARS-CoV-2 virus.

Why are we doing that? Well, we have seen that coronaviruses, which cause cold and flu-like symptoms in a fairly sizable population each year has already broken away 3 times to cause epidemics and now a pandemic. The first was SARS 1, the second was MERS, and now we've been living with SARS-CoV-2. So we believe that a human coronavirus vaccine could be an important adjunct and could be potentially added to this combination respiratory vaccine.

So let's talk about some of these candidates. The COVID flu vaccine will enter the clinic later this year and, as we discussed, has 5 sequences: 1 spike protein sequence as well as 4 hemagglutinin sequences. This will be conducted in healthy adults as a Phase I program. And we will be comparing the responses to this combination vaccine to each vaccine individually, mRNA-1273 and mRNA-1010, as well as the simultaneous co-administration of mRNA-1273 and mRNA-1010.

We have also some experience in the past with combination vaccines, and we have shown positive results from our Phase I study in pediatrics, with a human metapneumovirus vaccine plus parainfluenza serotype 3. So this contains 2 F proteins, 1 from each of the virus strains contained in the vaccine.

And this vaccine candidate has been found to have an acceptable safety profile and elicits neutralizing antibodies to both pathogens. So 1653 was evaluated in adults and was seen to have a similar reactogenicity profile to monovalent vaccine. The injection site pain was the most commonly

reported reactogenicity event. And in terms of solicited symptoms systemically, we saw headache, fatigue and myalgia as the most commonly reported events.

In terms of immunogenicity data, after the first dose, and again, this is a booster dose in healthy adults because all of us have seen human metapneumovirus and parainfluenza virus in various infections throughout the course of the lifetime, we observed neutralizing antibody titers against both hMPV-A and hMPV-B as well as against parainfluenza virus type 3, with no apparent dose response with escalating dose levels.

So preclinically now, we have investigated the combination of flu, RSV and SARS-CoV-2 in mice. And so what you see on this slide in blue are influenza responses to influenza vaccine, or mRNA-1010 alone, versus combination with mRNA-1273 or 1345, versus combination with all 3. And you see the same for RSV in orange and for COVID-19 in red. Overall, we believe these antibody responses in mice support moving forward into the clinic with a triple-component vaccine.

So we are announcing today our new combination respiratory vaccine, mRNA-1230. Combining the elements of our COVID-19 vaccine, Spikevax, with our mRNA-1010 and mRNA-1345. So this is an adult respiratory combination vaccine, which is intended to be a foundation on which future antigens can potentially be added, such as human metapneumovirus or the novel human coronaviruses that we spoke about.

So talking about human coronavirus, this is our new endemic human coronavirus vaccine, mRNA-1287. Human coronaviruses are responsible for over 1 million outpatient visits in the U.S. each year and approximately 350,000 hospitalizations, leading to approximately 20,000 deaths. These infections currently account for 10% to 30% of the overall burden of respiratory infections in adults. And we think this is a rationale to move forward with the development of this vaccine candidate.

So now I'd like to introduce our coffee break, where we will take a brief respite for 5 minutes and then come back and speak about our latent virus vaccine portfolio.

(Break)

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

Welcome back from the coffee break, and now is our section on our latent virus vaccine portfolio.

So what are latent viruses? These are viruses that have the ability to both induce a primary infection and then also remain dormant in cells without causing cell death for months or even years afterwards. This means that you can have a period of active symptoms with the primary infection or you may have no symptoms at all and then quite a long time can go between the first infection and when symptoms actually develop.

So there are really 2 key phases. The active replication phase, which is also called the lytic phase, and it's characterized by the release of new virions to infect other cells. And then there's the latent phase. This is when the virus is quiescent and resting inside the cell. And latent viruses can go back and forth between these 2 phases multiple times throughout the lifetime of an individual.

So what kinds of viruses cause latent infections? Most of them are from the family of herpes virus. And you see, on the left, a number of them listed. Herpes simplex virus 1 and 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus are the viruses that are part of Moderna's current pipeline. HIV is also a latent virus. However, it's not a herpes virus.

Why have we invested so heavily in this pipeline? Well, we believe that the mRNA platform is uniquely positioned to develop vaccines against these viruses. Why? Because as you heard earlier from Dr. Crotty, there is the ability of these vaccines to induce both B cells and T cells as well as memory B and T cells, meaning that we can induce a robust immune response upon vaccination and then the body will have a good recall response years after vaccination. And that recall response is critically important to address that latency of these viruses. So this should give not only near-term prophylaxis against disease but may also give us longer-term prophylaxis as well.

It gives me great pleasure to introduce Dr. Anthony Cunningham, who is the Director of the Australian Centre for HIV and Hepatitis Virology Research at the University of Sydney. He's a world-renowned expert in latent viruses and will now share with us some information on the biology of these viruses, including all of the herpes viruses with a specific focus on cytomegalovirus.

Anthony Cunningham

Hello, everyone, from Sydney, Australia. I'm at the Centre for Virus Research, Westmead Institute, Sydney Infectious Diseases, University of Sydney. And I'm going to talk to you today about development and trialing of herpes virus vaccines. These are my declarations.

And human herpes viruses are one of the major groups of what we call latent viruses. Viruses that go into dormancy after initial infection, last for essentially the lifetime of the host -- of the human host and recur at intervals to cause disease. The dormancy or latency protects them from the immune system.

And here are the 5 viruses -- 5 major of these viruses I'm going to talk about today. So herpes simplex virus type 1, a very common virus as you can see from the zero prevalence causes the well-known cold sores; orolabial herpes; keratitis or inflammation of the cornea, which can result in blindness; encephalitis, which can result in death; and an increasing proportion of people with initial genital herpes leading to neonatal herpes.

Herpes simplex type 2, very closely related, not quite as common, is the well-known cause of genital herpes. And it's still the major cause of recurrent genital herpes. Herpes simplex type 1 is eroding its prevalence, particularly in young women, and genital herpes can lead to neonatal herpes and death, and also HSV-2 causes meningitis.

Varicella-zoster virus, also very common, causes chickenpox in childhood and herpes zoster, particularly in the aging.

Cytomegalovirus, the human variety, is also quite common and causes an adult form of mononucleosis. It causes, however, severe congenital infection malformation and deafness, and I'll come back to that during the talk, and also often severe disease in the immune compromised, for which there is currently no prevention.

Epstein-Barr virus, the well-known cause of glandular fever often in adolescents, infectious mononucleosis, also causes lymphoproliferative disorder after transplantation. And this really looks like a lymphoma, but it's not quite got the characteristics of a malignancy. It causes true lymphoma, such as Hodgkin's disease, Burkitt's lymphoma and also lymphomas in people with AIDS, immunosuppression after HIV; a well-known cause of nasopharyngeal carcinoma in Southeast Asia; and, recently recognized, a cause of multiple sclerosis. So these herpes viruses are common causes of human misery.

Now when one looks at these herpes viruses and their target cells for latency, herpes simplex 1 and 2 and varicella remain latent within nerve cells and reactivate from nerve cells. Cytomegalovirus is latent and reactivates from myeloid cells in the bone marrow. And Epstein-Barr virus is latent and reactivates from B cells -- circulating B cells and in the lymph nodes. And to prevent target cell infection with vaccines, antibody is the thing. Antibody protects against the infection of these cells, whereas once they're infected, then you need something that can either kill them or control them with chemicals, such as cytokines, and this is CD4 and CD8 T cells. And this is why we often need both of these modalities to be induced by vaccine, and the relative importance of the 2 may vary according to the disease.

Now one of the difficult things about herpes viruses is that unlike, say, the coronavirus, which has one protein and really the tip of the protein, which is critical for virus entry, this group of viruses can sometimes use as many as 7 proteins to get into cells. We now understand that the back end of the pathway into cells, and that is the fusion of the virus because these all have a membrane around them, the fusion of the virus with the cell membrane is via these 3 proteins: glycoprotein H and L, which activates glycoprotein B to fuse the virus with the cell itself.

But the important things, as far as vaccines are concerned, are the binding protein. So for herpes simplex, glycoprotein D; for varicella virus, glycoprotein E; for Epstein-Barr, glycoprotein 350 and gp42; and then a trimer of 3 proteins for CMV and pentamer, which are used to get into different cell types. And the only reason I tell you this is that these are the targets, these viral attachment proteins are the targets for neutralizing

or protective antibodies induced by vaccines. So you're going to hear about them, and you can see that every herpes virus has a different protein to bind initially to the cell.

Now let's look at herpes simplex virus first. The virus gets into the anogenital tract with the sort of stratified squamous epithelium through cracks in the rather tough external layer, particularly over the male genitalia, which is less marked over the female genital, which is one reason why -- particularly vagina, one reason why women herpes -- genital herpes more frequently than men.

And once it gets through these cracks in the mucosa, and this is relatively infrequent, so between a couple, for instance, only 5% of a person within that couple who does not have any evidence of herpes simplex infection will get infected in the year. So it's very infrequent given the frequency of intercourse. And once the virus gets in, it's there very quickly into the nerve endings within the superficial area of the skin, called the epidermis, and drains quickly into the nerves and up into the dorsal root ganglion, where it stays dominant or latent, essentially hidden from the nervous system and only from the immune system and only really detected when the virus reactivates and then comes down the nerves, again, to cause recurrent herpes. It's a bit similar for herpes zoster as I'll show you. And herpes simplex infection is restricted to the epidermis.

Now we've been particularly interested in this, and the reason for this, obviously, is that this is such a short interval between infection and getting into these nerves. This is the target for vaccines. And this is why it's so difficult to produce a vaccine that's protective against herpes simplex. And you can imagine that when the virus gets into the epidermis, it's also being detected by the immune system, and the immune system immediately goes into overdrive to reduce these effector T cells. The only problem is this takes a while.

So if we're going to produce a vaccine that defends against this pathway here, then we really need to have the defenses on high alert, meaning antibodies ready to go, the interferons of the innate immune system are ready to go, and in essence, we need T cells right here that are gingered up and ready to protect against the virus as it comes across the protective upper layer.

Now one of the things that we've managed to do is to detect virus particles for the first time from herpes. So after a little puncture mark that actually brings herpes into the skin, you can see in red, very quickly, the virus expands. In fact, over 9 cells wide out from that puncture mark within 24 hours. So you can see exactly what we're up against in trying to create a herpes simplex vaccine.

And yet, this has been done. There has been some progress. So there's been early vaccine promise against herpes simplex type 2, with a partially successful vaccine candidate. And this vaccine construct consists of now quite a common type of vaccine, a single protein together with an immunostimulant or adjuvant. And this one is called ASO4, for adjuvant systems 4, produced by GSK, and it has an agonist against an important detector of pathogens called toll-like receptor 4. So this activates the immune system. It's found in the cell wall of bacteria, and it helps stimulate an immune response, particularly to T cells and antibodies.

So in the late 1990s, we trialed this Simplirix vaccine, multicenter, randomized, double-blind controlled trial and immunized partners or subjects with genital herpes disease. And we did indeed show, in this particular trial design, 73% and 74% efficacy. This one was retrospectively analyzed. This one was run more prospectively and was only effective in women who had no indication of herpes simplex type 1 or 2 infection previously, and it was not effective in men. And this reflects what I told you previously that women are more susceptible to herpes. And their defenses, their natural defenses are not as great as those of men because they don't have this tough layer of protection in the equivalent of vaginal skin, vaginal mucosa.

Now this trial was repeated only in the U.S.A. and published in 2012 by (inaudible) colleagues. And something completely different was seen: 58% efficacy only against genital herpes caused by herpes simplex Type 1. And this was the dominant type of genital herpes in young women. And the correlative immunity that we got for the first time were protective antibody and T cell responses, particularly those supporting antibody. We did not see the critical CD8 T cell responses in this particular vaccine.

Importantly, Genocera included in their vaccine for immunotherapy of recurrent herpes glycoprotein D, as with this vaccine up here, but also a nonstructural protein which was a target for CD8 T cells and a saponin-based adjuvant called Matrix-M2, very similar to QS-21 in the shingles vaccine I'm going to talk about. And they saw a 68% reduction in recurrent lesions and 55% reduction in asymptomatic viral shedding, which is the major reason -- or major way in which herpes spread, and increased memory CD8 T cell responses.

The only trouble is that the trial was flawed in they saw also a decrease in placebo, and all of these results were inadequate for progression of this vaccine or its licensure or even further development. So we are now left without a genital herpes vaccine.

And so ongoing science is necessary. And over the years, we have defined the important targets for CD4 T cells, which are limited in number and found on the outside of the virus. The only trouble is the CD8 T cell targets are many, and they vary according to the individual HLA type, which makes this really quite a difficult proposition. And I'll remind you that CD4 T cells produce defensive cytokines. They support the killing CD8 T cells and antibody production. And CD8 T cells kill infected cells after they are infected.

Now this is the -- this is the list of herpes simplex vaccines that are currently under development. It's an incomplete list, but it lists some of the more important initiatives.

So a DNA vaccine from Admedus, still a protein vaccine from BlueWillow, an RNA vaccine from Friedman and Weissman at the University of Pennsylvania using surface proteins of the virus, a specific mutated herpes simplex virus by David Knipe from Harvard taken up by Sanofi which knocks out 2 key proteins so that the virus can only replicate once and does not spread. And there are a number of these live attenuated viruses with specific mutations that others are trying. Another unique type of vaccine is to knock out glycoprotein D completely from the virus and look for what are called subdominant epitopes, that is to reveal new epitopes that might be stimulated in a vaccine administration and hopefully providing better protection. But this has only been tried in mice. And we summarize these in a review published in 2020.

And this just take -- gives you an idea of the wide scope of these proteins which are now being used in developmental herpes simplex vaccine candidates. So a whole range of glycoproteins on the surface of the virus: 2 proteins on the capsid, which protects the DNA of the virus; a couple of proteins in the tegument layer between the capsid and the viral membrane; and a nonstructural protein, as I mentioned, ICP4.

Now as far as chickenpox virus or varicella zoster virus is concerned, as I mentioned before, it causes both chickenpox and herpes zoster. So the initial infection causes chickenpox, which is, of course, a disseminated rash over the skin. And after this, the virus gets into the nerves, either in the skin or directly via blood seeding, and leads to virus becoming like simplex latent within this dorsal root ganglion.

And then it was thought to only reactivate once or twice throughout lifetime. We now know that it does, like herpes simplex, occasionally reactivate more than once, and yet it's still true that people usually only suffer one episode of herpes zoster in their lifetime.

And 99.5% of adults over the age of 50 are infected with this virus and, therefore, at risk for shingles. It's a very common disease and 1 in 3 people will develop shingles in their lifetime due to this clinical reactivation. And the likelihood of shingles rises rapidly over the age of 50, as shown in all of these OECD countries.

The other group who are at risk of shingles are people with immune compromised. And the reason why aging people are at risk is that they indeed also have immune compromised. And it's really their T cells that drop off over the age of 50, not their antibody. Their antibody stays up. So it was speculated that maybe one could use a chickenpox vaccine to stimulate T cell immunity in all people over the age of 60. And my colleagues, Oxman and Levin, figured this out and, in fact, developed a highly concentrated vaccine with Merck and administered this to people and published in 2005 a vaccine efficacy of 51% against all herpes zoster and 65% against its most feared complication, chronic pain or postherpetic neuralgia. However -- and this just shows you the whole virus with, again, the membrane around the virus, this protein studded in the outside of the membrane, and then the capsid surrounding the DNA of the virus and in between the tegument.

But the next vaccine, second-generation vaccine if you like, took a single protein. And because there's only a single protein and you lack the lipids and carbohydrates which stimulate the immune system, it was necessary to have a powerful adjuvant system.

This glycoprotein E was selected because it's a target for both antibodies and T cells and is essential for virus growth. And the effect of these immunostimulants or adjuvants is well shown here. If you just use the single protein without the adjuvant, then you get only a -- 10% of people responding with an adequate immune response, a T cell response, a bit more in people of age 60 to 69 and a bit more in people aged 50 to 59.

But if you use this immune stimulant or adjuvant system called AS01B consisting of not just MPL, as I mentioned before, but also the saponin adjuvant QS-21, which is similar to the adjuvant used by Genocea, then 90% of people over the age of 70 respond to the vaccine, which is a real revelation. And this was reflected in the Phase III trials in which I was involved in and which we published in the New England Journal of Medicine. And in people over the age of 50 and particularly 50 to 59, 60 to 69, to our astonishment, we saw the vaccine efficacy was 97%.

But even more astonishing was the trial -- current trial in people over the age of 70 which showed a vaccine efficacy of over 90% in people aged 70 to 79 and particularly in people aged over 80. And not until some of the recent COVID vaccines have we seen any vaccine that creates an efficacy of this degree in aging people. And not only that, it was effective, equally effective, against postherpetic neuralgia. So if you're protected against herpes zoster, then you also got the same degree of protection against postherpetic neuralgia in people over the age of 50 and over the age of 70. And in fact, that was true for all complications, including the eye disease, which is also a major concern with shingles.

Another major feature of this vaccine which really makes it a paradigm for vaccines, something we aspire to, is its longevity. So we just published last year that in years 6, 7 and 8 after vaccine administration, the efficacy of the vaccine was retained at about 84% to 85%, giving an overall efficacy 91% over a mean of 7.1 years. And in fact, this is reflected in measurements of the immune response which have now been taken out to over 10 years. And modeling the T cell response and antibody responses showed that this vaccine may indeed -- by 3 different modeling algorithms, may extend beyond 20 years. So this is an important vaccine and one that we want to know how it works so that we can make sure that our other vaccines and the aging and the durability of our vaccines is improved.

So the experiments to try and work this out were conducted in mice originally by my colleague, Arnaud Didierlaurent, at GSK and the University of Geneva and injected the -- with his colleagues the recombinant zoster vaccine and its adjuvant in the muscle. Within 30 minutes, these vaccines -- this vaccine appeared in lymph nodes. It was taken up by macrophages around the periphery of the lymph nodes. And then a real cascade of multiple immune responses occurred within the lymph node itself, and this resulted in antibody and T cells, particularly CD4 T cells, being produced which then circulate.

We have collaborated with Arnaud and colleagues at GSK to try and work out how this might work in human lymph nodes, essentially looking to see whether in fact the results are similar in mice. And this has been a revelation.

So we take lymph nodes from volunteers undergoing lymph node dissection, all with appropriate consent. And then we slice the lymph nodes and bathe them in media and then add the vaccine and then look at the cell responses via microscopy, which enables us to look at what's happening exactly where in the lymph node because there are very specific areas of the lymph node that respond to producing antibody and T cells. And also, we can dissect this with high-dimensional flow cytometry, and we can look at the cytokines that are produced.

And we have indeed found that the cascade of immune responses is similar to that of mice, that the vaccines are taken up by sinus-lining macrophages particularly in liposomes, a bit like the RNA vaccines in lipid nanoparticles; and that in these macrophages, the inflammasome is activated, a cascade of immunity is induced, and this results in the T cell responses that we want; and that you need the structure of the lymph node for this to occur. It doesn't occur if you just isolate all the cells in the lymph node and put them into a test tube. You need the unique structure and anatomy of the lymph node for this to occur. And in the future, we want to compare this to the mechanism of action of mRNA vaccines. We think this will help in improving all vaccines in the future.

So now moving on to cytomegalovirus. This is the largest and most complex of the herpes viruses and perhaps the most challenging target for vaccines in that it binds to some cells through the pentamer, the 5 proteins on the surface, some through the primer to macrophages and endothelial cells, and that it's now being shown, particularly in congenital CMV infection, that it's really important to have the pentamer there as well as gB to induce neutralizing antibody and protect the fetus.

For T cells, these are directed against gB and, as I'll show you, a number of other cells. Why do I emphasize gB? Well, I'll come back to that in just a minute.

So what are the disease targets for a human cytomegalovirus vaccine? Congenital CMV syndrome and post-transplant CMV syndromes. And I'm going to focus on congenital CMV, which is almost as common as Down syndrome and fetal alcohol syndrome, and had really been somewhat

neglected under the Institute of Medicine in the U.S.A. in 2000 pointed out what an important vaccine target this was, which led to a renaissance in candidates for CMV

(technical difficulty)

vaccines being produced.

Now the CMV syndrome is most severe in seronegative mothers, but there are still sequelae in seropositives. And in fact, because seropositives are more common, 2/3 of all congenital CMV infections occur, paradoxically, in these seropositives.

The other paradoxical issue is that 85% to 90% of children, of babies will have no symptoms at birth, but 10% to 15% of these will develop sequelae slowly over a couple of years and especially deafness, which makes life really quite difficult in terms of detecting these important diseases.

And this algorithm shows this complexity, that a pregnant mother with CMV infection may either be seronegative beforehand of a primary infection or have a nonprimary infection, and it's the primary infection where you see more transmission to the fetus compared to nonprimary, but there's still some here, and with fetal infection only 10% of symptomatic. And these are the important ones in terms of the majority of these people or these babies will develop sequelae. However, in the 90% that are asymptomatic, you still get a significant number of babies developing sequelae so difficult to tag.

Now if we look at some of the historical trials, the one that stands out is the Sanofi glycoprotein B-MF59 is the adjuvant in seronegative women, 3 doses. And Passat -- and colleagues in Alabama showed a vaccine efficacy of 50% to CMV infection.

Now notice I mentioned just gB. But a recent correlate of immunity in natural infection from Italy suggested that the pentamer should be added to glycoprotein B antigens for optimal neutralizing antibody.

And so three prominent trials are still underway: the Merck trial using a mutated attenuated live vaccine had -- showed induction of neutralizing antibody and T cell and memory responses in seronegatives; Sanofi are now looking at trials with both glycoprotein B and the pentamer and CD4 adjuvants; and Moderna are now looking at a gB pentamer vaccine Phase III trial in 7,000 seronegative and seropositive women, but the primary endpoint is prevention of primary CMV infection in seronegative women.

Now let's look at Epstein-Barr virus finally. And again, this infects 2 types of cells. And the glycoprotein 42 is the one that is most important in determining entry into B cells and yet gp350 has been a common target for trials. And really, this was started before we understood the importance of gp42. But there still is an importance of gp350 in terms of antibodies directed at this are still somewhat protective.

For getting into epithelial cells, another protein is important called BMRF-2. And of course, epithelial cells are important in the throat symptoms of infectious mononucleosis. And if we look at the disease targets for the Epstein-Barr virus, infectious mononucleosis is not just a benign disease. We now know that in a minority of people, there is a relative risk of -- for developing Hodgkin's disease over a median of 4 years and also a risk of developing multiple sclerosis with a relative risk of 2.2 over a median of 5.6 years.

And I mentioned before that this post-transplant lymphoproliferative disease is the bane of patients undergoing transplant and their clinicians, and this may occur within a year of stem cell transplantation, which is the most severe form of immunosuppression, and less than 3 years after organ -- solid organ transplantation. And this presents pretty much like a lymphoma. In 6% of seronegative transplant recipients, primary infection may occur, and this has a thirtyfold risk of developing lymphoproliferative disease. And the height of the virus load in the blood is predictive of the likelihood of this particular disease occurring.

Now with the EBV-associated lymphoma in HIV-positive patients that we saw at the height of the HIV pandemic, the viral load is also predictive. And this is an important point. So if EBV vaccines can't prevent asymptomatic infection, they could reduce the viral load and, therefore, the risk of these particular diseases.

I'm not going to talk about the more difficult targets despite the fact that nasopharyngeal carcinoma is so important in Southeast Asia.

So again, science progresses and the -- gradually, we've managed to define the key proteins which are targeted by CD4 T cells and CD8 T cells. And this is particularly important in protecting against people who are already infected and reactivated. In other words, the lymphoma patients.

Now there've been some key trials already with Epstein-Barr virus. The EBV gp350 has been combined again with the MPL adjuvant and alum to stabilize it. And in a Phase II double-blind controlled trial in 180 seronegative adults, the vaccine efficacy was 78% with -- and this was significant, but there was no effect on asymptomatic infection. Remember what I said before, that even if this is the case, an effect on viral load is an important surrogate. And similarly, a much more focused trial of using a peptide from one of the early -- the nonstructural proteins of Epstein-Barr virus with an oil and water adjuvant in subjects who are only HLA B showed a trend of protection against infectious mono.

And there are numerous trials ongoing against nasopharyngeal carcinoma, such an important cancer in Southeast Asia, for instance, again using these nonstructural proteins in vaccinia or using peptides for this particular protein. And the results are pending.

It's very clear that this particular vaccine needs to be repeated as a Phase III trial perhaps with a better adjuvant against infectious mono. And there are all sorts of vaccines in development. So different proteins of the virus, as I mentioned before, as tetramers, virus-like particles, nanoparticles like the Novavax vaccine, vectored and also messenger RNA.

In 2011, the NIH consensus conference ratified infectious mono and EBV-associated cancers as principal targets. And it was discussed that it would be really hurry up these trials if we had key surrogate markers for EBV malignancy rather than waiting the many years that people may require to develop these malignancies.

We need, like all the other vaccines, immune correlates of protection against both EBV infection and disease. We need better epidemiologic studies to define the benefits of the vaccine to energize the private sector and government. And we need academia, government and industry collaborations to accelerate developments.

Now as a final slide, I just wanted to address the commonality of vaccine development for these three herpes viruses for which we do not have vaccines: Herpes simplex, CMV and EBV. These are large viruses with multiple proteins, multiple proteins involved in viral entry into different cell targets. We're starting to understand this now and the commonalities and which to target for neutralizing antibody. But we're still developing a handle on the role of T cells and just how important they are. We do know they're important in transplantation. We know they're important, for instance, in shingles. And here, the problem is you have multiple viral protein targets with individual HLA-related heterogeneity between individuals, and this gives rise to great complexity in defining the immune correlates protection in multiple diseases.

And finally, we're really finding the importance of the relevant adjuvants, as I emphasized, for shingles, and we need to use these according to immune correlates of protection.

I just want to show you my group involved in a number of these vaccine development projects and my colleagues in the clinical trials, both academic and in industry, and also in the development of the lymph node model. Thank you very much for listening.

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

Thank you very much, Dr. Cunningham, for that outstanding overview.

Now let's talk about the personal impact of congenital CMV on a family. On the next slide, I would like to share with you a video produced by a family whose second child is living with congenital infection.

(presentation)

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

That video is a strong testimonial to the impact of congenital CMV infection. This is the most common congenital infection worldwide and results in over \$1 billion in annual health care costs each year in the United States.

At birth, congenital defects include microcephaly; chorioretinitis, which is an inflammation of the retina that can lead to blindness; seizures; and sensorineural hearing loss. And in the longer term, this infection can additionally lead to cognitive impairment, cerebral palsy and sustained seizure disorders. One in 200 babies in the U.S. are born with congenital CMV. And of those infants, 1 in 5 will have severe life-altering consequences.

The Moderna CMV vaccine candidate is comprised of two antigens. The first is glycoprotein B, and it's important to note that glycoprotein B was already a single antigen in a CMV candidate vaccine that had 50% efficacy. The Moderna vaccine also includes the pentameric complex, which is five mRNA sequences that naturally assemble into the larger protein. Pentamer in a natural infection is the dominant antigen against which humans make their immune response. Both of these antigens are important in cell infection, viral membrane fusion and cell-to-cell transfer.

So here, you see a picture of the 6 mRNA sequences that lead to these 2 antigens. The gB protein is a single sequence and has the ability to infect both fibroblast and epithelial cells. The pentameric complex, which is formed of the remaining five mRNA sequences, primarily infects the epithelial cells.

We've had a Phase II clinical study which led to the selection of a 100-microgram dose for the evaluation in our Phase III clinical trial, CMVVictory. In the Phase II study, 3 dose levels were tested at 50, 100 and 150 micrograms. And it led to the observation that mRNA-1647, our candidate CMV vaccine, was observed to be generally well tolerated with no treatment serious adverse events and no study pause rules being reported or met.

Like other vaccines in our mRNA portfolio, the most common solicited local reactions was injection site pain. The most common solicited systemic reactions were headache, fatigue, myalgia, arthralgia and chills.

In general, the solicited adverse reaction frequency and severity after the third dose were similar to after the second dose. And the kinetics were also quite similar to the 1273 vaccine in that the second dose had more reactions than the first in seronegative patients.

So in both seronegative and seropositive participants, strong immunogenicity was seen against the epithelial and fibroblast cells. After the third dose, neutralizing antibody geometric mean titers were twentyfold higher against epithelial cells than the benchmark in seronegative subjects and were sevenfold higher in seropositive subjects.

When we consider the fibroblast cells, which is primarily the target of the gB antigen, the seronegative subjects reached the benchmark, which are the preexisting antibody titers in initially seropositive subjects, and the seropositive subjects increased their antibodies twofold over baseline.

So these two graphs show you this information pictorially. First, in the top row of the epithelial cell infections. And in the bottom, you see neutralizing titers against fibroblast cells. In the solid lines are those who are seronegative and in the dotted lines are those who were initially seropositive. The gray bar lines show the placebo group, and the primary colors are the various dose levels of CMV vaccine.

And what you can see from the slide is that both the first and second doses induced those robust increases in neutralizing antibody titers described on the previous slide regardless of whether subjects were seronegative or seropositive.

After the third injection, we see titers have waned over the intervening 4 months, and we're able to reincrease them up to the level of the second dose. Why is this important? Because we know, for our congenital CMV vaccine, we will need protection to last a relatively long time between when someone may be vaccinated and when someone may be pregnant and transfer their antibody to their baby to protect against infection. And therefore, that third dose is critically important for sustaining antibody durability, similar to what we've observed in the SARS-CoV-2 program.

CMVVictory is our pivotal Phase III trial that's ongoing in women of child-bearing age. This trial is being conducted in women who are 16 to 40 years of age, and there will be approximately 6,900 women enrolled into 2 groups, those who receive CMV vaccine and those who receive placebo. The

primary endpoint of the study is the prevention of primary infection in women who are initially seronegative. Enrollment is currently ongoing in the U.S. and multiple countries internationally, and we will enroll at approximately 150 sites.

Participants who join the study must be at higher risk of contracting CMV by virtue of having direct exposure in the home or socially or occupationally with at least 1 child who's less than 5 years of age. This is because young children are the individuals known to have the largest transmission rates amongst people.

The goal is to enroll a diverse group of U.S. participants, and we have set ourselves a goal of at least 42% of subjects who are persons of color. Our primary efficacy analysis will be case driven, and it will be based on the number of cases where we see 0 conversion.

So now I've described to you how we're going to assess primary infection, which is a necessary antecedent to congenital CMV infection in seronegative individuals. We'll also evaluate seropositive individuals in order to ensure that we are inducing increases in antibody titers.

Birth defects are not the only impacts of CMV infection, and these impacts can increase over time as someone ages. The longer-term complications which have been associated with CMV infection can include cardiovascular disease, Alzheimer's disease, glioblastoma multiforme, which is a type of aggressive brain tumor, and autoimmune diseases.

So we are investigating the potential of preventing longer-term complications by preventing CMV infections. The CMVictory trial, as previously explained, will really look at primary CMV as its key outcome, and primary CMV is a proxy for preventing CMV infection in initially seronegative mothers. The longer-term impacts include autoimmune disease, cancers and cardiovascular diseases, and those we will need to evaluate over a much longer time horizon. So that will include potentially Phase III studies but also includes epidemiological, observational and other mechanistic studies.

So now I'd like to hand the floor over to Dr. Sumana Chandramouli. Sumana is our program leader for Epstein-Barr virus infection vaccine, and she will explain to you the background and the rationale and our progress to date on our EBV vaccine candidates.

Sumana Chandramouli

Thank you, [Jackie], and good morning, everyone. My name is Sumana Chandramouli, and I'm a Director in Infectious Diseases at Moderna. And I'm very happy to be presenting our Epstein-Barr virus vaccine program here this morning. But before I do so, I have the pleasure of introducing Dr. Alberto Ascherio.

Dr. Ascherio is a professor of epidemiology and nutrition at the Harvard T.H. Chan School of Public Health and a Professor of Medicine at Harvard Medical School. He is trained in internal medicine and has practiced around the world. And he has dedicated his career to the epidemiology of the causative agents of multiple sclerosis, Parkinson's disease and ALS. And today, he is here to present his groundbreaking work on MS and EBV.

So over to you, Dr. Ascherio.

Alberto Ascherio

Good morning. Thank you, Sumana, for a very nice introduction. It is my pleasure to be here to talk about EBV's causal factor in multiple sclerosis.

So multiple sclerosis, MS for short, was beautifully described in the 1800 by Charcot. It's a disease that cause multiple demyelination in the brain and the spinal cord.

The pathology show a mechanism consistent without immunity, but an infection in the CNS has never been excluded. Although until recently, the disease has been described as being of unknown etiology.

It's considered the most common disabling neurological disease in young adults in the U.S. and Europe. There are 2.8 million people worldwide suffering from MS, and the number is increasing. The incidence is higher in young adults, more common in women than in men. And in the U.S., the lifetime risk among women of getting MS is between 4 and 5 per thousand.

So this is a summary of what we knew before the study that I'm going to present to you. So there was evidence that individual who are EBV negative, who are not infected with the Epstein-Barr virus, are protected from MS. But this evidence was based on cross-sectional study that are open to multiple sources of bias.

So EBV is a common herpes virus that infect 95% of the population. And in most individual, it doesn't cause diseases. Rarely, however, it's cause of different conditions where we have heard about mononucleosis and is also a cause of rare lymphoma and a different type of cancer. So the hypothesis was that multiple sclerosis is one of the rare complication of infection with the Epstein-Barr virus. So what we needed is to find the right evidence that those individual who are EBV negative, when followed over time, they're protected against multiple sclerosis and they only become susceptible to multiple sclerosis following EBV infection.

So the idea is very simple, but the realization is very challenging because of the high prevalence of EBV infection, about 95%. And you need a very large population to have a sufficient number of individuals who are not infected with the EBV virus, follow them over time and determine the temporal sequence of events.

In addition, it's well known that there is a presymptomatic phase in multiple sclerosis. So the clinical onset of the disease shown here is not the very beginning of the disease process, which can proceed for a -- by a few years the clinical symptoms. So to do a rigorous study, you need to demonstrate the infection of EBV precede not only the clinical onset but also the first evidence of being in neurodegeneration.

So the objective of this study were to determine if EBV infection precedes in time the clinical onset of MS and also the elevation of serum neurofilament light chain that are the marker of neurodegeneration. In addition, we wanted to control and investigate the possible role of other viral infection to make sure that any association with EBV would be unique and specific to this virus. So this unique investigation was made possible by the Department of Defense Serum Repository in that it's a repository that comprise over 60 million serum sample collected from active-duty military personnel, 10 million young men and women who serve in the Army, Navy and the U.S. Air Force. So the occurrence of MS in this population is documented by the physical disability agency of the military branches. And MS is considered the medically disqualifying conditions, so individuals suspected of having MS go through a rigorous diagnostic process.

What is shown here, that this is a very young population recruited, typically around 18 years of age, and they're followed over time. And this show the occurrence of MS during the period of active duty. We'll not go through the detail of the study design. So I put this slide just to emphasize that all the comparison were measured on sex, age, race, ethnicity, date of blood collection and military branch.

The EBV status was determined using two different methods, an ELISA for screening at baseline which individual were infected with EBV, and the individuals who were EBV negative were then followed by Western blot to determine the time of EBV infection. Overall, we documented 801 MS cases in this population who were measured to 1,566 controls.

So the main findings are summarized here. So of the 801 MS patients, 76 -- 766 cases occurred in individual who were EBV positive at the time of recruitment, 35 occurred in individual who were originally EBV negative. But remarkably, of this 35, 34 occurred after EBV infection. As expected, the large majority of the population was EBV positive at baseline. We had 6.8% of individual who were EBV negative.

So this slide shows the rate of EBV seroconversion, comparing the individual who developed MS in green, the individual who remained healthy, control in blue. See, there are highly significant difference. The rate of seroconversion among control was similar to that observed in other populations like college students and military population, about 11%, 12% per year over the entire period of follow-up. 57% seroconverted to EBV. In contrast, individual who developed MS, virtually all of them except one, became EBV positive before MS onset.

CMV, which is a herpes virus, transmitted MS mainly similar to EBV, cytomegalovirus, was used as a control virus to make sure that the results were specific. And as you can see on the right panel, there was no increase in MS in -- no difference, seroconversion, in individual with MS compared to their mentioned controls for CMV.

When you look at this data in terms of risk of developing MS, if you take as a reference individual who were EBV negative and remained EBV negative throughout the study, those who seroconverted have an over thirtyfold increase in MS risk following EBV infection, and those who were already EBV infected at baseline had a relative risk of 26% compared to those who remain EBV negative.

There was no increase in MS risk in individual infected with CMV. In fact, if anything, those individual who were CMV positive at baseline had a slightly lower risk of developing MS. That is possibly explained by the fact that CMV infection can modulate the immune response to EBV.

Now in an observational study like this, there are concern about the causal interpretation because of possibility of two sources of bias. One is confounding. Confounding refer to the possibility that some unknown or known factor that is not EBV could explain the observed association. What is not often appreciated, however, is that for confounding, to explain a relative risk of 30, an increase of risk of thirtyfold, in individual who were EBV negative compared to those who are EBV positive -- sorry, thirtyfold who are EBV positive compared to those who are EBV negative, the confounding itself need to be associated with MS -- with risk of MS by over sixtyfold. In the same time, risk -- it needs to be associated with risk of being infected with EBV by over sixtyfold. So there is no known or even plausible risk factor that could approximate the strength of association.

To give you an example, the strongest genetic predictor of MS, which is the HLA-DRB15 (sic) [HLA-DRB1*15:01] allele, increased the risk of MS by two to threefolds. Other environmental factor like Vitamin D efficiency and cigarette smoking may double the risk of MS. So we are not really able to mention any relative risk that could be close to these trends.

Another concerned the possibility of reverse causation. So this refer to the fact that MS, because it's a disease associated with immune dysregulation, could increase the risk of getting infected with EBV. So it could increase the susceptibility to infection. So to address this possibility, we use the serum level or the neurofilament light chain, which is a sensitive biomarker of neurodegeneration. And also we measure antibody titers to engage the entire human virome to detect any possible dysregulation in the immune response to viral infection.

The results on NfL are shown in this slide. So if you see on the left, individual who developed with MS, their NfL level at baseline were comparable to those of the of -- controls. And this is taken as a reference. Then if you follow within person over time, at the time of the first sample that was EBV positive, the NfL level were still normal. It's [only in] the second samples that was EBV positive that we see a significant elevation in NfL. So this demonstrates quite clearly that the NfL elevation, the beginning of the neurodegenerative process follow EBV infection. It never occurs before an individual is infected with EBV. If you look at the individual without MS, NfL levels are stable within person throughout the duration of this study.

VirScan is a relatively novel technique that allow, with a drop of serum, to assess the antibody titers against virtually all the human virome that comprises all known human viruses, pathogenic human viruses. So screen over 100,000 overlapping peptide that are sequences from the different -- genomic different viruses. And the main result are shown here. So this comparison was done in 30 individual with MS and 30 controls; the individuals with MS at 2 sample, 1 collected just before the onset of MS and 1 collected after the onset of MS, to make sure that we would capture any potential triggering event. And as you can see in the pre-onset samples on the left, the peptides that were enriched [among MS cases] were virtually all EBV peptide. There was no other virus that emerged as being significantly associated with -- the new response being significantly associated with multiple sclerosis. Similar results were obtained in the post-onset samples. So this results were quite striking even to ourselves, that the signal for EBV is so strong that virtually overwhelms any other signal related to potential other viruses triggering the disease process.

I think we are confident to conclude based on this data that MS is a rare complication of EBV infections. [We know that] other factors are important. A family history of MS and genetic predisposition are known to be a risk factor for MS. The age at EBV infection, we know that history of mononucleosis is associated with a twofold increased risk of MS. We have previously demonstrated vitamin D deficiency or insufficiency can double the risk, and similarly for tobacco smoking. Finally, obesity during adolescence, in effect possibly mediated by low vitamin D, is also associated with risk of MS, but EBV stand out by having a association [of -- with MS] that is over 30-fold, and so the -- our conclusion that EBV is the leading cause of MS. And the main question that is left to clarify is what are the mechanisms by which EBV causes MS.

A very simplified summary is shown here. This was an editorial accompanying our recent paper in Science. So molecular mimicry is often mentioned as a possibility, that the neuro response against EBV cross-react with brain antigens. The fact that EBV is on B cells -- as you know, the most effective treatment of MS is anti-CD20 antibodies. The B cell are the site of persistence of the Epstein-Barr virus, so by depleting the B cell, most likely we get rid of the virus in the circulation. The virus in B cells is, of course, a latent infection but also transform the phenotype of the cells in a manner that make them less responsive to the regulatory signals. And finally, the possibility of a CNS [tropism that has] been suspected, someone will say demonstrated, for EBV-infected B cells in some studies being found in MS lesions, so -- though this is still controversial and other mechanisms remain possible.

This insert just show that 2 of the EBV-encoded protein, LMP1 and LMP1, activated the physiological signals that -- in B cells when -- that [activated] B cell when they recognize [their recombinant] antigen, the B-cell receptor and the co-stimulatory factor [CD40].

What we can say about the mechanism from an epidemiological perspective is that we know that, MS risk, it doesn't appear to be increased with immunosuppression. The EBV viral load in peripheral blood is elevated but only modestly. There is a very strong association with serum anti-EBNA titer. Anti-EBNA titers are antibody against latent EBV antigen -- EBV nuclear antigen. And the number of infected B cell is much smaller than the number of cytotoxic T cells against EBV, so almost certainly the immune response to EBV plays a role in causing MS. What we are most interested at this point is the possibility of preventing and treating MS based on its association with EBV.

In EBV-negative individuals, I think a vaccine that confers sterile immunity would almost certainly prevent multiple sclerosis. A vaccine that prevents mononucleosis but not EBV infection, I think, would be likely to reduce MS risk. That will depend on the specificity and the characteristic of the immune response, how the vaccine will modify the immune response to EBV infection. In individual who are already infected with EBV, a vaccine could modify the immune response to EBV and reduce the risk of EBV reactivation and MS. An example is the herpes zoster vaccine given to individuals who are infected with the virus just to prevent shingles, the reactivation of the virus. And finally, there is a potential for a therapeutic vaccine in individual with MS if we could modify the immune response in a manner that reduce the pathology.

So we are very excited that there is research ongoing in all -- possibly in all of these direction.

I just want to conclude, acknowledging several people who contributed to this study. I just want to acknowledge the [lead out of the] paper and my -- the senior (inaudible), Sandy Munger, in addition to all the active-duty military personnel and the military collaboration that made this study possible.

Thank you.

Sumana Chandramouli

Thank you, Dr. Ascherio, for the wonderful presentation.

And now I am happy to present our internal programs on the EBV vaccine. Epstein-Barr virus, as we just heard from Professor Cunningham earlier this morning, is a herpes virus like CMV, HSV and VZV. And like other herpes viruses, it is very prevalent across the globe. Like other herpes viruses, it also establishes a lifelong latency once it infects the host. EBV spreads through saliva and is contracted by young children and adolescents. Children in more developed countries generally tend to acquire primary infection at a later age. Infection in toddlers and young children is mostly asymptomatic, while it is more problematic when that first infection happens at a slightly older age.

Around half of the teenagers and young adults that get infected with EBV for the first time can go on to develop infectious mononucleosis or IM, more commonly referred to as mono. This is illustrated in the graph on the right that shows the age distribution of IM in the U.S., with a dramatic peak occurring in the young adolescent age group from the mid teens to the mid 20s. By some estimates, there are around 1 million cases of IM in the world -- in the U.S. And while other viruses like CMV can also lead to IM, EBV is the main causative agent accounting for more than 90% of the cases. Severity of IM can range from milder symptoms like fever and fatigue and sore throat to much more serious ones like lymphadenopathy. And in some rare cases, it can even lead to splenic rupture. [And this can] require hospitalization and extended care.

We are developing mRNA-1189 as the vaccine to prevent IM and potentially EBV infection. EBV infects 2 types of cells in the body: B cells that are a type of immune cells responsible for antibody production and epithelial cells. EBV, like other herpes viruses, uses a complex multicomponent viral entry machinery to infect [these] cells. In our vaccine composition, we've included 4 surface glycoprotein antigens. The first, gp220, is a naturally occurring variant of gp350 that facilitates viral attachment to [B cell surface]. In some studies of natural infections, this component accounts for the majority of neutralizing antibodies against B cell entry. The other component is a trimer of 3 glycoproteins, gH, gL and gp42. The gH/gL portion facilitates entry into epithelial cells, while gp42, by attaching itself to gH/gL, can trigger viral entry into B cells.

EBV tends to periodically reactivate and shuffle between the 2 cell types. By including the necessary components for entering into both cell types, we've designed our vaccine to train the immune system to tackle the virus from entering both of [its] host cell types. With this approach, we hope that our vaccine has the ability to protect not only against symptomatic EBV infection that leads to IM but to potentially also prevent EBV infection itself.

We are currently conducting a Phase I study in the U.S. to assess the safety and immunogenicity of mRNA-1189. This placebo-controlled observer-blind trial is testing 3 different dose levels of mRNA-1189 in EBV seronegatives and seropositives in the age range of 18 to 30 years. Our first subject was dosed in December 2021, and following review of initial safety data, we have expanded enrollment for all study arms.

Once infected, EBV persists as a latent virus over the lifetime of an individual and is also associated with a number of serious long-term consequences. EBV was the first virus that was definitively linked to human cancers and causes several lymphomas and nasopharyngeal carcinomas. It accounts for around 80% of a devastating post-transplant condition called PTLD, where EBV takes advantage of the immunosuppressed state of the patient following transplant surgery. We also just heard from Dr. Ascherio about the overwhelming evidence pointing to EBV as a causative agent of multiple sclerosis. Nearly all MS patients show evidence of EBV infection. And there is an even higher risk of developing MS in those that have a history of symptomatic EBV infection that is IM. Overall, EBV infection increases the risk of developing MS by an impressive 32-fold, as illustrated by the figure on the right and as we just heard in Dr. Ascherio's presentation.

Given the significant impact that EBV infection can have in the long term, we are developing a second EBV vaccine, mRNA-1195, with the aim of preventing some of these serious health conditions. EBV cycles between a lytic replication phase, where active viral particles are produced from the infected B cells and released into the surrounding tissues and bloodstream; and a latency, where the virus is largely [quiet]. A healthy immune system plays a key role in keeping the latently infected B cells under control. However, when immune control is lost due to a disease condition or due to immunosuppressive therapy, EBV has the capacity to make the infected B cells expand in population, leading to various types of lymphomas and possibly other autoimmune diseases. mRNA-1195 is designed to tackle both lytic and latent phases of EBV life cycle by including both glycoprotein antigens and latent antigens from EBV. The aim is to induce a strong antibody and T cell response against EBV with this vaccine.

This vaccine is currently in preclinical development. And we're investigating whether it can bring benefit to those who have already acquired an EBV infection, focusing on PTLD and multiple sclerosis as indications.

And with that, I would like to thank you for your time. And I'll hand it back to Jackie, who will now take us through the other latent virus programs.

Thank you.

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

Thank you, Sumana, for that review of our EBV programs.

Now I'd like to speak to you about our ongoing HIV program, which includes 2 complementary approaches. We are investigating with our partners at IAVI and the NIH germline targeting of antibody development. We know that broadly neutralizing antibodies, particularly against the CD4 receptor, can be protective against HIV infection, but it's very difficult to induce these broadly neutralizing antibodies. One philosophy is that, through an iterative approach where step by step we vaccinate with several antigens, directing the immune system towards this very specific epitope [in] conformation, we can educate the immune system in multiple vaccinations to induce the kinds of antibody that will ultimately protect (sic) [protect against] HIV infection. We have one ongoing program with 2 of those educating antigens.

Then with the NIH, we also have an ongoing program with HIV native-like trimers. Trimers are really the natural conformation of that protein that recognizes the CD4 molecule on T cells and is the basis of viral entry into the cells. We will be investigating with the NIH these native HIV-like trimers as an antigen, the thought being that ultimately they can be one of those educating steps in the germline targeting process.

So this is a real iterative cycle of vaccine development. We start with immunogen design, make our mRNA formulation, test the vaccine in mice and potentially other animal models. If those look promising, we go into human clinical trials. If not, we go back to immunogen design. And we do the same through our clinical trials as we attempt to educate the immune system towards these broadly neutralizing antibodies. And finally, our hope is that this will lead to a protective vaccine. So we are really committed to HIV development for the long run.

So mRNA-1644. This is the germline targeting approach I was describing on the previous slide, and it's a Phase I study to investigate 2 antigens in terms of safety and immunogenicity. One is eOD-GT8 60mer, and the second is the Core-g28v2 60mer. Both of these antigens have been developed by IAVI and The Scripps Research Institute. And in this trial, we will give 2 vaccinations at month 0 and month 2. In 2 of the groups, we will give only 1 of the 2 antigens. And in the other 2 groups, we will give a sequence of the 2 antigens in order to determine if we are able to induce more targeted neutralizing antibody responses. This study will involve 56 adults aged 18 to 50 years of age, and we have begun vaccinating in this study.

The next approach is mRNA-1574. This is the trimer approach with the antigen development from Dr. William Schief, who is Professor at Scripps Research Institute and a director at IAVI. This is another open-label study which will test the safety and immunogenicity of the native-like trimer as a mRNA sequence in adults who are otherwise healthy. And the intent in both of these studies is to identify antigens that are both safe and immunogenic at an appropriate dose level.

We also will be initiating clinical work in a human herpes simplex virus vaccine candidate. This is a candidate that targets specifically HSV-2, mRNA-1608. So this vaccine, yes, is targeted against HSV-2, which primarily causes genital herpes. And again it establishes lifelong latent infections, so subjects who acquire genital herpes, while they may go into quiescence, never truly get rid of their herpes infection. And this is a significant burden of disease. It's both painful as well as stigmatizing for those who are infected. It's estimated that approximately 18.6 million individuals aged 18 to 49 have been infected in the U.S. And globally, approximately 5% of the population is HSV-2 seropositive. The burden of disease really reduces the quality of life. And so our hope is to restore that quality of life through vaccination by reducing the number of exacerbations that people who have recurrent infection experience.

So we've investigated this in the preclinical mouse model. And in mice, we gave 2 vaccines separated by 3 weeks apart. 1 was a placebo. 1 included our HSV-2 mRNA sequences. And both of these immune responses were then compared to the immune responses in terms of HSV-2 neutralization in humans who have been infected with HSV-2. What you can see on the bar graph is that in the placebo group we see no immune responses. And in the mice who were vaccinated with mRNA-1608, we see antibody neutralization titers that were higher than those observed in humans currently infected with HSV-2. These results now need to be investigated in the clinic, and we're looking forward to initiating HSV trials and submitting our IND later this year.

And finally, I'd like to speak to you about a candidate we will be bringing to the clinic against varicella zoster virus. This is a vaccine candidate intended to prevent reactivation of varicella zoster virus leading to shingles. And you heard a lot about shingles in the clinic earlier with Dr. Cunningham, so I'd like to now focus on the right-hand panel of this slide.

In this graph, we show the data from a previous vaccine candidate, mRNA-1468, which was being developed in collaboration with Merck. And in that study in nonhuman primates, animals were first vaccinated with a dose of live activated varicella vaccine; and then received 2 additional doses of either the live activated varicella vaccine, a subunit glycoprotein E vaccine that served as a proxy for Shingrix; or 1 of 3 doses of an mRNA vaccine. And what you can see from this slide, where the Shingrix are shown in red -- Shingrix like are shown in red and the mRNA vaccines are shown in the other colors, the immune responses after the second -- first and second dose were comparable with similar antibody decline until day 224.

These data give us confidence that a gE-based mRNA sequence can lead to an effective mRNA vaccine against varicella zoster virus, and we look forward to reporting those data in the future.

So that concludes the review of the latent virus pipeline, and I'd now like to hand back over to Dr. Hoge to review our strategy for global health vaccines.

Thank you.

Stephen Hoge - Moderna, Inc. - President

Thank you, Jackie.

As I said before, I'd like to provide a little bit more detail now on our global health vaccines strategy.

So pandemic and epidemic threats will unfortunately continue to arise, as has been published extensively. In fact, there are 25 viral families known to infect people globally, many of them with epidemic ongoing infections in different regions of the world. And Moderna has been committed to using our mRNA platform to address these public health threats since our very founding. As a company that's pioneered the creation of mRNA vaccines, it's important to note that the first mRNA lipid nanoparticle vaccines were both against pandemic influenza strains. And subsequent vaccines, including against the Zika virus and chikungunya virus in 2016, '17, were critical to us advancing our platform. In fact, you can say that addressing public health threats has been a core part of our strategy since our very founding.

There are 3 key pillars now to our ongoing global health strategy. The first is addressing priority pathogens. As I said at the beginning of the presentation this -- today, we've committed to advance vaccines targeting 15 different priority pathogens into clinical studies by 2025. These are pathogens identified by the WHO and CEPI as specific threats to public health. The second is putting our technology in the hands of people who can generate the next great ideas for how to use it, something we call mRNA Access. And this is a new collaborative access program enabling global researchers to utilize Moderna's own mRNA technology platform in their hands and in their labs to pursue research on emerging and neglected infectious diseases. Truly, we want to democratize innovation in this space.

And the third is we have continued to commit to never enforce our COVID-19 patents in the Gavi COVAX Advance Market Commitment countries, 92 low- and middle-income countries, because we never want our innovation and patents to be a blocker to those countries getting COVID-19 vaccines.

I'd like to say a little bit more about the priority pathogens and mRNA Access. So first, our platform, we think, is uniquely suited to address the diseases of highest concern associated with either the WHO R&D Blueprint or CEPI's priority pathogens. If you look here, there's a long list of the priority pathogens that we think we can address. We are prioritizing many of them right now in our existing pipeline, but we're looking to start new collaborations, including through mRNA Access, to address all of them by 2025. This will also support our work to continue to address what is called Disease X or the threat of a future pandemic, which unfortunately is likely to arise at some point.

Now you'll note that many of these are programs for which we already have clinical data: chikungunya virus vaccines which we've been moving forward, COVID-19. We're moving forward in the clinic with an HIV program, as we've talked about. We've previously had preclinical work in MERS. And then obviously our work in Zika continues. And we've had success with our COVID-19 vaccine, so we think we're on the path, but there is much, much more work to do to complete these 15.

Secondly, I'd like to talk a little bit about mRNA Access. This is our effort to democratize the innovation around neglected and emerging public health threats. We are partnering with institutions globally to take advantage of using our own platform technology, in many cases the same technology that's available to the research scientists in our labs. These programs will leverage our capability to rapidly allow research to then move into early development, particularly preclinical development and eventually clinical trials. Our goal is that there will be many of these such collaborations across all of our work and that it will build capabilities and knowledge about how to use mRNA technologies to generate vaccines against public health threats globally.

mRNA Access powered by Moderna has 3 key components. So the first is an mRNA design studio which allows you to design the vaccine, in collaboration with Moderna scientists if necessary, that you want to be able to test. We have a high-throughput production system, the very same

that we've built over decades at Moderna, to allow us to manufacture that vaccine for, first, in vitro testing; and then even in vivo testing preclinically. And then it allows for iterative research. The speed and flexibility of our platform means that we don't have to commit to a single thing; and that in working with academic collaborators, we'll be able to rapidly design and retest this work together. We've signed up many leading institutions around the world, and there are many more in flight. We look forward to building out mRNA Access globally as we commit to bringing forward mRNA vaccines against emerging and neglected public health threats.

And with that, I'd like to turn it over to Stephane Bancel to provide some concluding remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thank you, Stephen. Thank you to the team. And of course, thank you to our guests for a very interesting and insightful presentation.

Before moving forward, I would like also to thank the Moderna team and all of our partners. If you look at what has happened in the last 12 months since the last vaccine day, it is really humbling to see the progress in term of the strength of our pipeline, the advancement of our pipeline and how we're getting closer day by day to well protect so many hundreds of million of people. That gives us a lot of energy.

So now let's start talking a bit about the commercial vaccine strategy. As you know, priority #1, respiratory vaccine; priority #2, latent virus vaccines.

On the respiratory vaccine, as we've talked many times, what we have to do from a development standpoint to get authorization or approvals is first start with single-virus vaccines, COVID, flu, RSV. And as you know, on the flu, as [Stephen] explained, [we're doing the] iteration of flu prototype to get better and better through efficacy, but we think it's very important from a public health standpoint and from a competitive standpoint that we get into the flu market as soon as possible. We think the world needs a COVID-plus-flu market vaccine that will help us tremendously. And then of course, it's all about the combinations, as we've talked before about the COVID plus flu; as we've announced this week, COVID plus flu, plus RSV; and also the endemic human coronaviruses combination vaccine. We are very excited about that one too. And then of course, the pediatric setting, whereas you see different combination of viruses because in different age groups you see different mobility and mortality from those viruses.

And what you see, and we'll come back about it in the next couple of slide, on how to think about the direction of this market. [This is a] market because there's a very high compliance in people that have high risk of disease and hospitalization and mortality. There is, if you are able to provide more value, a very good track record of being able to get premium pricing.

On the latent virus vaccines side of things, as you know, we have a pretty extensive pipeline. As we've said before, our goal is to develop vaccine against all latent viruses that hurts human over time. As you know, we've announced more recently a vaccine against VZV, a vaccine against HSV. And trust me: The team in the labs is working on more candidates, and we'll share them with you when they are ready for prime time. And the way we're going to think about the commercial opportunity for those vaccine is looking at [combs] in term of latent virus vaccine like VZV and HPV. And I'll come back to it in a minute.

So if you look at the respiratory viruses, what you can see on this list. And it's a list that actually a few people outside of a medical field are already aware of. Those are the vaccine with the attack rate, the incidence rate of infection in a natural population, in this example, in adults in the U.S. over the age of 65. And you can see that actually the list of viruses that has a very important attack rate is very long. And as we've said for many years, our intent is to develop vaccines against all of those families of viruses and to combine them. And if you look at the list today and you compare to [the Moderna] pipeline, it's [pretty of a nice] match.

And when you look at the global implication of those viruses. It is gigantic, \$20 billion to \$40 billion of an annual cost estimate every year from those viruses in people that are older than 65. When you add [all of the other] population at risk like health care worker, people that because of their jobs have risk of being infected regularly, people that have comorbidity factors, actually that number is much higher. And that's, of course, before SARS-CoV-2 number is added to those.

And then another way to look at it is actually what should this market become when you go from a flu-only market, because there is no vaccine available for any of the other respiratory viruses today. And you look at, well, this could become -- we believe the opportunity of this market should

be at least 1 billion doses per year. And we think this technology and Moderna's pipeline is really first in class and has the ability to change care for hundreds of millions of people very quickly.

Now how to think about latent viruses. We believe each of those latent viruses will be, over time, many billions of dollar of annual sales in an annuity setting. And if you look at just 2 proxy that many of you are very familiar, one is, of course, HPV latent virus. And you can see the sales of Gardasil over time and how we are increasing regularly. And they just keep going up, going up, going up. And then the same thing with Shingrix from GSK. And in the case of Shingrix, as many of you know, we not only had in 2021 the impact of a pandemic, where you see actually less vaccination because people are more focused on protecting themselves with flu and, of course, COVID boosters and COVID [prime series], but the other piece is that -- is -- public information by the GSK team is that they were not able to supply the market in the last few years because they didn't have enough manufacturing capacity. That is where our manufacturing platform, where we can use in the same rooms the same equipment to do all of the vaccine, is a great asset that we have. That's -- so if we build the manufacturing capacity at Moderna, to manage from a high-case scenario of demand, we should never be in a situation where we cannot supply the market and we limit people's access to important vaccines because we cannot make enough. And in that respect, we also destroy a lot of value because we cannot capture those sales. Because obviously the incremental sales of those products are pure EBIT -- additional income.

Then I would like to move to another topic that I've been reflecting a lot about as we are preparing for this day, which is if you go back to the slide of our first vaccine day, which was happening literally a few days or weeks after the WHO named SARS-CoV-2 as a global pandemic, in April 2020. If you look at where the company was at the time, it's quite remarkable to see where it was and where it is today. At the time, if you go back to the slides, we had 9 development programs in vaccines. We had, of course, no commercial product. We had never run a Phase III. And we had one program, the CMV vaccine, in Phase II; a few program in Phase I; and a few program in preclinical toxicology studies on their way to the clinic. That was Moderna's pipeline for our vaccines.

And if you look now at where we stand today in March of '22. Not only the pipeline has increased in size tremendously with 31 development program in vaccines. It has also advanced in a very material way towards commercialization; and of course, one commercial product, as we all know, Spikevax. We have now 4 program in Phase III; 9 program in Phase II; and many, many program in Phase I; and quite a number of program that will be in Phase I in the next weeks and months. So as you look at that and you think about it: Over the last 2 years, our team worked tirelessly to fight COVID-19; to get Spikevax, in 11 months, from a design on the computer to an authorized vaccine helping millions and tens of millions then hundreds of millions of people. And at the same time, look how the pipeline has increased in size and scope and has advanced.

So think about the next year, the next 2 years. Where are we going to be 2 years from now when we meet again for Moderna Vaccine Day in 2024? What is going to be the pipeline? How many products will be approved? How many product will be in Phase III? How big is it going to be given all the work happening right now in the labs, infectious disease team? They are working relentlessly because, as we saw in the introduction, there are vaccines available for around 10% of viruses that hurts human. Think about the opportunity that we have as a team, with our partners, to impact hundreds of million of people over the next years and decades. That's what Moderna is building, so I cannot wait to meet again with you in a year and in 2 year. And I think we're all going to be quite surprised.

So now let me turn to commercial. As I've said before, the pandemic has been for us a unique opportunity to build a strong commercial network that I don't think we have had the means to build without a Spikevax-type product. As you can see, in blue, those are the countries in which we established commercial presence with local Moderna team on the ground in 2021. What you see in pink is actually the countries that we announced that we're going to build subsidiaries this year. Our teams are currently incorporating Moderna entities in those countries and starting to hire new Moderna colleagues. What you see in orange is the countries where we have distributors for Moderna's product. And the other countries are supplied by, of course, as you know, our partnership with COVAX for low-income and middle-income countries where we do not have subsidiaries.

Now let me turn to manufacturing. So manufacturing, we keep on expanding our capacity for the future. As you can see on this slide, which kind of represent our current footprint that we are establishing or have established for drug substance, the mRNA in lipid: of course, here in Massachusetts and also in Switzerland for our partner Lonza. We are very pleased of a partnership with the Australian government which was announced earlier this week, with a new plant established that's going to build in Australia. You have heard recently of our decision to invest and build a plant in Kenya. And then we are continuing to have constructive discussion with the Canadian government to transform the MOU into a final contract. As I've said before, we're also discussing with quite a number of countries to build more plants, like Canada and Australia, to be able to provide a

unique, new business model but also an opportunity to protect people around the world. Because if you just look at the map today, we will have on several continents, North America, Europe, Africa -- and in the Pacific, [we'll have one other plant]. And I hope we will soon end up with [one other plants] in every continent.

Then if you look at the next slide. We also are preparing for future in many ways. The flexibility that the Moderna drug substance engine is going to have because we use the same process and the same raw material and the same machines is the ability to have a flexibility that's quite unique. At minus 70, we can store drug substance, the mRNA molecule forever.

So think about the flexibility we have compared to a traditional, let's say, respiratory vaccine manufacturer. [It was a] very intense period to prepare [for the fall and then as almost] several quarters with not a lot of things to do. Well, think about how Moderna can use that agility to [really dedicate] all of our manufacturing capacity for the important months ahead of the respiratory season in the North and in the South. And in the lower months, we can do drug substance for therapeutics or for vaccines like latent virus vaccines or vaccines that don't evolve too quickly so that we can store that drug substance and then we can fill it whenever we need it. And that's an extraordinary flexibility that will allow us to really manage whatever happens in term of demand and changes of demand, which is impossible to predict precisely, especially for products that are in Phase II or Phase III, which is one of the biggest issue pharmaceutical companies have. And Moderna will not have that issue.

The last piece that's important on this slide is the last bullet point, which as we've announced recently and we'll give more detail in coming quarters is the long-term partnership 10 and 15 years that we have done with Thermo Fisher for the U.S. and Rovi for fill-finish capacity. It was critical for us, as we prepare to build what I believe will be the first and best combination of respiratory vaccines with COVID, flu and RSV into the market, to have the ability to supply extremely large quantities of doses in the right product form. And we will give you more update at that time, but we have now signed and acquired that capacity at those 2 trusted partners.

Let me give you maybe a more of a short-term update because I know a lot of people are very interested in what's happening in the marketplace as we speak.

So let me start with low-income countries. I think there are some very good news here. It's that, thanks to the incredible work of all vaccine players around the world, in the U.S., in Europe but also, of course, in India and in China, we are now in a situation where there is an excess of vaccine supply since early first quarter of 2022. That's, of course, a great news for the world. What we still see in many countries, as you all know, that has been widely reported in the media is there is now an issue of last mile of vaccination in quite a large number of countries. And many people are helping to get more doses [in arms], but if you look at -- the world has changed tremendously.

For most of 2021, the world was clearly in a supply-constrained world for vaccines against COVID-19, but if you look at where we are now, since late last year, early this year, we [totally flipped] into an oversupply of vaccines. For example, recently, the African Union, after several delays of the agreement that we had together, has informed us recently that they do not need our vaccine; and have canceled the options for our vaccines given all of the gifts that have happened from the U.S. government, from China, from a lot of European countries and many other countries around the world and from, of course, the COVAX facility. Because of that, COVAX has also delayed some Q1 product shipment. COVAX did not exercise the option of 166 million in Q3. And COVAX still has an option for another 166 million in Q4 that expires April 1 that we currently estimate that there is a low likelihood that they will exercise, but of course, we will have to wait until that date to know because they have that right.

So what does that bring us? If you look at Spikevax commercial outlook in 2022: We have now, with the Japanese option that has been exercised for another 70 million doses, basically \$21 billion of signed APAs with upfront payment made to secure supply for a large number of countries or regions for distributors or through COVAX. Because of the Japanese options moving into signed APAs and the African Union and COVAX not exercising option, the current probabilized options, [as we look at] the risk-adjusted probability, is around \$0.5 billion.

We're still having quite a number of discussions with countries around the world, including about our bivalent vaccine 214 which many countries (inaudible) is the vaccine they want for fall of '22 season. They understand that waning is happening; and that this is going to be required, especially for people at high risk, to have a new booster. And we believe that, that new booster should be 214. Of course, we'll have, [like always], to wait for clinical data, but based on the fact that molecular biology doesn't cheat, we believe that 214 should be the best option to provide to countries around the world. And it's quite of a unique Moderna offering. As you know, the recombinant vaccine players do not have that option right now.

The adenovirus vaccines are not really used as much. And so I think we have a really unique opportunity to provide a very differentiated product that will help protect many, many lives.

I want to remind everybody, that has been reported in the media quite a lot, that at this stage there has not been any agreement signed with the U.S. government, so you will see no dollar assigned to signed APAs or to options. It's currently 0 in those numbers, as you can see. Given -- I'm sure we'll find a way [either for the] public market, for the U.S. government purchasing directly, or for the private market, but I don't see a world where we do not provide an important vaccine booster to the American people in the fall. And so that's another upside to those numbers obviously.

And now if I start to look at 2023. It's quite interesting that, as you can see on the list of countries that have already placed firm orders and made down payments for those orders -- that the countries that have already been at the leading front of thinking and protecting their population have already placed order for 2023, the U.K.; Canada; Taiwan; Kuwait; and this week, Switzerland. And we're in discussion with many countries because -- I am not aware of any public health experts, any infectious disease experts who thinks this virus is leaving the planet. We're going to have to live with COVID. And we're going to live with COVID like we live with flu, meaning if you are young, you might be -- after natural infection and/or [capital] vaccination, you might be okay for a while. You might get disease. You'll be fine, except if we have a variant, of course, that's much more severe. We think the [base] case scenario is what I described, if you had low risk, but if you are high risk, we believe with the data we have today that people are going to need an annual booster so we don't get severe disease. We don't get hospitalized and don't die.

And I think there's also a very large population who is not necessarily at high risk but who is going to want to get protected because they don't want to get sick. And they don't want to have close family members and friends and coworkers sick because of them. And I believe that a lot of people are going to want an annual booster, especially if it's combined with flu and RSV.

So now the other piece that I think is quite unique about how we are trying to innovate at Moderna is we have been thinking a lot of how do we set up unique partnership that you can do with mRNA technology but you cannot do with any other technology. And we've thought a lot about how do we set up a service or subscription business that has long horizon. And I'm really, really happy and very proud of what the team has achieved in partnership with the Australian government announced this week. This is 10-year strategic agreement for which the Australian government has committed, in exchange for us to build a plant on the Australian soil and we'll finance and that we're going to staff and run, that -- they, in exchange, have been willing to commit to a 10-year supply agreement for respiratory vaccines, which will allow us also to customize the vaccines for their need, working with their public health experts. We will choose with them which [strain of rubella] to protect people in Australia, not necessarily what the WHO is guessing that people will need to protect north or southern hemisphere of the planet; fully customize with them. We can add the components they want. And that's, I think, the power of this model. It's a win-win situation when we provide independence of supply on their national soil. We provide best-in-class technology and we provide customization. If there is a new strain in the middle of a winter, we will change it on the go with them because we will work with their regulator hand-in-hand.

We are having good discussions with Canada to make progress. Hopefully, we should be able to announce, I hope, soon the [finalization] of the agreement. And the teams are working with countries around the world, literally, to set up similar agreements. So if I had a magic wand, I would hope we will end up with having 5, 8, 10 agreements like this in the key countries of the world, where we have a 10-year subscription and service business model for pan-respiratory franchise. So I think that's one important innovation that Moderna is going to bring to market to improve, save lives.

The second one, which we have been thinking and dreaming about for quite a while. We never had the resources or the credibility to launch it, but I'm very, very pleased and proud of mRNA Access that was launched a couple of weeks ago as part of the CEPI U.K. big summit in London to prepare against the next pandemic or next outbreaks.

So what is the mRNA Access? As Stephen described it, it's a new design studio for mRNA where literally a scientist from any lab in the world, any region, any country, in an academic lab or in a government lab can access online exactly the same features that our scientists at Moderna can access for vaccine. They access exactly the Spikevax technology, the same lipid, the same manufacturing process, the same chemistry [for their mRNA]. They design their mRNA online from their lab in their country. They click [order]; a few weeks after, will get mRNA candidates in little vials arriving by FedEx in their lab. They run the work. And then if you have a good candidate, we will work with them to take those into the clinic.

You see on the list, as Stephen talked about it, but a few partners that have already signed up on the platform. What we want to do is to leverage the best minds in the world [to make the] best vaccines. We believe there's a very urgent need for the world to get vaccine against every virus that hurts human. That is our mission. It's our commitment to the world. And this platform is going to enable that, a bit like in the tech world when companies open their platforms for people to write code from around the world. You see incredible apps appearing. We believe we can do the same. Some vaccine that we'll bring to market will have been invented in our labs by our scientists, but I believe [dearly] that some vaccine that we will bring to market that will protect dozens, hundreds of human or people will have been developed in partnership with people around the world that are expert at the biology around a disease. Like for example, Institut Pasteur, on this slide, they have deep expertise on tuberculosis. The world deserves a better TB vaccine, and we're going to work with them and many others to find the best vaccine we can to fight TB.

So as you can see from this last example, there are many examples where we want you to expect more from Moderna. We believe we have a huge responsibility to this planet. We believe it's a unique moment for the company. We now know that Moderna's mRNA vaccine technology works safely in hundreds of millions of people.

For the last 10 years, we believe that will be the case that we didn't know. For the last 10 years, we were very constrained on capital because we are losing money, investing in the business every year. Now we are generating cash and want to put this cash to good use to change the world. A

good example is the manufacturing facility that we've announced in Kenya.

We're going to be building there with the local government. It's the ability to do country-specific pathogen, like I used the example in Australia a few minutes ago, is the ability to target population of the elderly, kids, pregnant women, teenager. We're going to be able to do a combination that makes less injection needed but very broad protection to targeted population.

We've committed, as Stephen described, to go after the 15 viruses that have been discussed for years by infectious disease experts as the viruses that could lead to the next outbreak of pandemic. Ebola, Zika, coronaviruses, flu. People have said that for years, but no pharmaceutical company of scale has taken the leadership to commit its technology, its talent and its capital to develop the biology, clinical and to take those candidates into the clinic, to understand what dose do we need for each of those family of viruses.

If we had known that for Moderna's platform, those 100 micrograms was a good dose from a primary series for SARS-CoV-2 or for MERS before that virus appeared, I believe we could have got directly into a Phase III, maybe a Phase II for it to get the regulator comfortable with a couple of hundred people of safety at that dose that we would have tried before for another coronavirus. And then been expanded that into a Phase III. That could have led to an authorization as early as July 2020.

Think how the pandemic will have looked different if we'd have vaccines available within 6 month-ish of the virus sequence being discovered. That would have changed because of the pandemic, that we would have literally saved millions of lives. And this is what we want to do as a company. We are committed. We're going to partner with labs around the world to find the best experts for each of those 15 viruses and bring the best biology we can, whatever mix of mRNA we need to do the right biology, to have high efficacy. We take those to the clinic to know what dose do we need. Those where we can run the Phase II we will, those where we won't be able to because we just don't have cases we will propose those programs, but be ready in case something happens to do what we think is right, to protect as many of you as we can. And I just spoke about MRNA access.

If you think about the next 5-year time frame, it's going to be very cool to see the amazing biology and vaccines that are going to come out of labs around the world.

So if you think about it, in the last couple of hours, we have only talked about vaccines. And by the way, we did not review the entire pipeline for lack of time. But as many of you know, if you look at Moderna, it's an incredible information medicine-based platform company. I'm more excited about the rare disease, the readout that we should have in the coming months. We have a peer program, an M&A program. I cannot wait to see the personalized cancer vaccine the cancer data that as we said, we should see in the Q4 time frame. And I cannot wait for scientists in the lab to keep expanding more modalities, more application of VMI. I cannot wait to take the CF program that is delivered into the lung via aerosol with our partner, Vertex, into the clinic. And to keep expanding the potential of this platform to help as many people as we can in the world.

As you know, since the beginning, our mission has been to use this technology, to deliver on this technology to help as many patients as we can. That is what has been driving us. Many of you have known us for 7, 8 years. Some of you have known us for a few months or a couple of years. But it has been the same thing that has driven us for all those years. And I can tell you, I have not been energized as much as I am about the company's future as I am today. And I can tell you it's the same with my colleagues. I have never worked as hard about for this company than I've ever done in the last 10 years. It's because today, I know Moderna's mRNA vaccine technology works in human extremely well.

I know they are only vaccine against around 10% of the viruses that hurt our families, our friends, our colleagues every day. And we have this unique once-in-a-lifetime opportunity to use this information medicine to help so many people around the world. And today, we have the financial power to invest, to do the best version that we can of Moderna.

So I want to thank my colleagues around the world. I want to thank all of our partners who make this possible. And I would like now to open the line for questions with my colleagues. Operator?

QUESTIONS AND ANSWERS

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

Thank you, Stephane. I will be the operator today and will moderate the Q&A session. Joining you Stephane is Stephen and Jackie from the Moderna team, and it is my pleasure to also welcome 2 of our KOL speakers, Dr. Ali Ellebedy; and Dr. Alberto Ascherio as well. We will take questions through 1:00 p.m. Eastern today. And our first question is coming from Salveen Richter from Goldman Sachs.

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

Will the go-forward dose be 25 micrograms just given the safety profile? And what type of trial is required for approval? And perhaps you could talk about the timing there. And then just secondly, given the vaccine efficacy for children against Omicron is relatively consistent with the 2 doses for adults, can you just speak to the intent to file with the 2 doses versus 3?

Stephen Hoge - Moderna, Inc. - President

Maybe I'll take a first stab at the first question, Salveen. I think I just caught the tail half of it, and that's around flu and the dose selection. And then maybe Jackie, I invite you to take the second one on our near-term plans for 1273.

So first, we're obviously very encouraged by the data that's consistent with superiority against the influenza A strains that we see. And you're right, you do see that at 25 micrograms. For some populations, you obviously see at 50 micrograms more clearly. We are still in the process of making a final dose selection, but I actually don't think that we've automatically chosen the 25 micrograms. And in a lot of ways, there are some things that would recommend the 50-microgram dose as a path forward.

In terms of the safety profile, we didn't see a difference in safety. I think you were referring to the reactogenicity, the acute reactogenicity solicited 7 days after, where you do see, as we said, about a twofold higher rate across both systemic -- principally systemic features but also local between the standard dose and the 1010 dose. And that was pretty much the same with 25-micrograms and 50 micrograms, which is why you might actually choose the higher GMTRs that we saw in some groups and some particular older groups with the 50-microgram dose.

Ultimately, once we make that decision, we'll communicate it. One of the things we're also going to be doing is obviously working -- engaging with regulators globally on understanding the path forward for registration of the flu program. Again, we think we have a chance at an enhanced vaccine here, one that we're quite proud of the fact that those GMTRs are actually higher than perhaps even some of the enhanced vaccines, if not all, against some of the strengths.

And so we're pretty excited to engage in those conversations. We will be informed by them. And as soon as we've made a final dose selection on what that -- for that Phase III study, we'll be sure to let you know. Jackie, do you want to take the pediatric question?

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

Absolutely. So yes, it's very busy times currently with respect to the pediatric program on 1273. So we are working actively with -- in discussions with regulatory agencies, and this is agencies worldwide to take those data that we've just discussed yesterday in the press release to worldwide regulatory filings.

In addition, in the U.S., we have also initiated a rolling submission for our 6211 file, which is at the 50-microgram dose that has been approved in Australia, Canada and some other countries. And then finally, the FDA has asked us to update our adolescent file at 100-microgram primary series with 6-month duration of safety data.

So we are preparing all of those submissions in parallel and looking to really complete them in the next month or so. So looking forward to the FDA's review and hopefully proceeding from that.

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

Thank you both. And our next question is coming from Gena Wang from Barclays.

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

Thank you for a comprehensive update. So I also have 2 questions. The first one, also regarding the flu Phase II 1010 update to date. Just wondering why you choose AFLURIA as comparator, instead of FLUAD or Fluzone HD. And also efficacy seems largely met the criteria for a stellar approval but safety, as you mentioned, seems worse or reactogenicity seen some of the worse than comparator. Where do you see your regulatory path here regarding accelerated approval or full approval?

My second question is regarding the KidCOVE data you reported yesterday. Do you think that the effective rate of 38% and 44% will be sufficient to support approval? And regarding 6 to 17 years labor expansion in the U.S., will you need a lower dose booster data for approval?

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

Stephen, do you want to take the flu question first?

Stephen Hoge - Moderna, Inc. - President

Sure. So Gena, thanks for the question. Again, we are pretty pleased by that higher GMTR ratios that we're seeing above the standard dose control. The reason for the standard dose control is much a scientific one as anything, which is the enhanced vaccines are not for use in -- they're not authorized for use in for 18-plus populations. And so it's wanting to have a consistent control as we look across age groups. And because we do want to look at 18-plus, we want to use the standard dose control that's commonly used in that population.

Then you also want to make sure that you have a consistent control from a scientific perspective as you then look at older populations so that you can infer the right ratios across. And in fact, in the publication that was shared by Raffael, that's actually kind of the norm about how people have looked at comparison with these GMT ratios. Particularly the enhanced vaccines have been looked at as a function of GMT ratios to a standard dose. And so it is both a regulatory path, it's also from a scientific perspective, the right way to look across age groups as we move forward. And that's really what drove the selection of AFLURIA for this first comparability study. Jackie, do you want to...

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

Sure. So now switching gears to talk about our flu efficacy data in the KidCOVE trial, which, as you mentioned, was approximately 40% when comparing in the Phase III primary definition. We actually are really encouraged by these vaccines for several reasons. I think the first is we've recently seen the publication from New York State looking at children who received the other mRNA vaccine, where basically no efficacy was seen in the Omicron surge. As we were conducting our study through the Omicron surge, we know that we were challenging our vaccines more than we've had previously, for example, in adolescents and children 6 to 11 who enrolled primarily during the Delta phase.

Our trial actually was powered on immunobridges. And we talked about immunobridging a few times. The idea was to incur effectiveness because we publish on the data correlating those neutralizing titers to efficacy. That really comes from the COVE trial. We challenge the vaccine by comparing only to the most immunogenic population, so those youngest, 18 to 25. And we met the primary endpoint for both age groups which we're also really encouraged by. And this has really played out in that secondary endpoint for efficacy.

Important note, it was a secondary endpoint so the study was not powered to show efficacy. Nonetheless, we were able to capture a sufficient number of cases to show an efficacy estimate that during the Omicron surge is really similar to what we observed in adults 18 years and above in the effectiveness study we have ongoing with Kaiser Permanente Southern California.

So Dr. Chang published on this data and the effectiveness was 40% or so, so really spot on with what we observed in these youngest children. And with a 95% confidence level that rolled out the value Zero, which means we've observed positive efficacy in this population. So based on the strength of these data, we will be moving forward to submit those data and are really confident in the 25-microgram dose being selected.

Stephen Hoge - Moderna, Inc. - President

Gena, if I might just also offer one other comment, supporting what Jackie said, is that really the data says the vaccine is doing the same for kids, at the dose levels we selected, as we're seeing for adults. And I think we're all comfortable with the benefit that's being provided even from 2 dose, which is considered a full vaccination series, in adults against the worst outcomes, hospitalization, certainly death, but even severe disease.

And at the end of the day, that's the objective we've been asked to meet by regulators, and we committed ourselves to meet, which is can we demonstrate a dose of the vaccine that provides the same benefit to children in this case, under the age of 6 that is provided to older adults? A not obvious implication of saying we want to evaluate, for instance, the third dose here, then you should ask the question about all other age groups, including adults as to whether or not you're going to start to think of it instead of a 2-dose series as a 3-dose series.

And I think that's a very complicated path to go down in the near term. We believe the benefit that we've been able to demonstrate scientifically here with immunogenicity and even the efficacy that is consistent with adults, gives us every reason to believe that there will be an ability to extend that to severe disease, hospitalization, all the outcomes that we desperately want to prevent which, although much rarer in children and therefore, hard to observe in a clinical trial, do in fact happen.

And as we all saw in the last Omicron surge, we need to do better and trying to prevent that. So we're confident moving forward with the filing, as Jackie said, and we think overall, the data is actually reassuring because it says we've got the right dose to replicate the strong results we've seen in adults.

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

We'll take our next question coming from Matthew Harrison at Morgan Stanley.

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

I guess 2 for me. So one, just first as you think about COVID heading into this winter season, if Congress and the U.S. government don't authorize a purchase, you obviously talked about the private market. Can you just speak a little bit about what you're doing in terms of preparing for that, whether it's contracting or otherwise in terms of being able to supply through the private market, if that's necessary?

And then secondly, just on the pan-coronavirus vaccine. Can you just talk a little bit about how quickly you think you can move ahead with that just given your obvious experience here with other coronaviruses? And then would you consider selling that as a single vaccine? Or should we think of that as a component that will be added to the pan-respiratory vaccine?

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

Great. Stephane, do you want to take the commercial question, please? And then Stephen can help with the human coronavirus vaccine.

Stephane Bancel - Moderna, Inc. - CEO & Director

Great. Yes, Matt. So indeed, we are doing all the works with our U.S. commercial team. Assuming that the U.S. government does not place an order, just to be ready because as you see, there's a lot of work that needs to happen. We were always planning that this will happen one day once we have BLA. And so the commercial team that we have been hiring over the last 2 years in staffing and spending a lot of time with already PBMs and the pharmacy chains and so on, is actually working assuming there is a scenario where there is no funding, by the U.S. government.

Of course, if the spending will obviously partner and collaborate with U.S. government. So we just want to be ready because we don't want to be in a world, obviously, where American don't get access to vaccines in the full.

Stephen Hoge - Moderna, Inc. - President

And Matt, thank you for the question on the pan-coronavirus vaccine. So I'd be careful what I say about timing because I wanted to go as fast as possible. But Jackie will kick me under the table if I overpromise here.

Look, we do have a lot of experience with coronaviruses. As you know, actually all the way back to MERS, but obviously, we've got a lot of experience with 1273. And we've shown the ability to move very fast into clinical trials even with bivalent vaccines through the COVID epidemic. In this case, we want to set up the right study. It's -- we're looking at 4 different viruses. But we will, in fact, evaluate it in combination, as I said, with Sars-CoV-2 to try and have a pan-coronavirus vaccine circulating human coronavirus vaccine, one that deals with all 5 of the strains that we think will be endemic.

The question of whether or not we develop it alone or in combination, it's a little bit of both, right? The answer for us, the benefit of our platform is that we can combine pathogens based on the epidemiology and ultimately addressing the unmet need that payers and health care systems feel. To the extent that it makes sense to combine the endemic coronaviruses in all 5 of them in the future into a single vaccine and not combine it with perhaps something like RSV or one of the other virus because the epidemiology doesn't line up, the frequency in which you'd want to inject it or alternatively the interest in payers who are paying for it, we would be able to adapt that combination of products.

And so we do feel that in the case of respiratory viruses, as we said before, it's really a syndrome. It's an unfortunate syndrome of waning immunity in older adults who have a weakened ability to develop rapid innate immune responses to rapidly mobilize their cell-mediated immunity in their memory. And so they find themselves at risk of any declines in their neutralizing antibody titers to prevent infection that those infections will break through the first 2 levels of immune defense and lead to more symptomatic disease and unfortunately, more severe disease. And that syndrome has many different viral actors in it.

And we do think as we age, and unfortunate reality is to become more dependent on that neutralizing immunity to protect us, and there will be benefits to providing that as a single injection seasonally across as many of those viral actors as possible. But we'll prove that out over time. And ultimately, we'll let the epidemiology decide it. So the short-term answer now is we will study it in both ways and ultimately let the unmet need or the benefit that we hope the vaccine will provide to determine which one we bring forward.

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

And our next question is coming from Tara Bancroft from Cowen.

Tara A. Bancroft - Cowen and Company, LLC, Research Division - VP

So I have 2, if I may, but -- the first is for mRNA-1283. I noticed there were more severe or higher-grade systemic adverse events relative to 1273. So I'm trying to understand why the refrigerator stable vaccine would be more reactogenic. I know it includes more targeted epitopes that elicit potentially stronger immune responses. But if that's so, why aren't titers also higher and mirroring reactogenicity like we saw with flu?

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

Jackie, do you -- or Stephen, do you want to start off on that? And then Jackie, please.

Stephen Hoge - Moderna, Inc. - President

Either way, I love good science questions. I think, look, from a scientific perspective, first and honest answer is we don't know. We've got to develop data and understand those things. I would also, from a scientific perspective, observe that the reactogenicity, it's hard to overread small numbers in some of these percentage graphs. And so we have seen things invert in subsequent studies. And until you get to a very large sample size, it's -- you don't want to overinterpret those things.

However, in the category of answering the question as asset face value, if you assume that was a case, look, there are other things that need to be measured. Many of them actually, Dr. Ellebedy and others have talked about, when you're thinking about what is the strength of the immune response, not just neutralizing titers in the neutralizing type of assay, but cell media immunity is an important other feature. And we've obviously seen strong T cell responses in our vaccine. So until we get that CMI and understand those differences, we don't actually know whether or not there is, in fact, a difference.

The important part for us, overall, is that the 10-microgram dose was already exceeding the titers of 1273. And I think we all know based on published data, 1273 has had the highest titers generally out there of any other vaccines, and that's because it's a 100-microgram dose.

And so we're already, in our opinion, off the scale to the right, and we actually -- that's why we're going to look at lower doses as we described today, 5 micrograms and under in that 1283 platform. And so we're kind of going the other direction already and not thinking about how we might go up in that dose level, but something from a scientific perspective, we'll be exploring through some of these other measures. Jackie, anything you would characterize differently there or add?

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

No, I think you covered it, Stephen. Thank you.

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

Okay. Our next question is coming from Andrew Galler from Wolfe Research.

Andrew Francis Galler - Wolfe Research, LLC - Research Analyst

Great. And just 2 for me as well, if I may. So do you see the potential for mRNA flu vaccines to differentiate from traditional flu vaccines on other immune measures besides the germinal centers? And there may be IgA induction as one of them? And then secondly, maybe for Dr. Ascherio, do you think an EBV vaccine that prevents mono? [Do you think] EBV will lead to lower MS incidents? Or will it be -- do you need to have a sterilizing immunity to prevent MS incidents?

Stephane Bancel - Moderna, Inc. - CEO & Director

Who do think, Lavina?

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

I'll ask Stephen to take the flu question and Dr. Ellebedy, if you have any thoughts on that as well, we welcome your thoughts. And then we'll turn it over to Dr. Ascherio for the EBV question.

Stephen Hoge - Moderna, Inc. - President

So the part of the question is, do we think there's a potential for it? We absolutely do. And we're excited about the high GMT ratios we're seeing. We're excited about the high efficacy our platform has shown in COVID space. And we do think, and I'll let -- invite Dr. Ellebedy to share his thoughts on it. We do think that there are reasons to believe that the platform can generate differentiated immunity.

The important thing to note, though, in all of this is that HAI titers, seroconversion rates, all those things are terrific. But we're going to have to prove efficacy with efficacy stakes. And so they provide confidence that we can go in that direction. They may be sufficient for accelerated approval as another questioner had asked. But we expect to have to demonstrate that we do think we will have the opportunity to demonstrate that with 1010 in their term. And that will ultimately be what decides.

The last thing I'd say about it is, we are not done with 1010. We think there are other ways to extend with mRNA pharmaco -- potential protective immunity by adding additional strains we talked about and adding antigens like neuroimmunities. So there's a lot more work. But in 1010 itself, we do think it already has that potential to be differentiated on efficacy, and we look forward to eventually studying them.

Ali Ellebedy

Thanks, Andrew, for the interesting question. I think having a strong germinal center can really have really different and many consequences. One of them is having a really persistent high systemic antibody levels, will eventually lead to having higher levels of (inaudible) sites. That's -- it's a very simple -- whether this is an IgG or IgA. This is a very simple concept of having a systemically higher level of antibodies will actually lead to high levels mucosal in any systemic immunization. So I think it's -- there is really -- there's obviously a lot to learn from that. We haven't really done this mRNA vaccination for a long time. So there's a lot of things to learn there. But yes, at this stage, I would say, in that assumption, I were willing to take. But yes, we will have higher because of antibodies.

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

Dr. Ascherio, do you want to take the EVB question, please?

Alberto Ascherio

Sure. So I think a vaccine that is not sterilizing, but preventive mononucleosis would most likely reduce the incidence of multiple sclerosis. We'll not completely prevent the disease, I believe. But based on the epidemiological data, considering that we'll achieve a reduction in viral load and the intensity of the immune response against EVB. I would expect it between 2 3-fold reduction in MS risk. But I have to say this is not based on data, it's just a guess of what will happen. It will depend on the property of the vaccine itself.

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

Okay. Our next question is coming from Ted Tenthoff from Piper Sandler.

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

Great day today, super informative, learned a lot, so much going on. I wanted to follow up on the last question with respect to the flu vaccine and understand better the timing towards licensure and sort of, firstly, with 110, but then really how you layer in the [Pental] and the 5 and 6 HA and then ultimately layering in the neuraminidase antigen. How do you kind of rectify all that? And when do you think we could anticipate those additional studies starting things?

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

Stephen, it sounds like you.

Stephen Hoge - Moderna, Inc. - President

Jackie is kicking me on to the table, don't overpromise. We're going to start them as soon as we can -- no, Jackie, I'll invite you in just a second maybe to comment. But the -- so first, we're moving forward 1010 because we feel actually the obligation to quickly bring forward this vaccine. We think it actually could provide a benefit. And we also -- we had recognized that one way or another, whether it's before an accelerated approval or after approval or the part of an approval, we have to demonstrate efficacy of this platform against influenza. And we actually want to know that ourselves.

So we selected 1010 as that first-generation product to move quickly towards those efficacy studies. I'm not going to commit to win, but we want to move very quickly towards those efficacy studies. So that we get to ask that question for ourselves and ultimately for public health officials including regulators. The benefit of 1010 will be, once we've established that efficacy for mRNA, which really truly should not be surprising, but we do have an obligation to demonstrate. Then we might be able to add features like the pentavalent or hexavalent HAs on a different standard, where we might demonstrate with neuraminidase or things like that.

It's all subject to regulators agreeing with that. But we do need to demonstrate first the platform does have efficacy before we could bring in those other entries. And neuraminidase is its own challenge because it's not something for which there is so much of a well-established path. And so we'll work with our regulators to first generate the early development data and then hopefully demonstrate the benefits of adding that in.

And over time, whether it's through clinical studies of efficacy or real-world effectiveness studies, we would also want to demonstrate that benefit obviously, to public health officials. And so it's really a question of when does it happen preapproval, postapproval and how do we add these pieces together. But we hope to demonstrate across all of these steps, either efficacy or effectiveness gains in the coming years, I will say. Jackie, again I said that you...

Unidentified Participant

I guess what further complicates it. I don't mean to cut you back -- I'm not sure if I was muted or not. But sorry, the -- just to add to that before Jackie turns in is obviously the complexity of layering in the combos, too. So like it can kind of envision maybe establishing efficacy with 110 first, taking that into a combination of -- in sort of advancing the flu and then also advancing on the combos, but I didn't need to interrupt Jackie but just to, kind of, layer that part of the question.

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

Actually, that is a really important nuance. And it's actually, I think, supplements what I wanted to say to begin with. So if this is the year of regulatory submissions for COVID-19, it's the year flu study starts. And so as Stephen was explaining, what we are intending to do. And we're currently in active discussions with regulatory agencies to understand what that pathway to licensure will look like for 1010. It may look different, by the way, in different countries. But that efficacy as a foundation is really important, not just to establish that this is a flu vaccine that can be put into the toolbox, but also to look at the relative efficacy to that seasonal flu vaccine to understand if this is going to behave like a seasonal flu vaccine, might just behave like an enhanced flu vaccine.

So layering that in, in the next quarter, we're actually starting our neuraminidase Phase I study. And I want to draw another parallel to COVID-19, and in this case, the pediatric trial. So we spent actually a good amount of time in [beast mode], really investigating different dose levels in different agents because we think that this platform may not require the same dose in every age group. And I would say that, that really translates to our strategy for layering in the neuraminidase and then later on, the hexavalent pentavalent.

It's important to get that Phase I study design right and really do your dose range being careful because that facilitates everything that comes afterwards. And as Stephen also mentioned, once we have foundational efficacy, there are options to potentially look at how we add in and layer in these other factors. But I think, first, we need to understand what dose of those factors and how they combine together before we would really take a licensure proposal to a regulatory agency and then watch the Phase III programs for those iterations on our flu vaccine.

Stephen Hoge - Moderna, Inc. - President

One other thought I had just building on -- or maybe this is on me to take the question, Ted. But building on what Jackie just said is that we -- we do think we're going to in many of these cases, RSV is another example, COVID is an example is behind us. We're going to go demonstrate the efficacy of the platform in that vaccine. You have to do that as foundational, right?

The question of then how you do the combinations is usually less about reestablishing that efficacy. It's just making sure that the different combinations you might pursue don't have any concern from a safety perspective and don't have any interference with each other in terms of an immunogenicity and performance perspective. In that sense, they tend to be -- they may be subject to regulatory discussions. They may be much smaller and easier to execute studies.

And so you'll see us in this strategy as we roll forward, consistently when we go establish the efficacy against the pathogen and then go confirm the safety and immunogenicity combinations. And we think that will probably allow us to look at many different combinations more flexibly as we go forward.

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

And our next question is coming from Cory Kasimov from JPMorgan.

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

Two questions for me as well. First is a follow-up on flu and just thinking about the future market. Can you talk about the potential commercial impact of higher levels of adverse reactions relative to established vaccines? Is this a point that your future competitors seem to be driving home, do you think potentially better efficacy is enough to overcome that?

And then secondly, on the RSV front, how do you look at potential duration of protection for your vaccine candidate? And how do you expect this to stack up versus others in development, such as GSK's adjuvant product, the protein vaccines or viral vector protein combos?

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

Great. Stephane, do you want to take the commercial question and what we're hearing from our customers?

Stephane Bancel - Moderna, Inc. - CEO & Director

Sure. Thank you, Cory. So I think as we discussed in the past, I think it will depend on the population you're looking at and how multiple value efficacy. And also if you look at the data of all our vaccine in the clinic, you tend to see lower -- at the same dose, lower reaction in the older cohort versus what you see in the younger. And that was Jackie was pointing exactly, we need to think about learning about the platform and what dose for different populations.

And so could you see a world where the dose that we are seeing is a good dose for people at high risk. And those people, because of the risk they incur, they are willing to potentially -- if they are still younger because there are people like high risk that are young, like not even to compromise (inaudible), they exist unfortunately. And then you have the older population who, if you look at all the data, even the 1273 Phase III by age group, you see consistently a different immune reaction. So that's the first point.

And I think as Jackie was saying, we can also think from a commercial standpoint to go at different doses for different age group of different population. And so as we've said many times, the discussions we're having with health care ministers and their teams, thanks to our COVID work and as we presented the pipeline and we talk about the data of a new product and the value of combination and compliance, we stay extremely energized by the possibility that we think we have to really change there in a very profound way.

Stephen Hoge - Moderna, Inc. - President

I might just -- the only thing I might offer from a truly scientific or clinical perspective on top of that is that we actually don't think that the current efficacy of the vaccines is sufficient. We are talking still about a top 10 killer in this country in latest CDC data. And for that reason, we think it's worth -- it's evaluating whether we can demonstrate higher efficacy. And then if it is, let's engage in that conversation about whether hopefully preventing more hospitalizations, more deaths is beneficial or not.

But we start from the -- maybe the premise of your question, which is that it's the efficacy of these vaccines may not be sufficient or at least there are patients or people with comorbidities or by age who may choose to do something that's more protective if we can demonstrate that. So that's what we're working to study. We have an obligation to generate that data. But the data that we have right now gives us reasons to believe whether it's on the platform side, whether it's the COVID experience or whether it's the 1010 GMTRs that we have a chance at that, and that's where we're moving forward.

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

And our next question is coming from Ellie Merle from UBS.

Eliana Rachel Merle - UBS Investment Bank, Research Division - Analyst

Just a quick one on your COVID and your perspective on the BA.2 subvariant. What are your thoughts on the implications of this BA.2 subvariant for vaccine efficacy such as from the bivalent or Omicron-specific booster? And then second, sort of how are you interpreting the data on hospitalizations and COVID rates given kind of the degree of potential incidental COVID hospitalization stays?

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

Stephen, do you want to start us on that question?

Stephen Hoge - Moderna, Inc. - President

Yes, I'll try to take both. So the -- first, on the -- how do we think about the BA.2. So there is actually a preprint data put out by our collaborators at NIH showing that for both BA.1, BA.2 and BA.3, the 3 subvariants of Omicron, the neutralizing titers that vaccination of 1273 provide are essentially equivalent. And so although that's again neutralizing titers, I think it's an evidence to suggest that although there are changes between the subvariants, they are not sufficient to change the new titer types, in the same way that Omicron changed the game versus Delta, for instance.

And secondly, I'd point to the real-world efficacy data affecting this data, for instance, out of the U.K. that the NHS has been publishing show -- and then essentially, the vaccine efficacy for the mRNA vaccines deployed in the U.K. are similar between the subvariant. So we're -- we currently don't believe that the BA.2 substrain requires a dramatic change to the vaccine, point one.

Point two, we do think the vaccines generally will benefit from being updated with Omicron-like antigens. And so our bivalent, as you mentioned, is after we've looked at all the data, we think the correct path forward. We are, by the way, also studying just an Omicron booster, the 529. But we believe that bivalent is the right answer for a very simple reason, which is the bivalent data we've shared previously and that which we have shows that if you add more antigens, you get slightly better durability at 6 months against those new antigens again -- and against other variants. It all fits with what Dr. Ellebedy was saying, which is the immune system can learn new tricks, but you have to actually teach it, and show it what it needs to learn on.

And so by providing the Omicron variant to germinal centers, what you will see maybe at day 29 is not much difference because there's a strong anamnestic memory response that's pretty good and cross protected. But what we have seen at day 180, which these seasons may last 6 months or a year, what we see at day 180 is higher neutralizing titers against the new antigens. And that fits, right? That's what the immune system is supposed to do. Give it a little more time, it gets even better.

And so we feel pretty strongly that the right answer scientifically is to advance that bivalent vaccine and then demonstrate either at 90 days or 180 days at the right time that we've been able to show that more durable response. Lavina, can you help remind me on the second part of the question?

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

Ellie, do you -- can you just repeat the second part of your question, please?

Eliana Rachel Merle - UBS Investment Bank, Research Division - Analyst

Just on incidental COVID hospitalization versus hospitalized due to COVID and how you're thinking about that and interpreting the data, particularly, I guess, in light of kind of the evolving debate around booster frequencies?

Stephen Hoge - Moderna, Inc. - President

Yes. It's also important -- so yes, there is clearly an evolving picture of what do we have to really be concerned about and how we characterize in hospitalizations.

The effectiveness data that we've seen some -- many governments put out does try to control for that when they look at hazard ratios, for instance, against hospitalization for those who are symptomatic. And there is a decline in hazard ratios, for instance, a worsening, I should say, it's a risk, but a worsening in hazardous for vaccinated people, even on things like measures like hospitalization. So when I look at that public health data, I think there is still something there, assuming those governments are doing the best they can to control for it.

Now all that said, there is going to be more incidental COVID-19 for sure. And the -- we have to be careful about looking at raw hospitalization numbers without that kind of public health narrative or independent model-based assessment that tries to control for some of those confounders. And so it is something that we have to be judicious about how we manage now.

Now right now, the challenges we're trying to interpret really short periods of time. I mean think about where we were a year ago today, we weren't -- we weren't even talking about Delta. It had not dramatically emerged as a threat, and we're -- that really became a primary concern in Northern Hemisphere in the summer months of this year. And then, of course, Omicron 3, 4 months later.

And so populations have been -- also been vaccinated, they've been boosted, and we've seen multiple waves of variants move through. I think the fact that we're even having the debate, and we're only several months out from many of these boosting situations, shows that actually there's going to be a risk of waning. And if we look at the things that project into the future, like neutralizing titers, it's not perfect, Dr Ellebedy talked about it, it's not perfect. But it's a thing that we can use. You do see that neutralizing titers will be back down to baseline levels in 8, 9 months post third dose.

That causes us to say, for those populations that are older, that are more dependent upon their neutralizing immunity to prevent the risk of a breakthrough infection exacerbation of underlying comorbid conditions, I think that's a population that we're going to need to make sure that we maintain high levels of neutralizing titers to keep them out of hospitals. And that's frankly not that different than flu. Frankly, not that different than a lot of respiratory viruses. And I think as we look forward, even before a variant -- a new variant that maybe has another level of immunoscape, we believe that another dose is going to be necessary.

The decision of when you do that, different governments are making different choices. And ultimately, we have to defer those public health officials. Obviously, the United Kingdom has been recommending a fourth dose in the spring and does expect to do something again in the fall. Other governments maybe make different decisions. We all don't know. And it's a question of whether or not we're trying to stay ahead of the problem or make sure that we can react quickly if a problem emerges.

So our obligations as a company is just we're going to bring forward the best boosters we can. We're going to generate all the data that we get asked to, to try and support public health decision-making. And our assumption is boosters will be necessary. A bivalent will provide a better view of the current circulating viruses, which will extend durability over time. And that's really what we're working around the clock on right now.

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

Great. So we're going to break our own rule and take our last question from Hartaj Singh from Oppenheimer.

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

Can you hear me? Sorry.

Stephen Hoge - Moderna, Inc. - President

There you are. Yes.

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

Yes, there you are. I have a specific question just on febrile seizure that you saw in that COPE study. Stephen, just isn't that pretty serious? And I know it was unwitnessed, how does that affect your application and possibly makes it to the label? And then my second question is maybe with the KOLs, you're sort of unpacking the mechanisms of vaccine protection immunity.

It's really fascinating how you're able to get deeper and deeper into that. Of course, you've got the money, now you've got the talent to go really get into it and collaborate. But could you talk a little bit about how you can -- this will help your vaccines become more specific you know what potential decreasing their reactogenicity going forward?

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

Great. Jackie, do you want to take the 1273 pediatric question?

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

So febrile seizures are really a consequence of fevers and higher children and also the rate of rise of temperature in higher children. Their biology, when they respond to infections, is just different than what happens in adults. Actually adults very rarely get fevers. And so when adults have fevers, it's something to worry about. Kids often get fevers and actually work quite well.

It's a side effect that we commonly see in vaccines, especially in the youngest children. And this really parallels the age at which children are most likely to have a febrile seizure. So the age range is really from about 6 months of age to 5 years of age with a peak of age 2. This particular patient who was a 1-year old is really right in the middle of that age range. So having the febrile seizure at the expected range. With -- child actually went to hospital was well upon coming into hospital and was subsequently discharged.

So typically children who have either severe or complex seizures would be hospitalized for observation. So that's sort of a proxy to say that once that child made it to the emergency room, they were already looking better. And then the next stage develops their rash, which can be suggestive of concomitant viral syndrome. So recall that this study was conducted during the Omicron surge, it was between November and February. So the time when we've seen any viral infections.

Not to actually minimize the febrile seizures and certainly, it's an event that we expect to continue to follow in the safety studies that we will be conducting post licensure or post authorization just as we have been doing in the other age groups. But pediatricians are actually quite experienced at coping with fever as a side effect of vaccination and also have very good tricks and tips to help families deal with fever in a way that minimizes the risk of febrile seizures.

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

And Stephen, on the last question?

Stephen Hoge - Moderna, Inc. - President

Sure. So I think the answer for us is we'll always want to explore the way we can lower dose and perhaps in certain populations that don't need as high an efficacy, whether we can be dose sparing. And we do believe, I personally believe that as we -- as and if we pursue lower doses, we'll lower reactogenicity.

If you look across the data even that we presented today, you see very different performance of different antigens, right? So 10 micrograms of the next-generation 1283 program generates high reactogenicity. It's like 100 micrograms of the 1273 program. We talked about the flu program, the 25 and 50 micrograms. But if you look at the RSV program in the same population, older adults, at say, 25 microgram, it's hard to distinguish the systemic reactogenicity from placebo in that study.

And I think it just highlights that this is broadly speaking, about not just a platform technology, it is also about the antigen, the population. It's also sometimes about the eccentricities of clinical research in smaller populations. But as we move into the thousands, some things might change and become more normal in distribution.

So we have an obligation to do a study all of that. And in younger adults, for instance, in flu, that may involve looking at a lower dose because the risk, the morbidity, and obviously, there's not much mortality, but the morbidity in that population, you might need a lower dose. You might benefit from a lower dose. And so we'll certainly be looking at a range of different things like that. But ultimately, we need data to guide us here, and that's what we'll be doing is developing clinical data.

I personally believe that a lot can be accomplished through exploring lower doses. We just want to do that sparingly. because as I said a moment ago with flu or as was our experience with COVID, there is a difference, and there is a real difference in terms of public health in terms of morbidity. And unfortunately, even a difference in mortality if you dose lower in some of these vaccines. And we actually want to make sure that we're making the right choice between that potential benefit and the reactogenicity or discomfort that people might feel immediately after vaccine.

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

Okay. Thank you, everyone, for this Q&A session. I'm going to now hand it over to Stephane for closing remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Great. Well, thank you so much all of you to participate in our 2022 Vaccine Day. We would like to thank the Moderna speakers, but more especially all of our outside guests. Thank you so much for joining us today. And the next 2 events scheduled are the Q1 call, obviously, and Science Day. We look forward to welcoming you on May 17. Have a great day. Thank you.

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