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MRNA.OQ - Moderna Inc COVID-19 Vaccine Update

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MRNA provided COVID-19 vaccine update.

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PRESENTATION

Operator

Good afternoon and welcome to Moderna's COVID-19 vaccine update. (Operator Instructions) Please be advised that this call is being recorded.

At this time, I'd like to turn the call over to Lavina Talukdar, Head of Investor Relations at Moderna. Please proceed.

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

Thank you, operator, and hello, everyone, and thank you for joining us on today's call to discuss new data points, including clinical data and analysis from our 1-year follow-up of our Phase III COVE study. You can access the press release issued this afternoon as well as the slides that we will be reviewing by going to the Investors section of our website.

On today's call are Stephane Bancel, our Chief Executive Officer; Stephen Hoge, our President; Paul Burton, our Chief Medical Officer; and Jacqueline Miller, Senior Vice President, Therapeutic Head of Infectious Diseases at Moderna.

Before we begin, please note that this conference call will include forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Please see Slide 2 of the accompanying presentation and our SEC filings for important risk factors that could cause our actual performance and results to differ materially from those expressed or implied in these forward-looking statements.

On Slide 3, please see the important indication and safety information for our COVID-19 vaccine, which has been authorized for emergency use in the United States and in many other countries around the world. Stephen will take us through the slide presentation and will be joined by Stephane, Paul and Jackie during the Q&A session.

With that, I will hand you over to Stephen.

Stephen Hoge - *Moderna, Inc. - President*

Thank you, Lavina. Good afternoon and good evening being, everyone. Thanks for spending the time with us. I'd like to cover a few topics today that were covered in the press release just sent out a half hour ago. First, we'd like to review some of the recent vaccine effectiveness data from the real world about the Moderna vaccine and against the Delta variant. Second, I'd like to provide an update on some recent data from our Phase III COVE study looking at breakthrough infections that might inform the use of booster dose as well as immunogenicity data on the vaccine booster. And then lastly, summarize our current thinking about a booster dose.

So first, summarizing some of the real-world evidence data. One of the papers that recently came out, for which Moderna participated, was a Kaiser Permanente Southern California prospective cohort study looking at real-world efficacy of the mRNA-1273 vaccine. That study matched 350,000 recipients of 2 doses of vaccine with 350,000 vaccinated individuals in Southern California and demonstrated real-world efficacy of 87% against COVID-19 and 96% against hospitalization, adding to the substantial amount of data demonstrating that the mRNA-1273's real-world effectiveness against all circulating variants of concern remains quite high. This has been posted to a preprint server and the references below.

Additionally, there was publication of data last week from the CDC showing the very high effectiveness of Moderna's COVID-19 vaccine in the United States, specifically during the period of Delta predominance in the United States. This data, summarized in the table below and in the reference at the bottom, examine the efficacy of the vaccine across 9 states really during the time in June, July and August when Delta surged in the United States. In fact, Delta, the Delta variant accounted for over 50% of the sequenced isolates in the medical facilities incorporated in this analysis. Moderna's COVID-19 vaccine remained effective in the face of that Delta surge through a median of approximately 3.5 months post completed vaccination. In fact, as highlighted in the red bottom, you could see vaccine efficacy from Moderna's mRNA-1273 that was 95% with a 95% confidence intervals, 92% to 97%. That was the highest vaccine efficacy across the different vaccines.

That real-world effectiveness is very encouraging and gives us confidence that as of today, the mRNA-1273 vaccine is really providing strong protection against all variants of concern, including Delta. But the big question we're all wrestling with right now scientifically is what does this look like in the future? Not today, but towards the end of this year, as many people across the world will start approaching their first anniversary of vaccination. Where will we be at about 1 year?

And the best way we can look at that is through our Phase III study. And that's because these -- the folks who participated in our Phase III study are among the earliest recipients of mRNA-1273. In fact, most of them were vaccinated over a year ago when they received their first dose in August and September of 2020.

We're able to look at the effectiveness of the vaccine because we can compare those that received vaccine and vaccination, as you can see here highlighted in blue, in the early 1273 group in August, September and October against those who are who were originally randomized to placebo and therefore, participate in the blinded study but yet EUA and crossover were then offered the vaccine and overwhelming we accepted it and were vaccinated in January and February this year. That creates a window, 2 different cohorts in the same study that we're following in our Phase III, many of whom have been vaccinated on median of about a year ago. And a second half who have been vaccinated in a median of about 7 months ago as we entered the period of time when Delta surged in the United States.

Now as we started to look at the increase in cases of Delta in our study, as you'll note at the bottom, the number of COVID-19 breakthrough cases among vaccine recipients surged quite significantly from single digits to the low double digits prior to June 2021, to 81 and 169 cases in July and August, respectively. So that large Delta surge was captured as vaccine breakthroughs between those 2 groups. And by comparing those groups and the relative risk of being in the 11- to 13-month cohort, approximately vaccinated a year ago, and those that are 6 to 8 months since their first vaccination during that surge, we can develop a view of what the impact of waning immunity between 1 year and approximately 6 to 7 months would be. And that data was summarized in the preprint that we posted today.

Now briefly, if you look at those 2 cohorts on the next slide, you'll see that at baseline heading into that risk window, they were largely the same. And so first, looking at the mRNA-1273e cohort on the left, you'll note that there were 14,700 participants. And in the original placebo group, call them mRNA-1273p here, there are 11,400 participants. The difference, approximately 3,000 participants, is made up of 2 main groups those that had come down with COVID-19 prior to vaccination in the placebo group, of which there was nearly 1,000 cases. And secondarily, those that decided to leave the study at the end of last year to pursue vaccination through another means and ones that were being notified that they were on placebo.

But if you compare the groups across the different demographic and risk factors, you'll note that they are still substantially the same, In fact, the age group, the age between the groups is similar at 51, 52.

The risk stratification for COVID-19, which is in that third row there is nearly the same, with roughly 50% to 60% of folks in the 18 to 65 and not at-risk category, 16% to 17% that are below the age of 65 but at risk of severe disease because of comorbidities or occupational factors and about 25% over the age 65. In fact, across all the demographic factors and risk factors, there is no substantial difference between these cohorts, which allows us to confidently compare between the groups.

Next slide. So here are the summary of the difference in cases and incident rates we've observed at the at-risk window, again, between July 1 and August 27 of this year when Delta was surging. Again, you're looking at 2 different cohorts here. The mRNA-1273 original vaccination group is the first set of columns. And then to the, in the middle set of columns, those that received placebo. So the more recent vaccinees. And again, I'll just remind you that the more distant group was vaccinated on average about a year ago and the more recent group is about 6 months since completion of their primary series.

Looking first at all cases of COVID-19, that first highlighted blue row, you'll note there were 162 cases in our original vaccination group of about a year ago, and that equates to a rate of about 77 per 1,000 person-years. That compares with about 88 cases in the more recent vaccination group of about the last 6 months and a rate of 49 per 1,000 person years. That actually leads to a significant relative reduction in risk. In fact, if you look at the difference in the reduction in risk observed with being less than 6 months or 6 months -- approximately 6 months from your last dose of vaccine, there's a 36% reduction in risk. And the 95% confidence levels, as you can see, are significant with a range of 17% to 51%.

That is also true if you look at the 18 to 65 population underneath, and there's a numerical trend in the same direction, although numbers are substantially lower for the 65 and over population.

Now as we go down, you'll also note that the numbers become smaller, but the trends generally hold. And so first, looking at severe disease, you'll see that there are 13 cases of severe disease in the folks vaccinated last year, comparing with 6 cases of severe disease in those more recently vaccinated. That's approximately a twofold increase or a 46% reduction in risk, and perhaps a trend toward -- numerical trends towards slightly higher numbers as you move to the 65-plus population with 6 cases of severe disease in the older vaccination group and only 2 cases in the more recent group.

Now on the next slide, I'd like to provide a little bit more of an overview of the severity that we're seeing across this group for context, again, all present in the manuscript. So if you look at overall per protocol COVID-19 cases, there were 250. And as you'll know, there was approximately a 2:1 ratio between those that were early versus more recently vaccinated.

In terms of severe cases, I just covered a moment ago, 13 and 6, and again, directionally approximately a 2:1 ratio. There were 3 instances of hospitalization in those, and all 3 were in the cohort that was vaccinated over a year ago. And there were 2 tragic cases of death from COVID-19, both present in those vaccinated in the early cohort, then median follow-up of 13 months.

So overall, severe disease was present in this population and accounted in total for about 7.6% of the cases. All severe diseases, when present, had over 5 symptoms for COVID-19 with a range of 5 to 13 symptoms. The majority of cases did meet the protocol criteria based on low O2 sat with a range of 88% to 93%, so hypoxia.

And if you look along the severe cases, there was a trend towards greater severity in the earlier vaccination cohort, and as you'll note in the preprint, severe cases we're seeing across all age groups, including in participants who do not have any known risk factors for severe COVID-19.

So how do we estimate what that impact would look like? And what does this quantification from the Phase III study suggests to us?

So first, the Phase III study does give us a direct approximation or estimate of the impact of waning immunity on protection against COVID-19 and allows us to estimate what the increased risk of COVID-19 breakthrough will be as we look forward into the future, which is the question that we're all wrestling with right now.

If we estimate the impact of being greater than 7 months from your last dose in the United States, which is comparison to those 2 groups, and we extrapolate again within the United States where the study was conducted, across the 66 million adults in the U.S. who received 1273, you'd expect approximately 28 cases per 1,000 person-years of exposure. That would be about 1.9 million cases per year of exposure or if you divide by 12 months, that's an incremental 150,000 cases of COVID-19 per month that are related to what we would characterize as waning immunity. Again, all of the participants in both arms of the study were exposed, we believe, to the same risk in this country, having previously randomized geographically across the country, and they were all exposed during the time between July 1 and August 27 when the majority of the sequences and cases were Delta variant of concern.

So what does that mean for us as we look forward? Now this is only 1 estimate and 1 way to look at it, but we do believe that this means as you look towards the fall and winter in the United States, we would estimate the impact of waning immunity at a minimum to be approximately 600 -- additional 600,000 new cases of COVID-19. And as I covered a moment ago, although they're not the low, we would expect some of those cases to be severe and unfortunately, some might result in hospitalization and death. This begins to form the impetus for why we think a booster vaccine is necessary.

So in the last few slides, I'll try and summarize how we're viewing the booster in the context of this data and the clinical data that we have on a 50-micron booster.

So first, we do believe a third dose booster will reduce the risk of COVID-19 based on the data I just presented. Illustratively here, we're showing a view of what immunity might look like. And again, strength of immunity in the study as we conducted it. This is a surrogate for neutralizing titers perhaps, but it is not actually neutralized titers. This is an illustrative representation. But nonetheless, you get the idea of what we believe we've now measured in the Phase III study, which is we have a group of participants who are vaccinated approximately a year ago and a second group who were vaccinated at the early part of 2021, approximately 8 months ago. Both, we believe, achieved similar levels of immunity given the similar profiles, and we would have seen some waning in that immunity over time. And what we're able to do today is to take a snapshot in July and August of this year, as denoted by the #1 here, and say, what's the impact of that difference in the level of immunity that was achieved as a function of time, as a function of waning.

And what we now know is that there is a significant difference between those that were 8 or 13 months from their last dose of vaccine. And we believe that, that's approximately equivalent to 150,000 potential incremental cases of COVID-19 per month in the United States as a result of waning immunity. It's not the only breakthrough infections that are happening, but it is the Delta measured by that month.

Now that becomes something we hope to try and address with a booster vaccine, which would boost that immunity back up, hopefully, to levels that are more like where we were immediately following vaccination.

Now on this slide, I'm sharing again some data that has been previously presented at our R&D day, showing neutralizing titers following the 50-microgram booster that we've filed with regulators for mRNA-1273.

Just quickly to orient you to the data that's on the slide. All of the data here has been done in the clinically validated NIH assays for, which we are very grateful for their help, and it is the data that covers both our Phase III study on the left-hand side and immune cohort and our Phase II Booster study, which was recently completed, filed with the FDA.

Now first is the Phase III COVE study. 1 month post-vaccination, as you can see, the geometric mean titers in that cohort, 1 month after vaccination, was approximately 1,000 or 1081 with a very nice and tight 95% confidence interval. That's the bar that we want to get back to or perhaps slightly exceed, but get back to that bar to make sure that we address the question of waning immunity because that is ultimately what we believe fell away.

As you'll note in the Phase II portion, we did have pre-boost titers, and again, this has previously been presented, but 6 to 8 months after people have been vaccinated, those titers had waned substantially, down to approximately 126. And that was responded very well to boosting. And as Jackie presented a week ago, a post-boost titer in that same booster study, 50 micrograms of 1273 as a dose 3, increased titers in all participants up to a level that was significantly higher than the Phase III benchmark that we set ourselves in fact, titers of 1893. And if you just look at the 65-plus

sub-cohort within those roughly 300 people, 76 of them were 65-plus. And you see again the titers were significantly above the Phase III benchmark, even including younger healthy adults in that Phase III benchmark, reaching titers of 1762. So we do believe that a 50-microgram dose not only achieved the objective of getting to the same level of protection that you had prior to waning immunity but actually significantly exceeds that by a factor of 1.7.

So on the next slide, if I bring us back to that illustrative picture, what we think that means is that a booster dose given today will increase the strength of that immunity, not just to levels that you had to the left of the chart, but the levels that are significantly above it, maybe perhaps 1.7-fold above it. And we know that a 50-microgram dose will be able to do that. That should counteract, at a minimum, the waning immunity. And we believe, this will reduce COVID-19 cases to an even greater extent than is measured by the waning immunity in -- as noted by number 1. How much greater? We can't say. We believe there will be some benefits but it's -- but it is not currently possible to give a specific answer on that number, but we believe it will be better.

But that's not the only advantage of boosting. So on the next slide, we also believe that a third dose of mRNA-1273 has a chance that it will -- of extending, significantly extending immunity throughout much of next year as we seek to end the pandemic. And it has been well just demonstrated both in our prior work, including with the CMV vaccine, mRNA-1647, as well as in other vaccines that a delayed booster does help refine the immune response and actually can lead to a different curve for waning immunity. So longer, more durable protection. And we do not currently have any data on what that would look like. We are going to be collecting it through our Phase III study, including those that just recently received their 50-microgram booster in Phase II, but also Phase III by continuing to study -- in the value of any boosters. And we hope over time, we'll be able to add evidence that there's more durable immunity following that third dose.

So overall, while we think that there is a clear benefit to the vaccine right now and continued evidence of waning immunities we've quantified as a moment ago, we do think that there are additional benefits that can emerge with a second dose, both by increasing titers significantly above the level seen in Phase III and by perhaps extending the durability of immunity.

So with that, I'd like to turn it over to the operator and invite any questions from any of you about the data we've covered today or our focused review on boosters.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from the line of Salveen Richter from Goldman Sachs.

Unidentified Analyst

This is Elizabeth on for Salveen. So in light of your data, the real-world data that's been emerging over the past few months now and ahead of the FDA meeting this Friday, what do you view as the key outstanding debates around the timing of booster administration? So how long after the primary series the boost is given and around the use outside of immunocompromised individuals?

Stephen Hoge - *Moderna, Inc. - President*

Thank you for the question. It's a great one. And it's one that really, I'd say, is only partially directed to Moderna because they're -- at the end of the day, the deployment of intervention is like a booster, in the pandemic, really should be decisions made by public health officials, including the CDC and FDA. That said, the questions that we have or the position that we have as a company is we do think there is building evidence already, for instance, from a Phase III study I just presented here, that there is a benefit to be had from boosting and not just boosting those that are immunocompromised.

We already have a third dose for immunocompromised population to help them get to the highest levels of immunity, get to the same levels of immunity, we would hope as we saw with healthy people. But instead actually adding 50 micrograms to help get everybody else who may be 6 months or later from their vaccine booster back to the level of immunity they had immediately following vaccination.

We think that's prudent this year because there is still so much circulation of SARS-CoV-2 virus, particularly the Delta variant that's happening right now. The pandemic is not over, that we're all going to be exposed to it repeatedly. And we think the risk of waning immunity is particularly high, the risk of that breakthrough.

Now we happen to think that the time for doing that is too early rather than too late. You would rather not be too close on this thing. And so from our perspective, the data we have right now shows an obvious potential benefit at about 6 months after your primary series, 6, 7 months, give or take.

And so our filings and requests with regulators have been to consider amending the authorizations to allow a 50-microgram dose 3, approximately 6 months after completing a primary series. And we think the data today supports that. Now the decision of whether or not that actually happens and then if it is recommended for broad use is not one for Moderna to make. That really rests with public health officials, but we're doing our best to make sure they have the data and the tools in hand if they choose to deploy it in that way.

Operator

Our next question comes from the line of Matthew Harrison from Morgan Stanley.

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

Stephen, I'm wondering if you can just talk more broadly about, I guess, risk benefit. I think when I read the Lancet editorial, I think there was a focus also on risk of a third dose. So maybe what data have you collected more broadly around safety and reatogenicity from a third dose? And how do you think about risk benefit in that context?

Stephen Hoge - *Moderna, Inc. - President*

Right. Well, I'll maybe take a first crack at the clinical development data. And if I missed anything, I'm sure Jackie will fill in, but then I'll ask Paul to chime in because there's just so much more data that's emerged from the real world on safety and efficacy, that's probably the best place to answer the question.

So first, on our clinical trials. We have continued to see a safety and tolerability profile of a third dose booster that is consistent with the second dose of our vaccine, which has generally been very well tolerated. And we have now quite a lot of experience from our clinical trials on that third dose. And as you all know and we all will recognize, fortunately, these vaccines have been really well tolerated in mRNA vaccines generally. And therefore, the adverse events that we're now talking about are exceedingly rare in the -- you count them per million doses delivered and not something we will ever really be able to see effectively in clinical studies. And that's where we have to defer to public health officials, and I'll now invite Paul come in and sort of summarize our perspective on the recent data there.

Paul Burton - *Moderna, Inc. - Chief Medical Officer*

Yes, absolutely. Thank you. I think there's a couple of important studies to think about. One is we know the data by Victoria Hall recently in New England Journal, where they actually randomized people, immunocompromised individuals having undergone organ transplantation to that third dose and then able to carefully assess them. And we see there a robust safety profile consistent, as Stephen says, with the larger populations that we've studied. So that's, I think, very comforting, very reassuring. And last week as well, we saw published in JAMA by Klein and colleagues, a very

nice analysis, 6 million people, 11 million doses looking -- using the vaccine safety data link versus a network here run by the CDC to be able to look at cases and carefully adjudicate them and look at them.

23 different safety endpoints were identified, prespecified, criteria for statistical significance were defined. Not one of those characteristics was met across all of those different 23 safety endpoints. So in the conclusion, I think, we have, based on the available data is that this is a very safe and effective vaccine, And with the available data we have in those other settings that Stephen mentioned, I think we would expect the same to be seen in the booster setting as well.

Stephen Hoge - *Moderna, Inc. - President*

Thanks, Paul.

Operator

Our next question comes from the line of Michael Yee from Jefferies. Michael Yee, you might have your phone on mute. We're still not hearing you. Should we move on to our next questioner?

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

Yes, please.

Operator

Our next question comes from the line of Gena Wang from Barclays.

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

So I have 2 questions. First is, given Pfizer seems show less effective in terms of durability and they proposed 6 months, do you think it will be longer phase will be required for your booster strategy, i.e., longer than 6 months?

And then second question is, do you expect adcomm for your boost regimen? We know that we will have one this Friday, but do you also expect one for your booster strategy, the regimen? And then quickly, when should we expect full approval of the vaccine?

Stephen Hoge - *Moderna, Inc. - President*

Great. Thank you, Gena, for all 3 questions. I'll try and take a first crack and then invite others to see if I miss anything. I don't think I could transcribe all 3. So first one on Pfizer's lower observed effectiveness in the CDC literature and elsewhere, I think we're probably not as guided by the fact that Pfizer has lower effectiveness and therefore, is boosting at 6 months. I think what we're guided by is we have great effectiveness right now in the face of Delta, but we do not want it to wane. And if anything, we think the Phase III data suggests to us that the last, the first 6 or 8 months are great, but you can't count on that being stable out to a year and beyond.

And so that is really what guides us to sit there and say 6 months is the right time. At the end of the day, our goal is to maintain our high effectiveness, which in the CDC data, was 92%, 95%, not wait until we fall to a lower effectiveness like the 77% or 80% that we reported in Pfizer. We would argue that is too late to be boosting and addressing waning immunity.

The question on -- a couple of regulatory questions, and I'll of course, say that I have to defer on all of these matters to the FDA. As far as whether or not there will be an Advisory Committee for mRNA-1273, we do not have any guidance on that. We'll, of course, be happy to participate in one if the FDA deems that necessary.

It is important to note that we are still proceeding under a slightly different regulatory framework than Pfizer. So we are still operating under an Emergency Use Authorization, although we have completed our BLA filing, as you noted in your last question. And this will be an EUA amendment as opposed to -- in Pfizer's case, they're doing a full SBLA, and so it's quite logical that the FDA may be viewing the obligations of those 2 differently. But of course, we'd be happy to proceed in any way we are asked.

On the question of when you expect authorization -- or sorry, full approval with our BLA. We completed the filing, as everybody knows, in August, towards the end of August. And we are actively working constructively with the FDA as we are with any global regulator to try and answer all of their questions and make sure they have the information they need. We do not have any guidance or insight into what that time would be. And I suspect they would say the same, which is that they want to make sure they do all the correct work. But I know that our regulatory partners at the FDA are working as hard or harder than we all are.

They have an incredible amount on their plate right now. And I know they are working around the clock, and we're very grateful for all that effort and the engagement that we've seen around the BLA filing. So I'm optimistic it will happen quickly, but we recognize there are a lot of things happening right now.

Operator

Our next question comes from the line of Geoff Meacham from Bank of America.

Alec Warren Stranahan - *BofA Securities, Research Division - Associate*

This is Alec on for Geoff. First, in your illustrative example, what is the minimum value of the Y axis or the strength of immunity? Just trying to get a sense as to your view on the timing of when immunity from the initial vaccination course is effectively depleted. I'm assuming you don't think it's as early as this fall or winter. And then can you just remind us for the supply agreements currently in the U.S., I believe, it's somewhere near 500 million and whether you think this would cover the third dose booster given the current rate of uptake or if an additional agreement would be needed.

Stephen Hoge - *Moderna, Inc. - President*

Great. Thank you, Alec. I'm going to go to Stephane in a second on the manufacturing and commercial question. But first, on the illustrative graph, it is exactly that, illustrative. And so I think you capture a fair feature of the cartoon that we didn't mean to represent, which is we don't think it will go to 0 this fall or winter, for sure. And so please don't take the cartoon to suggest that.

In fact, if you look at the data, in the Phase III publication that we just posted in the preprint, you see very strong protection still, we believe, even in those that are a year out from vaccination. And so please let me be clear, the valuable thing somebody can do, we can do to end the pandemic is vaccinate the unvaccinated. Even without a booster, that provides a dramatic benefit, and it looks durable despite the waning, it still looks quite substantial out to a year.

So -- and the question is, is there a benefit over and above that protection that you have from that original vaccination, and when does that benefit start to become clear and what is the magnitude of that? And I think that's where we're trying to follow these 2 cohorts and anticipate that question.

3 months ago, the answer was no, there wasn't a benefit because there weren't a lot of breakthrough cases. And you'd sit there and say, "Look, if people cross the 9-month threshold, there was no real obvious advantage here," but 2 things happened. Delta emerged, and that was a dramatic change in the transmissibility of that virus and therefore, much more exposures, and then the second thing that happened is we played the clock

forward in another 3 months. And by the time we got to about 12 months, on that original vaccination cohort, you start to see and view Delta, you start to see the emergence of a significant difference in the rate of those cases. I believe that if you play that plot forward, you should expect that to become even more significant over time.

Now I don't know how much more significant. But if we imagine that there are going to be additional surges of infections through the fall as people go back to school and as we all move indoors during the winter fall/winter season, which are respiratory virus seasons, that we're going to see continued transmission, continued infection and that waning immunity, if not addressed, would become a more significant concern. It will -- I would hope never go to 0 level of protection. And so your question of what the origin is, I don't know. It was an illustrative picture. But it's fair to say there's still some protection at that point. We are mainly focused on the difference between the 2 groups, and that was what we're trying to illustrate here. But thank you for the part of the question.

Stephane, do you want to take the question on the -- on whether we would need another agreement and supply?

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

Sure. Thanks, Stephen. So Alex, I think if you look at where we are, as you know, since around May in the U.S., we've had more vaccines than people wanting to be vaccinated. Thankfully vaccinators spike in the summer of vaccine use. And the 200 million doses to be delivered, 100 million in Q4 and 100 million in Q1 should cover, I would guess, most of the booster needs. That is why I believe the U.S. government has exercised those last options in the contracts set up in September 2020 to be able to provide boosters.

We should not forget that it's a bit of a complex picture because on the one hand, you have also adolescents and kids that have to be vaccinated as well with prime series. In reality, that is very hard to monitor and model for us. It is how much wastage is happening right now. If you think about it, the U.S. FDA has so far filed those already for immunocompromised. But as you can imagine, if immunocompromised person goes to hospitals or to a CVS today, I have no idea how many doses in that are going to be used. And I remind everybody, we have currently 10 dose per vial. And so the wastage amount right now is tough to quantify, which is why we believe that once we get the BLA, there's going to be some opportunity to be able to provide a product market with the right product to be able to protect every American that needs to be protected. Back to you.

Stephen Hoge - *Moderna, Inc. - President*

Thank you.

Operator

Our next question comes from the line of Michael Yee from Jefferies.

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

I had a 2-part question. What I see here is that you're saying that there is reduced efficacy between the 2 different arms based on the timing of vaccination. I think that's clearly outlined there by 36%. My question is what do you believe the VE or vaccine efficacy rate is versus a unvaccinated cohort. And I think that's what people are trying to struggle with because even though it might be reduced efficacy, it's still very high efficacy. And I think that, that's what people are trying to struggle with. So question 1 is, what do you think that is? Maybe the Mayo Clinic addressed that data?

And then number two is, how do you address the idea of this political discussion around just the idea that everyone just wants to prevent severe -- and hospitalizations versus actual infections because I feel like that's actually the issue that's preventing people from being more on board with this.

Stephen Hoge - *Moderna, Inc. - President*

Michael, thank you for both those questions. I'm going to take a stab at the first one and maybe invite Paul to offer his perspective as well from the real-world evidence side because this question of what is the relative efficacy of the vaccine right now as it wanes is very hard to answer in clinical trials. And particularly in our Phase III study, we do not have that answer because we no longer have a placebo group. And so what we can talk about here is the 36% reduction in the risk of having a breakthrough case, but a 36% reduction if it's 95%, that could be very different than if it's 70% efficacy, which is your point. And it's very hard for us to know what a reasonable control group would be here. And therefore, there is 2 sides to that coin.

One is that there's perhaps even greater benefit to boosting than is quantified by a number like the 1 we're talking about today. But it's very, very difficult absent real-world evidence to answer. I might invite that -- do you want to Paul, do you want to take a stab at what the real-world evidence might suggest for us in terms of that exactly.

Paul Burton - *Moderna, Inc. - Chief Medical Officer*

Yes. Thanks, Michael. So look, I think another important paper is from Qatar, a paper by Patrick Tang, where they actually are able to look at people unvaccinated and then without Moderna vaccine and other mRNA vaccines. And what they see when you get into July is in the face of Delta, and they actually genotype cases for Delta, we see vaccine efficacy going down, effectiveness going down to maybe 75%.

So the Mayo paper, which you mentioned as well, clearly shows that we're in the maybe 85% realm. But in Qatar, exactly as you say, in face of Delta, we're at maybe 70%, 75%. So if you take a third cut from that, you can see that you're getting into the sort of 50% to 60%. So that really underpins our recommendation for the booster and the timing. We have to be somewhat pragmatic. We know that 3 months ago, there were only 13,000 people hospitalized. In this country today, there's 91,000. And so we have to have a pragmatic approach to timing that is going to protect people as much as possible and really protect the health care systems here in the U.S. and around the world.

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

So I think it's the idea of trying to get a range of that and not knowing. And then my second question, which you might want to address, which is would people just feel like it's preventing severe hospitalizations and still probably prevents infection, so let's just wait?

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

So Michael, this is Jackie Miller from the development group. And I guess you're asking a very insightful question, but I want to emphasize that even in real-world evidence, we're never going to be able to get back to the world where we have placebo-controlled trials. And placebo-controlled trial is really the only way to answer the question you're asking. Why is that? Because an -- unvaccinated people are actually very different than vaccinated people. When you choose to enter a clinical trial, you're randomized, but when you choose to be vaccinated in the real world, that often comes with a number of very different behaviors.

So for example, attitudes towards masking and congregating in large groups inside shopping malls and the like. So the point I'm trying to make is that, yes, we still see very high effectiveness in vaccinated versus unvaccinated people. And that should be reassuring to everyone and a good reason to get vaccinated if you haven't already done so. But it's not also entirely reassuring in terms of waning persistence and the complex interplay with the emergence of Delta because we know that individuals who are unvaccinated are already engaging in higher risk behaviors.

Amongst the vaccinated populations, we're starting to see a difference, and what component of that is long-term antibody persistence, what component of that is the emergence of Delta, which is a much more highly infectious variant, it is really difficult to tease out, But nonetheless, maybe to emphasize your final point, certainly, vaccination is the best way to prevent severe disease. We believe that additional vaccinations, especially for people who may have been vaccinated at the beginning of the vaccination program in the U.S., so in particular, the elderly, people

with other kinds of high-risk conditions that may not be covered by the current immunocompromised mandate, we believe they would benefit from additional vaccination.

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

I hope the FDA understands as well.

Stephen Hoge - *Moderna, Inc. - President*

Yes, just a closing thought on the political question, Michael, because it's a great one is I think we're all trying to figure out, are we okay with COVID-19, right? From a societal disruption perspective, from a health care and morbidity perspective, even from a risk of mortality perspective, and let alone the economic perspective because we all -- those of us with family members that are either at high risk or those of us with kids have all had to live with the disruption of risk of COVID-19, what it means for our lives.

And so I think there's an aspect of this debate, which is playing out in real time, which is COVID-19 all of a sudden acceptable? From a company perspective, from a product development perspective, our answer is no. Our goal with a product is to prevent COVID-19. And so that was the original case definition that was in our study, and it was obviously very successful to date with 1273. And we think we need to continue to provide evidence for how the product can do that, how it can prevent symptomatic COVID-19 that meets the criteria in the study, and that's where we think a third dose is necessary.

If the public health debate moves off of that, shows, "No now we accept the disruption economic, social or health care otherwise around it," that's not for us to decide as a company, that's really besides that. But it's definitely not clear to me personally that we are yet ready to just accept an incremental 0.5 million cases of COVID-19 and the impact that it will have on our society over the next 3 months, let alone the ability of people to travel, see family for Thanksgiving, all things we'd like to do.

So I personally hope we are aggressive in trying to suppress as much COVID-19 as possible while the pandemic is raging because I think it's for our collective benefit.

Operator

Our next question comes from the line of Joseph Stringer from Needham & Company.

Joseph Robert Stringer - *Needham & Company, LLC, Research Division - Associate*

My question is sort of related to a previous question. But just in terms of sort of the appetite, that based on your extensive clinical experience and talking to clinicians and patients and physicians and the like, and KOLs in the field. What's sort of the temperature and the appetite regardless of what the regulatory outcome is for the booster shot -- for patients getting that booster shot?

Paul Burton - *Moderna, Inc. - Chief Medical Officer*

Thanks, Joseph, it's Paul. Maybe I can just start. I mean, look, one thing we have seen this week is in the United Kingdom, where the JCVI recommended with the partnership with MHRA there to the government, which was endorsed, to bring out the booster shot and indeed the 50-microgram dose of the Moderna vaccine both in the homologous and heterologous boosting setting. I think that speaks to the sentiment of physicians around the world. We see in other geographies as well that there is a certain fear going into winter.

Governments want to protect their health care systems, to keep beds open, to keep functioning, and they know that waning immunity will be a barrier to that. It will be a hurdle to do that. So I think there is well-balanced caution about what to do with waning immunity and that a realization that boosting is a way to protect patients and to protect systems.

Operator

Our final question for today comes from the line of Mani Foroohar from SBV Leerink.

Unidentified Analyst

This is Rick on for Mani. So I just wanted to touch on the development of the various specific boosters. Will the authorization of the 1273 booster changed the way the company is currently thinking about the development of the Delta-specific booster? And also, would you anticipate that the availability of 1273 booster would affect either the pathway to authorization for the variant in either how the trials are conducted or how regulators would look at the data?

Stephen Hoge - *Moderna, Inc. - President*

Great. I'll try and take that, Rick, and then invite Jackie to come in if I miss anything. So thank you for the questions. So first, on a very specific booster. Our strategy remains, we believe that a multivalent booster is the best way to plan for the future. When it comes to the Delta-specific booster, the good news is we think that the data we have so far on the prototype vaccine mRNA-1273 is that we're going to do well against Delta. And that's both real-world evidence data, but also immunogenicity data from the same, including the paper that was published today in Nature.

And so we are confident that the prototype vaccine works against Delta. We're advancing a Delta booster candidate in the clinic as we speak to make sure that we have it if it's necessary. We don't think it's going to be necessary. But we do believe that continued expansion of our very boosters is important, and we think that it's mostly about anticipating where the virus goes next. And so for us, that is a combination booster called 213, which is a beta Delta combination. We think it will cover all of the mutations across Beta, Gamma and Delta that actually keep us up at night and not because of the mono variant version of that. But because we think over time, there's a risk that all of the things that made Delta so good at infecting people could show up in a Beta- or Gamma-like string, which is very good at hiding from our immune system.

So a combination of transmissibility mutations and immune escape mutations. And the only way we can anticipate what that might look like we take the things that keep us up at night that scare us about the current variant is when we combine them in a booster. And so that's our 213 program. do expect that to progress fastly quickly this fall, and we would hope to have that available early next year, if necessary, broadly, although we hope it's never necessary. But if some new very scary variant emerged, that could be used for that. So we are committed to continue to bring this forward.

On the question of regulatory path. In general, the path for these boosters is related to immunogenicity and safety studies and so bridging immunogenicity studies, the FDA and others have put out guidance of what that needs to look like. And those do not require thousands of people, it's more like hundreds to demonstrate that you can provide neutralized protection against COVID variants of concern if they were to emerge. And that allows an opportunity for us to develop in smaller numbers and -- point one. And point two, I would offer is that not all countries are going to choose boosting, as Paul just described, the U.K. has already made those recommendations and move din that direction, including for 1273.

Maybe the U.S. will as well, but those are countries that are on the leading-edge of the first round of vaccination, and there are going to still be countries that maybe are going to be looking for boosters and have proven opportunities for development of novel booster candidates throughout perhaps most of the next year. So we don't think we're foreclosed and we don't think it's a huge risk if boosters are broadly made available in those countries that are currently 6 to 12 months from vaccination.

Jackie, anything you'd add to that?

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

Yes. Thanks, Stephen. I think you really covered most of it. I guess the one other thing I would say is that just building on what you said about we're not sure if these boosters would be needed or not. I felt a lot in the last year that we are fighting a war against this virus in the pandemic. And it's really -- the best weapon in that war is clinical information, clinical data. And so even if the Delta variant, hopefully, actually begins to retract as boosters get implemented, we still will have learned from this clinical development program. We will have learned about cross-protection and the reproducibility of being able to generate neutralizing responses against multiple variants.

We'll have learned about our ability to combine different sequences in the same vaccine candidate, and that really contributes to the overall strategy for combination respiratory vaccine. And we will have learned more about dosing and administration and longer-term shelf life. So I think for all of these reasons, our continued clinical development program is really central to our strategy in the COVID-19 program.

Stephen Hoge - *Moderna, Inc. - President*

Thank you, Jackie.

Operator

Thank you. And this does conclude the question-and-answer session of today's program. I'd like to hand the program back to Stephen Hoge for any further remarks.

Stephen Hoge - *Moderna, Inc. - President*

Well, thank you all for taking the time to speak to us today and discuss this important data. We continue to believe that the vaccine, our vaccine mRNA-1273 has been a really important tool in combating the pandemic and the real world evidence supports it. But as we talked about today, we think there are reasons to be cautiously concerned about the future through the winter season and boosting might be necessary for many populations, and that's where we expect or hope we will go in the near future.

With that, thank you for the time. Thank you for speaking to us, and operator we'll end the call.

Operator

Thank you, and thank you, ladies and gentlemen, for your participation in today's conference. This does conclude the program. You may now disconnect. Good day.