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OPEN SESSION

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This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: All right. Good morning and welcome to the 169th meeting of the Vaccines and Related Biological Products Advisory Committee. I'm Mike Kawczynski, and I will be managing today's activities. You will see me pop in here and there over time to assist some of our presenters just in case they have any technical issues. Keep in mind this is a live event, so we do anticipate that things should go well. But every once in a while, if we do hit a technical glitch, we may have an unexpected temporary pause just to get that addressed, so with that being said, I'm going to hand this meeting over to our chair, Dr. Arnold Monto. Dr. Monto, are you ready?

DR. ARNOLD MONTO: I am ready.

MR. MICHAEL KAWCZYNSKI: All right. Take it away.

DR. ARNOLD MONTO: I'd like to add my welcome, Mike, to the 169th meeting of the Vaccines and Related Biological Products Advisory Committee. This is a two-

day meeting, and the topic for today is to meet in open session to discuss the EUA of the Moderna COVID-19 mRNA vaccine for the administration of a booster dose following completion of the primary series. So that is our voting topic for the day. We are going to have other discussion topics, so it's going to be a very busy meeting. And I'm going to, as usual, try to keep us on schedule because we need to get done because we have another day awaiting us tomorrow. So, having welcomed you -- do you hear me, Mike, because my phone's been beeping?

MR. MICHAEL KAWCZYNSKI: Yeah, we hear you.

DR. ARNOLD MONTO: What I would like very much now is to turn the meeting over to our designated federal officer, Prabha Atreya, who will give the roll call, go around for introductions of the Committee and handle the housekeeping items that we always have to start the meeting with. Over to you, Prabha.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Mike, can you all hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can. You can go ahead and turn your camera on too if you'd like.

DR. PRABHAKARA ATREYA: Yes. Okay. Thank you, Dr. Monto. Thank you, Mike. Good morning, everyone. This is Dr. Prabha Atreya, and it is my great honor to serve as the Designated Federal Officer, that is DFO, for today's 169th Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the Committee I would like to welcome everyone for today's virtual meeting.

As Dr. Monto mentioned before the topic for today's meeting is to discuss in open session the emergency use authorization of the Moderna Texas Incorporation's COVID-19 mRNA vaccine for the administration of a booster dose following completion

of the primary series to individuals 18 years of age and older.

Today's meeting and the topic were announced in the federal register notice on October 7th, 2021. I would like to introduce and acknowledge the excellent contributions of the staff in my division and the great team that I had in preparing for this meeting. Ms. Kathleen Hayes is my co-DFO, providing excellent support in all aspects of preparing for and conducting this meeting. Other staff who have been contributing significantly are Ms. Monique Hill, Ms. Karen Thomas, and Ms. Christina Vert who also provided excellent administrative support.

I would also like to express our sincere appreciation to Mike Kawczynski in facilitating today's meeting. Also kudos to many FDA staff working hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous VRBPAC meetings on the COVID topics. Please direct any press or media questions for today's meeting to the FDA Office of Media, which is at FDAOMA, one

word, @fda.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles and Erica Denham.

We will begin today's meeting by taking the formal roll call for the Committee members and temporary members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name. And then when finished, you can turn off your camera so we can proceed to the next person. Please see the member roster slides in which we will begin with the chair. Dr. Arnold Monto, can we please start with you? Thank you.

DR. ARNOLD MONTO: Yes, thank you, Prabha. I'm Arnold Monto. I am a professor of epidemiology and public health at the University of Michigan School of Public Health, and I've had a long experience in vaccines, respiratory disease prevention at the University of Michigan. Back to you, Prabha.

DR. PRABHAKARA ATREYA: Thank you. Dr. Cohn.

DR. AMANDA COHN: Good morning, everyone. I'm Dr. Amanda Cohn. I'm a pediatrician at the Centers for Disease Control and Prevention with expertise in

vaccine-preventable disease and vaccine policy.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning, everyone. My name is Archana Chatterjee. I am a pediatric infectious diseases specialist. I'm also the dean of Chicago Medical School and vice president for Medical Affairs at Rosalind Franklin University. My area of expertise is in vaccines.

DR. PRABHAKARA ATREYA: Thank you so much. Next Dr. Meissner. Cody, we can't hear you.

DR. CODY MEISSNER: Thank you, Prabha. Thank you, Mike. My name's Cody Meissner. I'm a professor of pediatric infectious disease at Tufts Children's Hospital in Boston.

DR. PRABHAKARA ATREYA: Thank you. Next slide, please. Dr. Gans.

DR. HAYLEY GANS: Good morning, everybody. I'm Dr. Hayley Gans, pediatric infectious disease at Stanford University, and my area of expertise (audio skip) vaccines of children and adults with normal

immune (audio skip).

DR. PRABHAKARA ATREYA: Thank you, Dr. Gans. Dr. Kurilla next.

DR. MICHAEL KURILLA: Good morning. Michael Kurilla. I'm the director of the Division of Clinical Innovation at the National Center for Advancing Translational Sciences within the National Institutes of Health. I'm a pathologist by training. My expertise is in infectious diseases and vaccine development.

DR. PRABHAKARA ATREYA: Thank you, Dr. Kurilla. Next, Dr. Paul Offit.

DR. PAUL OFFIT: Hi. I'm Paul Offit. I am a professor of pediatrics in the Division of Infectious Disease at Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. And my interest is in the area of vaccines and vaccine safety. Thank you.

DR. PRABHAKARA ATREYA: Dr. Annunziato.

DR. PAUL ANNUNZIATO: Good morning. I'm Paula Annunziato. I lead global critical vaccine development

at Merck, and I'm here today as the non-voting industry representative.

DR. PRABHAKARA ATREYA: Thank you, Paula. Next, Dr. Pergam.

DR. STEVEN PERGAM: Hello, everyone. I'm Steve Pergam. I'm an associate professor at Fred Hutchison Cancer Research Center in Seattle, Washington, and the University of Washington. And my expertise is in infectious disease in immunocompromised patients.

DR. PRABHAKARA ATREYA: Thank you, Dr. Pergam. Next, Dr. Fuller. We're introducing our temporary voting members. Dr. Fuller.

DR. OVETA FULLER: Good morning. I'm Dr. Oveta Fuller. I'm an associate professor of microbiology and immunology at the University of Michigan Medical School and also faculty in the STEM initiative of the African Studies Center. And I'm a virologist by training as well as implementation science in the community.

DR. PRABHAKARA ATREYA: Thank you, Dr. Fuller.

Next, Dr. Rubin.

DR. ERIC RUBIN: Hi. I'm Eric Rubin. I'm an infectious disease physician. I'm at the Harvard TH Chan School of Public Health, Brigham and Women's Hospital, and the *Journal of Medicine*.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Hildreth.

DR. JAMES HILDRETH: Good morning. I'm James Hildreth. I'm the professor of medicine and president and CEO of Meharry Medical College. I'm in immunology by training, and I started out in neuro system respond to virus infections. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Hildreth. Next Dr. Hawkins.

DR. RANDY HAWKINS: Good morning. Dr. Randy Hawkins, position in private practice, internal medicine and pulmonary medicine. Charles Drew University. I'm the consumer representative.

DR. PRABHAKARA ATREYA: Thank you. Mike, can we have the next slide, please?

DR. JEANNETTE LEE: Good morning. My name is

Jeannette Lee. I'm a professor of biostatistics and a member of the Winthrop P. Rockefeller Cancer Institute at the University Arkansas for Medical Sciences, and my area is biostatistics in clinical trials. Thank you.

DR. PRABHAKARA ATREYA: I lost connection, so can we go to the next slide, please?

DR. MARK SAWYER: Good morning. This is Mark Sawyer. I'm a professor of pediatrics and a pediatric infectious disease specialist at University of California, San Diego, and Rady Children's Hospital San Diego. My area of expertise is in vaccines.

DR. PRABHAKARA ATREYA: Thank you, Dr. Sawyer. Dr. Nelson.

DR. MICHAEL NELSON: Hello, I'm Dr. Michael Nelson. I'm professor of medicine at the University of Virginia and Chief of the Asthma, Allergy and Immunology Division there. I'm also President of the American Board of Allergy and Immunology. My interest and work in vaccines centers on adverse effects and originated during my military career at Walter Reed.

DR. PRABHAKARA ATREYA: Thank you, Dr. Nelson.

Last but not least Dr. Melinda Wharton.

DR. MELINDA WHARTON: Good morning. I'm Melinda Wharton. I'm an adult infectious disease physician by training, and I serve as the Associate Director for Vaccine Policy at the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you, Dr. Wharton. We have a total of 19 voting and 1 non-voting members today, and I will now proceed with the reading of the conflicts of interest statement for the public record.

MS. KATHLEEN HAYES: Dr. Atreya, we have a couple other people to introduce.

DR. PRABHAKARA ATREYA: I'm sorry. Okay. Thank you. Dr. Levy. We can't hear you.

MR. MICHAEL KAWCZYNSKI: Dr. Levy, are you muted on the top of the screen. Go ahead and --

DR. OFER LEVY: Good morning, everyone. My name is Ofer Levy. I'm a physician scientist who directs the Precision Vaccines Program at Boston

Children's Hospital, and I'm a professor of pediatrics at Harvard Medical School.

DR. PRABHAKARA ATREYA: Thank you, Dr. Levy. Dr. Patrick Moore.

DR. PATRICK MOORE: Good morning. I'm Pat Moore. I'm at the University of Pittsburgh Cancer Center. I'm a professor here. My expertise is in molecular biology and epidemiology, and I specifically study epidemics as well as new human cancer viruses.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Perlman.

DR. STANLEY PERLMAN: My camera's not turning on, so I don't know why that is. But I'm Dr. Stanley Perlman. I'm at the University of Iowa in the Department of Microbiology and Immunology and a pediatric infectious diseases specialist, and my expertise is in coronaviruses.

DR. PRABHAKARA ATREYA: Thank you. All right. Today we're going to be joined by Dr. Peter Marks who's going to make a presentation also later after the FDA introductions. Dr. Marks, do you want to introduce

yourself and thank the Committee?

DR. PETER MARKS: Hi, I'm Peter Marks, Director of Center for Biologics. Thanks.

DR. PRABHAKARA ATREYA: Thank you. I think now I will proceed to reading of the conflicts of interest statement for the public record.

The Food and Drug Administration is convening today virtually October 14, 2021, the 169th Meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Dr. Arnold Monto is serving as the acting chair for today's meeting.

Today on October 14th, 2021, under Topic I, the Committee will meet in open session to discuss the emergency use authorization, EUA, of Moderna Texas Incorporation's COVID mRNA vaccine for the administration of a booster dose following completion of the primary series to individuals 18 years of age and older. The topic is determined to be a particular matter involving specific parties. With the exception of the industry representative members, all standing

and temporary voting members of the VRBPAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subjected to federal Conflicts of Interest laws and regulation.

The following information on the status of this Committee's compliance with federal Ethics and Conflict of Interest laws including, but not limited to, 18 USC Section 208 is being provided to participants in today's meeting and to the public. Related to this discussion at this meeting, all members, regular government employees and special government employees, and consultants of this Committee have been screened for potential financial conflicts of interest of their own; as well as those imputed to them including those of their spouse or minor children; and, for the purposes of 18 U.S. Code 208, their employer. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements -- or CRADAs -- teaching, speaking, writing, patents and

royalties, and their primary employment. These may include interests that are current or under negotiation.

FDA has determined that all members of this Advisory Committee, both regular and temporary members, are in compliance with the Federal Ethics and Conflict of Interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and/or regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by the Committee members and consultants, there have been one conflict of interest waiver issued under 18 U.S. Code 208 in connection with

this meeting.

We have the following consultants serving as temporary voting members: Dr. Oveta Fuller, Dr. Randy Hawkins, Dr. James Hildreth, Dr. Jeannette Lee, Dr. Ofer Levy, Dr. Arnold Monto, Dr. Patrick Moore, Dr. Michael Nelson, Dr. Stanley Perlman, Dr. Eric Rubin, Dr. Mark Sawyer, and Dr. Melinda Wharton. Among these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure.

Dr. Paula Annunziato of Merck will serve as our industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as only non-voting members of the Committee. Industry representatives act on the behalf of all regulated industry and bring general industry perspective to the Committee. Industry representative on this Committee is not screened and does not participate in any closed sessions we have and do not have voting privileges.

Dr. Randy Hawkins is serving as the temporary consumer representative for this Committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

The guest speakers for this meeting today are Dr. Sharon Alroy-Preis, Director of Public Health Services at the Ministry of Health located in Jerusalem, Israel; Dr. Ron Milo, a professor of Plant and Environmental Sciences Department at the Charles and Louis Gartner and a professional chair at the Weizmann Institute of Science in Rehovot, Israel.

Disclosure of conflicts of interest for speakers and guest speakers follow applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships they may have with any affiliated firm, its products and, if known, its direct competitors.

We would like to remind standing and temporary

members that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record.

This concludes my reading of the Conflicts of Interest statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. Arnold Monto. Dr. Monto, take it away. Thank you.

DR. ARNOLD MONTO: Thank you, Prabha. We got through this very promptly, so we're right on time. To start the meeting and to tell us about the roadmap today, I'd like to introduce again the director of the center, Dr. Peter Marks, who will give us the introduction of the topic. Dr. Marks.

WELCOME REMARKS

DR. PETER MARKS: Thanks very much, Dr. Monto.

Good day. I'd like to welcome you to this 169th meeting of the Vaccines and Related Biologic Products Advisory Committee meeting. First, I do want to take a moment to thank our staff, the sponsors, and our Advisory Committee members for devoting the time for considering the important topics at hand today.

Our theme of today's meeting is focused on the topic of the use of additional doses of the authorized or approved COVID-19 vaccines to boost immunity in order to prevent adverse outcomes from COVID-19. We'll hear updates on the results on the effectiveness and safety of the deployment of the booster vaccines in Israel. We'll consider the issue of boosters for the Moderna and Janssen or Johnson and Johnson vaccine, and we'll discuss the results of a study in which a booster from different manufacturers were given to individuals who had received different primary series for their initial vaccination. If I can have the next slide.

The spectrum of COVID-19 ranges for asymptomatic infection to death, and in between these is a range of infection ranging from mild to severe,

including severe disease requiring hospitalization. Vaccination is most important for preventing severe outcomes from SARS-coronavirus-2 infection, such as hospitalization and death. However, in considering the value of vaccination one may also need to consider the potential comorbidity from mild to moderate infection such as blood clots and long COVID-19. In this regard, we now know from recently published studies that vaccinated individuals can develop long COVID-19 if they experience breakthrough COVID-19 infection of any severity. These issues may need to be considered in discussions of the value of booster vaccinations.

The next few slides -- if I can have the next slide -- show the relative preservation of effectiveness of the vaccine over time. Most of the evidence is based on neutralizing antibody titers or real-world evidence on symptomatic infection, and the data I'll show you comes from real-world evidence. But there are other data as well. Separating waning effectiveness from reduced effectiveness against the variants, such as the Delta variant, can be

challenging, and what you'll see on all of these slides is that the vaccines are still very effective against serious outcomes such as hospitalization. So, on the right of each of these slides, you'll see the hospitalizations, and, on the left, you'll see the overall infections. If I can have the next slide.

So here for the Pfizer-BioNTech vaccine, you can see that over time there was still relative preservation of the effectiveness of the vaccine against preventing hospitalization. Yet there seems to be a decrease over the course of time against overall COVID-19 that was observed, and that occurs across the various age groups. There's a suggestion from some studies that it may happen most in older individuals. If I can have the next slide.

A similar trend is seen with the Moderna vaccine. Here, things are reversed when you're looking at this, but, on the right, you see, again, the flat orange line at the bottom shows that hospitalization remains an event that is well prevented by the vaccine, whereas there is a somewhat trend of that orange line

upwards showing that there seems to be some waning of protection against the overall observed COVID-19. If we can go to the next slide.

Similarly, here -- now reversing again, you can see here that on the right hospitalization from COVID-19 with the Janssen vaccine is something that is relatively prevented and that efficacy is relatively preserved over time. And then, for overall infections on the left, how you can see that the unvaccinated curve in orange and the vaccinated in blue. And the blue does seem to drop off some over time. So the final slide.

Just to summarize here, we'll be talking about booster vaccination today, but it's important to remember that the vaccine still provides strong protection against serious outcomes, especially for younger age groups. I didn't show those data, but some of that will be shown subsequently. The vaccine effectiveness against mild and moderate disease does appear to wane over time for the different vaccines, and we do need to account for the fact that mild to

moderate COVID-19 can be associated with adverse outcomes such as blood clots and long COVID-19, even in those who have breakthrough infections after vaccination.

But it's important not to forget as we move forward that facilitating higher primary coverage of the entire vaccine eligible population with the initial series of vaccination should still be a key priority.

I just thank you today and for today and tomorrow. We greatly appreciate the input that this Advisory Committee will provide. Thank you again.

DR. ARNOLD MONTO: Thank you, Dr. Marks. Next, we are going to be hearing from Dr. Sudhakar Agnihothram -- excuse me for murdering your name -- who is going to present from the Division of Vaccines and Related Products Applications, from OVRR. He's going to give us the background for the day's activities.

MODERNA COVID-19 VACCINE APPLICATION FOR EMERGENCY USE AUTHORIZATION OF A BOOSTER DOSE

DR. SUDHAKAR AGNIHOTHRAM: Thanks, Dr. Monto. Can you hear me, see me, and then see the slides?

DR. ARNOLD MONTO: We can see you and hear you very well.

DR. SUDHAKAR AGNIHOTHRAM: Okay. Thanks very much. Good morning, everyone. I'm Sudhakar Agnihothram from Division of Vaccines and Related Products Applications, OVRR, CBER, FDA, and today I'll be talking to you about Moderna COVID-19 vaccine application for emergency use authorization of a booster dose.

Here is the outline of my talk. I'll start with the description of Moderna COVID-19 vaccine and EUA request for a booster dose. Then, I'll discuss the considerations for emergency use authorization of a COVID-19 vaccine booster dose, and I'll be talking about COVID-19 vaccines available for use in the United States. Then, I'll be presenting the overview of today's agenda. That will follow with my presentation of the voting question and the discussion question for the Committee.

Please note that the part of my presentation pertaining to the second and the third bullet also applies to the Advisory Committee discussion tomorrow and is relevant for tomorrow's AC discussion.

The Phase 1 trial of Moderna COVID-19 vaccines started in February of 2020, and Moderna COVID-19 vaccine was authorized for use under emergency use on December 18, 2020. Moderna COVID-19 vaccine is indicated for active administration to prevent COVID-19 caused by SARS-coronavirus-2 in individuals 18 years of age and older. Regarding the dosing regimen, Moderna COVID-19 vaccine is administered as two doses one month apart. The third dose for administration appears one month after the second dose, was authorized on August 12, 2021, for use in certain immunocompromised individuals. Each 0.5 mL dose of Moderna COVID-19 vaccine contains 100 micrograms of the nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2 (Wuhan strain) formulated in lipids.

Regarding the Moderna COVID-19 vaccine booster dose amendment, the amendment was submitted to the EUA

on September 3rd, 2021. Moderna aligned their proposed indication with the population that was authorized for the Pfizer-BioNTech booster dose and the proposed use of booster does for Moderna COVID-19 vaccine under the EUA is a 50-microgram dose, 0.25 mL volume, to be administered at least six months after completing a primary series to individuals 65 years of age and older, 18 through 64 years of age at high risk of severe COVID-19, and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19. The clinical package in the amendment includes safety and immunogenicity data from 171 clinical trial participants who received 50-microgram booster dose of Moderna COVID-19 vaccine approximately six months after completing the Moderna COVID-19 vaccine two-dose series, which is 100 micrograms each.

Pertaining to the rationale for the need of COVID-19 booster dose, the emergence of the highly transmissible Delta variant of SARS-CoV-2 has led to

considerations of the potential need for booster doses for fully vaccinated individuals. Data from post-authorization effectiveness studies conducted suggest that the currently U.S. authorized or license vaccines remain effective in protecting against severe disease. However, some data suggest that effectiveness may be waning against mild disease and against severe disease in elderly individuals. Concerns have been raised that declining neutralizing antibody titers or reduced effectiveness against symptomatic disease may herald significant declines in effectiveness against severe disease.

Talking about the emergency use authorization, FDA may issue an emergency use authorization of an unapproved medical product following an EUA declaration, if the following statutory requirements are met: the agent referred to in the EUA declaration can cause a serious or life-threatening disease or condition; the medical product may be effective to prevent, diagnose, or treat the serious or life-threatening condition caused by the agent; the known

and potential benefits of the product outweigh the known and potential risks of the protect; and then, if no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition pervades.

I will now be talking about the COVID-19 vaccines available for use in the U.S. Pfizer-BioNTech COVID-19 vaccine, or COMIRNATY, is licensed for use as a two-dose primary series in individuals greater than or equal to 16 years of age. Pfizer-BioNTech COVID-19 vaccine is available under EUA as a two-dose primary series in individuals greater than or equal to 12 years of age, and a third primary series dose is available under EUA for use in certain immunocompromised individuals.

The booster dose of Pfizer-BioNTech COVID-19 vaccine is available for use at least six months after completion of the primary series in individuals greater than or equal to 65 years of age, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age whose

frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.

The Moderna COVID-19 vaccine is available under the EUA as a two-dose series in individuals greater than or equal to 18 years of age and for use as a third dose in certain immunocompromised individuals. The Janssen COVID-19 vaccine is available under the EUA as a single dose in individuals greater than or equal to 18 years of age.

Continuing to the benefit-risk considerations for a booster dose. The available data should support the effectiveness of the booster dose, specifically against currently circulating SARS-CoV-2 variants. That is benefit of the booster dose should be considered relative to the benefit provided by previous vaccination with the primary series.

Available data should at minimum characterize the most common adverse reactions associated with the booster dose. There are uncertainties regarding risks, for example, myocarditis, that are also considered and

would be further evaluated during post-authorization surveillance. FDA's evaluation of the safety and effectiveness data of a booster dose of the Moderna COVID-19 vaccine and additional input from the VRBPAC is essential for weighing the known and potential benefits and risks.

Digging into today's agenda, we are currently in the FDA introduction, which will then have a five-minute Q&A session, and that will be followed by a presentation of data relevant to the need of the booster dose from Dr. Alroy at the Ministry of Health Israel and Dr. Milo from Weizmann Institute, Israel. There will be a 15-minute break after that.

Then, there will be a sponsor presentation titled "Safety and Immunogenicity of a 15-microgram Booster Dose of mRNA-1273 (Moderna COVID-19 Vaccine)" to be given by Dr. Jacqueline Miller from Moderna Therapeutics. This will be followed by FDA presentations from Dr. Tina Mongeau and Dr. Hui-Lee Wong. There will be a 10-minute question and answer session after that, followed by a 30-minute lunch break

and an open public hearing for 60 minutes and a 15-minute break. There will be an additional Q&A session regarding the sponsor and FDA presentations, followed by the Committee discussion and voting.

Here is the voting question for the Committee for today's AC. "Do available data support the safety and effectiveness of Moderna COVID-19 vaccine for use under EUA as a booster dose (50 microgram of mRNA-1273) at least six months after completion of a primary series in the following populations: individuals 65 years of age and older; individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19?"

We also have a non-voting discussion question for the Committee. "Considering the information presented today and at the meeting of the VRBPAC on 17 September 2021, including the updated information on effectiveness of mRNA COVID-19 vaccine, please discuss

whether available data support use of a mRNA COVID-19 vaccine, that is Pfizer-BioNTech or Moderna booster dose administered at least six months after completion of the same mRNA COVID-19 vaccine primary series in the general population of adults in an age group less than 65 years." For the purposes of this question, age groups below 18 years should not be considered.

I'd like to thank the Advisory Committee, supervisors, and management for providing the opportunity to present here. Thanks and now it is open for Q&A session.

Q&A SESSION

DR. ARNOLD MONTO: Thank you very much. We have our first Q&A session, and we have a little more time because we're ahead of schedule to discuss what we're going to be doing today and to get going in terms of our thoughts. And Dr. Kurilla has raised his hand.

DR. MICHAEL KURILLA: Thank you, Dr. Monto. Yeah. One question, could you clarify the relationship

between the six-month booster EUA with regard -- does it supersede the EUA that was issued for the immunocompromised, or do both of those stay in effect? It seems like there might be a little bit of confusion because the immunocompromised would also be at risk for serious COVID disease, but that's one month after versus six months. I'm just wondering how those will play out.

DR. ARNOLD MONTO: And what about the dose?

DR. MICHAEL KURILLA: Good point, Arnold.

DR. SUDHAKAR AGNIHOTHRAM: I can answer that question. Yeah, thanks for the question. The third dose for immunocompromised is actually 100-microgram dose, and then the six-month EUA for the booster dose is for 18 to 64 years in individuals who have comorbidities, and then, above 64, it is for everyone. For Moderna COVID-19 vaccine, the dose is 50 micrograms for the booster dose -- that is the third dose. But the dosage for immunocompromised for Moderna is 100 micrograms, which is the third dose, and the immunocompromised may also opt to get another booster

dose that would be 50 micrograms. And, if anyone else from FDA wants to jump in to answer that question, they're welcome to.

DR. PETER MARKS: Dr. Kurilla, I take your point, and I think we've gotten some feedback that, when we reissue the fact sheets for the current emergency use authorizations, we'll make it clearer about the distinction between the third doses for the immunocompromised and the issue of a booster for an individual who's received three doses of the primary series. And that's a very good point that we have to just make sure we clarify. Thank you for that.

DR. MICHAEL KURILLA: And so, just to be clear, for the immunocompromised population, you have changed the primary vaccination sequence then to a three dose?

DR. PETER MARKS: We have not changed it, but we have allowed -- it's permissive if a third dose is desired based on the considerations of that individual such as an individual who has been through solid organ transplant where there's good evidence that they often

don't make a good immune response to two doses that, at the discretion of a provider, a third dose could be administered. We note in the authorization that, even then, the protection may not be perfect, and that's why we recommend that people still continue to use reasonable precautions such as mask wearing, et cetera.

DR. MICHAEL KURILLA: But the six-month boost, then, for them would be a fourth dose? They would still be -- you would still consider them eligible under this EUA for a fourth dose?

DR. PETER MARKS: You know, I think this is one where we probably need to discuss this. This is far enough in the future that I don't want to make a definitive statement here. It's something that we do, though, have to cover when we reissue our fact sheets, and I'd be very welcome to have the Advisory Committee, Dr. Monto, later on have a conversation about that because I think there is some dialogue that could be had.

DR. MICHAEL KURILLA: And there's potential for a lot of confusion of who needs what.

DR. ARNOLD MONTO: All right. Dr. Kurilla, I don't know that we're going to be able to fine-tune the whole national program in the next couple of days. I think there are going to be -- we really need to think of broad concepts, especially when we get into our discussion after the vote later this afternoon. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Arnold, and thank you both presenters. I think my question is going to be a little bit easier than Dr. Kurilla's question for you, and it's for you, Dr. Marks. You showed three slides that demonstrated real-world effectiveness for the three vaccines, and could you just remind me? There were vaccinated and unvaccinated curves that were demonstrated there. Who was in the unvaccinated group? Did that group have the same degree of risk factors, such as age, as the group who were vaccinated? Because they probably weren't from the original trials, right? Because didn't most of the placebo recipients cross over?

DR. PETER MARKS: So both of those -- both for

Pfizer and Moderna, those were from Kaiser-Permanente studies, and the papers are published in *The Lancet*. The references are on the slides. They did match for age, disease score. These were from their HMO databases, so these were cohorts that were matched. And our statisticians in looking these over, feel that reasonable matching was done, but you know the limitations of all of these. These were covered at the last meeting, the limitations that are present with these studies. Although, the one thing that is true is that, in the studies, one might see differences in magnitude. They do all seem to trend in the same direction here.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Sawyer.

DR. MARK SAWYER: Thanks. I just want to go into the discussion today with a clear understanding of whether the voting question that was presented is the only question we would deal with. Last meeting, we decided that the voting question -- we voted against the overall question that was posed, and then a revised

version was presented. And we then voted again on that, and would we follow the same process today?

DR. PETER MARKS: I'm happy to try and respond to that. I mean, we anticipate having the vote on the question that's there. Wanting to make best use of the Advisory Committee's expertise, if the Advisory Committee did not -- you know, if there was a problem with that question that became apparent during this meeting, we would potentially take it upon the Committee, if acceptable, with revising it. But it is our intention to vote on the one question that was presented and to have the one discussion question.

DR. ARNOLD MONTO: Right. And just note that the voting question derives from the sponsor's request to the FDA, and that's the reason we did what we did at our last meeting. Dr. Offit.

DR. PAUL OFFIT: Yes. Sudhakar, I had a question that hopefully you could clarify -- one of the statements that was on one of your slides. You cited that, because there was a decrease in effectiveness associated with the vaccines over time regarding

infection, that that likely presaged a decrease in effectiveness against serious disease. But one could argue that decrease in effectiveness against all infection is more likely mediated by neutralizing antibodies, which are going to erode over time, whereas immunological memory is probably more likely associated with protection against serious illness. So I'm not sure why one would argue that one would presage the other.

DR. SUDHAKAR AGNIHOTHRAM: Well, thanks for the question, Dr. Offit. I can try to answer that question. The decrease in effectiveness against mild to moderate disease can apparently be also driven by a decrease in quality of the neutralizing antibodies that are present. And then that can eventually lead to severe outcomes such as hospitalization, et cetera.

I mean, point well taken that the immunological memory can also play a role in protection against severe disease, but over time vaccinology and immunology when the immune response declines over time, then that can also eventually lead into severe disease.

So that is the explanation that I can give. But if anyone else from EPA wants to jump in --

DR. PAUL OFFIT: So, Sudhakar, you're arguing that arguably immunological memory would decline over time. I mean, and I think that some of the Israeli data show that in a 70- to 79-year-old, that's very possibly true, but I just wonder whether in a younger group that really would be true. But again --

DR. PETER MARKS: Dr. Offit, my suggestion is let's see the Israeli data that they present today because they may answer some of that question today, I think. I'm sorry, I didn't mean to cut you off. I just think that may be a -- I totally take your point, and they may address that today.

DR. PAUL OFFIT: Okay. Thank you, Peter. Thank you, Sudhakar.

DR. SUDHAKAR AGNIHOTHRAM: Thank you.

DR. ARNOLD MONTO: Dr. Moore.

DR. PATRICK MOORE: I assume we don't have anyone presenting from VAERS or CDC on giving us an update on serious adverse events, particularly

comparing Pfizer to Moderna mRNA vaccines. Is there a chance for us to get that information before we evaluate this booster? This is on the primary series of course. That is, is there a chance for us to get that information before we evaluate Moderna's booster, or how do we deal with that, especially with the issue of myocarditis particularly in males that suggests that may tailor our recommendation more?

DR. SUDHAKAR AGNIHOTHRAM: Thanks for the question, Dr. Moore. We have a presentation from Office of Biostatics and Epidemiology from Dr. Hui-Lee Wong who will be talking about that. That will be followed by Dr. Tina Mongeau's presentation, so that will address your question. Dr. Marks or anyone else, if you want to jump in.

DR. PATRICK MOORE: Great. Thank you.

DR. ARNOLD MONTO: And just to note that our voting question actually is, for the most part, down to 65 years of age. The rest is going to be part of the discussion afterwards in which we're going to be looking at and can ask some questions about age groups

as such. We can unusually have a little more discussion here because I've heard that Dr. Alroy-Preis is not in place yet to give her presentation from Jerusalem, so any of our Committee that wants to ask a few more questions, we've got exactly seven minutes to give her time to get in place. Dr. Meissner, is that you from before or new?

DR. CODY MEISSNER: No, it's new, Arnold. Let me try and position myself here. I have another question.

DR. ARNOLD MONTO: It's all very tricky when you're virtual.

DR. CODY MEISSNER: Thank you. Another question for Dr. Marks, so the question from the sponsor relates to individuals 65 years of age and older, people 18 through 64 who have underlying risk factors. And then my question relates to the third category. It seems to me there's some confusion between people who are at risk of severe disease and people who are perhaps at greater risk of being exposed.

First, are there any data to say that people at greater risk of being exposed are likely to get more severe disease? And I worry because that's been interpreted as, for example, a person who bags groceries at a grocery store, and to me, that wasn't quite the intention of what we discussed during the last meeting. Could you comment on that -- your perspective on that?

DR. PETER MARKS: Thanks for the question. It's one where -- I take your point. We discussed it a fair amount internally. The question is some people are at greater risk of getting COVID-19. You're right because they are just constantly exposed. If they get it, you're right. The grocery store worker, for that infection, there's nothing that says that they would be -- because they're a grocery store worker does not mean that they would get more severe infection than another individual, but it was part of kind of the overall consideration there. Again, if this Committee -- as they discussed, that was the purpose of the second question today, to allow the Committee to refine what

we have.

And we'll very much value that because we know it's not perfect, and to the extent that I'll just say this -- to the extent that we can try to harmonize between the various vaccines to the greatest extent, we greatly appreciate that because, in the practice of rolling things out, we think that will make things easiest and create the least confusion operationally. But I really welcome that discussion. That was the purpose of the second discussion question. Thank you, Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Marks.

DR. ARNOLD MONTO: Dr. Rubin.

DR. PAUL RUBIN: Thanks, Dr. Monto. I have a question about the FDA's view of what a reasonable safety sample is for a third dose. The difference between -- you know, Pfizer did a relatively small trial, and Moderna is going to present the results of a relatively small trial of third doses. Pfizer had all those real-world data from Israel, a million people who had received the vaccine. So how do you think about an

adequate sample size to view safety?

DR. SUDHAKAR AGNIHOTHRAM: Thanks for that question, Dr. Rubin. I can attempt to answer that question, but, as to Moderna, we have safety data from 171 participants and additional safety data from 173 participants as well, so approximately around 320 participants for a booster dose, which is being reviewed for the emergency use authorization of the booster dose. So we believe that for emergency use authorization that is adequate for authorization of the booster dose, but if there's anything that anyone else wants to add from FDA, Dr. Marks or Dr. Fink.

DR. PETER MARKS: I think the most important piece of this to understand is that I think we take the totality of the evidence. I think some of this is understanding what the most likely adverse events have been from mRNA vaccines, and I think probably the major thing we'll be looking at in post-deployment surveillance would be myocarditis. Given the incidence rate of that, I think this is one of those areas where we will look at using our large databases to make sure

that the incidence as it's deployed is not excessive compared to what we would expect. And I think Dr. Fink looks like he wants to chime in here.

DR. DORAN FINK: Thank you. I just wanted to add -- and this was discussed several weeks ago with the Pfizer booster dose request -- that we did issue guidance regarding emergency use authorization of modified vaccine to increase protection against variants. And even though we're not talking about modified vaccines, the considerations that we outlined in that guidance for booster doses of modified vaccines we do think are very applicable to these homologous booster doses that we're considering then and also today.

In our guidance what we said is that based on a well-characterized safety profile of a primary series that a safety database of around 300 or so individuals who received a booster dose would generally be sufficient provided no signals are identified to support emergency use authorization of a booster dose. It was very nice that we heard about data from the

Israeli experience with the Pfizer vaccine last time.

Of course, FDA did not independently review those data, and so they did not contribute in a major way to our consideration of the risks and benefits for the U.S. population, although we certainly did consider those data in part. So I think what Moderna has provided us today, which you'll hear more about today later, does align with the principles outlined in our guidance for the study of booster doses to support emergency use authorization.

DR. ARNOLD MONTO: Thank you. Final question from Dr. Fuller because Dr. Preis is now ready to go. So Dr. Fuller.

DR. OVETA FULLER: Yes, thank you, Arnold. So I just want to say to the question that Dr. Cody Meissner asked about the third category of high risk that at least some of us think that a person who's at a grocery may not be -- we don't know if they're at higher risk for disease, but they're certainly at higher risk for exposure.

And I for one am grateful that we have that

allowance that someone who would like to get the booster is able to do so, so if I understood him correctly, he was concerned that that maybe wasn't what the Committee meant. And, for one member of the Committee, that is exactly what I meant. I would like people like that to have the choice, so I just want to clarify that for everyone or if that's something that we need to talk about later.

DR. ARNOLD MONTO: Okay. Well, thank you all. We've had an unexpected and rather robust discussion of the day's activities, and now I'd like to give over to Drs. Sharon Alroy-Preis in Jerusalem who will give us "Booster Protection across ages - data from Israel."

BOOSTER PROTECTION ACROSS AGES – DATA FROM ISRAEL

DR. SHARON ALROY-PREIS: Thank you. With me is Professor Ron Milo, and I want to use this opportunity again to thank the four leading academic institutions in Israel who have helped us create this data and analyze the data. And I am trying to move to

the next slide.

MR. MICHAEL KAWCZYNSKI: At the bottom of the screen, you'll see the two arrows. There you go.

DR. SHARON ALROY-PREIS: Yeah. So we are presenting Israeli data. We have no competing financial interests. I do want to say again the Israel MOH, Ministry of Health, and Pfizer have a data-sharing agreement, and in relation to the booster effectiveness, also this data that we're showing now, only the final results of the analysis were shared with Pfizer and was done by the four academic institutions independently. And, again, I want to say, like we said last time, we're coming here not to tell anyone what to do.

We think every country has not just the right but the obligation to do what is needed for their citizens. This is the decision we've done for Israel based on our data, and, if our data can help anyone else in the world, we're happy to share it. But it's not that we're telling anyone else what to do.

So what has happened since the last time we've

been here, which was about a month ago, a large majority of the elderly population received a third dose. You see in the blue line that over 95 percent of the 60 plus have been vaccinated with the third dose. And similarly, the other age groups that we've opened gradually by steps is increasing, and so we have nearly in all populations over 50 percent already with a booster dose.

This is a slide we showed last time showing that shortly after starting the booster dose in the age group of 60 plus we saw a decrease in the number of confirmed cases among that group, whereas the other groups, age 60 and below, were continuing to rise.

And where we now are looking nationally at the data, we're seeing now a decrease in the percentage of positive tests, also in the reproductive number once we're adding more and more age groups into the booster protocol. And what we're seeing basically is a break in the pandemic curve in Israel.

You see here a separation in the green line the people who were vaccinated with a booster dose --

the adults who were vaccinated with a booster dose and in the black line those who are unvaccinated. And you see that, with the beginning of the booster dose, we saw a decline in the infection rate. Here you see the severe cases among those who were vaccinated, and those decreased sharply. But you see at the end of the slide on the right that now we are seeing a decrease also in the unvaccinated population.

So the fact that we have high coverage of vaccinated individuals with a booster dose is now leading to a decrease in the overall severe -- in the overall pandemic curve but also in the severe cases. And I'll move it to Ron now.

DR. RON MILO: Okay. So I will be continuing what Dr. Preis was suggesting, to look at the detailed study that they did of those several million booster shots that were given.

So the data which I'll be presenting is based on those aged 16 and above who were fully vaccinated before May 2021. These are the people who have been vaccinated at least five months prior to the booster

dose and consists of all together 4.6 million people who were vaccinated until that time, and this consists during the study period of about 100,000 confirmed infections, over 1,000 severe illness cases, and over 250 deaths.

These happened in the study period, which is between August and the end of September and maybe even beginning of October as you can see in the left-hand of the slide. This is following the booster campaign. And we'll be looking at a different age group as you'll see in a minute.

Let me begin with ages 60 and above, and I'll be talking first about the confirmed infection. This is complementing the results that were already published in the *New England Journal of Medicine* and were presented last time, and all the results that I'll be showing you are also shared online through the medRxiv. We'll be looking at the time following the third dose, so after getting the booster.

That's what you see on the X-axis, and on the Y-axis you see the fold reduction in the rate compared

to those with two doses. Mainly we're taking people that had the third dose, and we're comparing them to people who had only two doses. And we're looking at what happened to the rates of confirmed infection and time progressed following the booster.

We expect in the beginning to have some (inaudible) effect and some time delay until we start to see the effect both because of the timed response of the immune system which takes several days but then also the inherent delay between the time between a person gets infected and the time the infection is confirmed, which in Israel is on the order of five days, which is also consistent with the latent period.

I, therefore, want to look at the time window from days 12 and beyond, and this is what I'll be showing. I should say also that everything I'll be showing you is based on a performed regression where we're adjusting for age, for gender, demographic group, second dose period and incidence, and area of residence, meaning we're looking at each location where the people live. And, at that given time, we're taking

as a confounder something to be adjusted for the rate of incidence at that time point.

What I'll be showing you is based on an observational study that will be very clear here. So observational studies have their limits. We did everything we could in order to adjust in the way that I'll be showing you. And we thought it was best to try and share with the community, as we do also receive, but to share it for peer review as fast as we could and to put it all publicly available online as I'm suggesting. And I'm trying to put all the links to enable everybody, including the general scientific community, to be able to comment on our work.

When we take this data and we're looking at what is the level of protection, meaning what decrease in the rate of infection is being observed, we see on the order about 10-fold or 12-fold -- somewhere about 10-fold -- overall protection when doing the analysis based on the Poisson regression. You can see that the confidence interval -- this is 95 percent confidence interval is relatively small. That's also the fact

that we already have, you know, several tens of millions of risk-days both in the non-booster -- those who only had two doses -- and those at day 12 and over. And overall, we're talking about somewhere about 1,400 cases of infection within this age group in the study period, which is between July 30th, which is the time when the booster campaign has begun for those age groups, and October 4th.

This is the last update that we had for the data. So this is presenting the results for the age group of 60 and above. It continues and I think enforces what we also presented last time about the effectiveness of the Pfizer dose and the regiment of three weeks between the first and the second dose after five months to give a booster dose.

Let me move on now to present what we've been observing when analyzing all the other age groups where, as Dr. Preis was presenting, most of the Israeli population has now taken that booster dose. So this is a bit of a busy slide. Let me walk you through. I think you also saw this, which is the ages 60 and

above. You can see with a similar format what happened in ages 60 to 69, 40 to 49, 30 to 39, and 16 to 29. Again, I'm sorry for the small font, but this is days following the booster. And this is the fold reduction in the rates.

I think you can see that the patterns are relatively similar. You can see, by the way, for the ages 60 and above, we have two months of follow up for 50 to 59. We have two weeks less reduction. We did this in a serial manner such that there was some delay, so if we waited two weeks, we could open it to ages 50 to 59 and then about a week for ages 40 to 49. And therefore, we have a limited follow-up time for those age groups, but we can see that the effect begins similarly, about 12 days following that. And the results are summarized here in terms of the rate ratio for day 12 and over versus the non-booster, and you can see they're on the order of 10-fold protection.

You can see the confidence interval, and you can see we have quite a few cases in order to perform the analysis within all age groups. And all the

results, as I said, are summarized and updated and are now under revision for publication. I will also say that we see similar patterns across the age groups in terms of both the timing and the magnitude but not completely identical, which probably would be of interest for further analysis.

All the data that I've shown you is trying to correct for those different confounders for which we have data that we're able to do that, and in all cases, we're doing the analysis from the time of booster eligibility. That's for the different age groups because one to the other change somewhat until the first week of October.

Beyond looking at the fold rate of reduction, we also looked at the absolute rate and what happened to them. So what you see here is the confirmed infection rate for 100,000 risk days, and we're comparing between those who took the booster versus those without the booster, only second dose. And you can see in yellow the non-booster, which is on the order of 100 confirmed infections per 100,000 risk days

in the prevalence that we had during the study period in Israel. And in green, you can see what happened to the absolute rate for confirmed infections for those that took the booster 12 days and onward, everything per risk day.

And it's important to try and look at it from different perspectives. We were trying to be as careful as we could, and beyond the approach, which is often being used (inaudible) to study such analysis, the Poisson regression, we also took a second approach based on a different framework. And that is using matching, so basically for every person who took the third dose, we're matching a person who took only two doses. And we're following them through time, and we're making sure that the matching is such -- and you can see also what is being done in the literature -- such that you're comparing properties as much as possible, meaning the age, the demographic sector, look also at some things as much as you can in order to ensure that the comparison is as similar as possible. And we find that the results also in terms of the rate

ratio between the two cohorts are such that we get a similar protection as we show during the Poisson regression.

We followed another approach, and that is looking -- using a temporal comparison, such as your control group. Instead of being the ones that only took a second booster, we have an alternative control where you're looking just at the people that also took the third booster, but you're looking within the timeframe of days, which is between three and seven days post-vaccination. So this is the rationale for that is that one expects little effect of the booster on confirmed infection in days three to seven.

The reason for that is the combined effect of the delay until the effect of the vaccination with the booster -- the other with the delay for being confirmed. So even though there is some response already in days three to seven of the immune system, you would not expect that you would already get the symptoms to be confirmed. Therefore, it's another way to perform the analysis.

I would say that it's also confirmative in the sense that, even if there is some effect, there may be small (inaudible), there is some effect. There are also other effects which is now known as the healthy vaccinee bias which relates to the fact that the people that take the booster are those that feel better because those that do not feel well tend to not come and take the booster although would be some seemingly protection level which is you might even be seeing it here and that would make it such that, when you take the ratio from the control group, it means that you get the lower protection than the actual one. But we thought it's important to try and use as many alternative and optional ways, and this approach -- let me show you the results.

You can see them compared here for the different age groups. Again, this is using the alternative control group where the control group is three to seven days post-vaccination when the booster has little effect. And we see on the order of indeed somewhat lower levels between 4.8 to 11.2, where I just

want to point out when we're talking around 5-fold protection, that means 80 percent lower rates of infections. Okay? So that's not something -- I would say in absolute terms, it's still 80 percent decrease in the rates for those age groups in terms of confirmed infections.

Following our analysis of confirmed infections, we wanted to look further at what happens in terms of severe disease, so let me move on to that. What you see here are results for severe disease, and we've been following the definition of the NIH regarding the resting respiratory rate and the oxygen saturation for the definition of what is severe disease. And we're looking across the age groups. You can see that the numbers are generally -- number of outcomes is obviously lower, but still we find that we had -- at least in the age group of 60 and above and even in the ages of 40 to 60 -- unfortunately, we had quite a few cases in Israel.

And you can see here what happened in some of the rate ratio, and we can see very significant

decrease in the rates of severe cases in those age groups of 60 and above and 40 to 60.

In the age group of 16 to 39, the number of cases for the booster group is very low, and therefore, there are too few cases to estimate reliably the rate ratio, even though you can see the raw numbers here where you can see the number of cases and the risk days, the number of cases and the risk days at risk. And all of this is, again, done in the same approach of using -- trying to control for all of these confounders as much as possible. This is the analysis of the severe disease of those age groups using the Poisson regression.

Here is the same analysis but now using the alternative control group where you're looking -- or you're comparing the people 12 days over and days three to seven as your control. And you can see here's the level of protection that we're finding, so 6.5 for this age group, 3.2 for this age group, and too few cases to estimate reliably in the lower age group. Just to clarify again, 3.2, that means roughly 60 percent lower

rate or somewhere above that -- actually 70 percent lower rate of severe disease.

These are the changes in terms of absolute rates of severe disease, again, for 100,000 risk days. You can see that for the non-booster -- this is the booster and the non-booster. This is the booster. There is some fine line here -- thin line here, sorry. And you can see that the numbers, obviously, they will be dependent on age, but we see that there is quite a dependence on whether a person takes the third dose or does not take the third dose.

Finally, I want to present our results we got in the amounts of death as an outcome in the ages 60 and above in both approaches, both with the day 12 and over versus those with non-booster and only two doses and the comparison for those with the alternative control for days three to seven. We see a very significant protection where about 4.8 -- that's about 80 percent decrease in the rate of death. For the ages 40 to 59, there are two few cases to be able to estimate those values.

So, in summary, on this analysis, we find that the booster dose improved the protection over the second dose and also regarding both in terms of confirmed infection and in terms of severe COVID-19 where the exact values of reduction depend on the age group. But I would say overall, we see high levels of protection and the decrease in the rates. In terms of severe disease, over 80 percent decrease in rate ratio over the second dose for the ages 60 and above and in ages 40 to 60 over 60 percent decrease in the rate ratio over the second dose. And finally, we see that the booster dose decreases the COVID-19 associated death rate around three to 10-fold among the elderly.

With that, I want to go back for two minutes to the nationwide observations following the booster dose before Dr. Preis presents our results regarding the safety of the vaccine across the different ages. So just going back to here, I remind you that in Israel we're doing the confirmed infection based on PCR testing, so it's both following symptoms and without symptoms as far as contact tracing and for other

reasons. And looking at the number of daily cases, we saw them rapidly increasing, which was the rationale for beginning the booster dose administration for the ages 60 and above. And then we had a delay of about two weeks, which is roughly what one would expect given what we just talked about.

We saw a specific decrease, whereas the below 60 continued to increase rapidly. And we also checked within this assay the ages of 50 to 59, 40 to 49. They also continued to increase until later on where a booster was administered. I'm showing here values until September where -- in September you already started to see the effect of the other booster doses. And, if anybody's interested, we could afterwards talk about it further.

This is looking at the positivity -- percentage of positive testing as well. So what I think is of interest to note is that when we started the booster dose, even though I showed you that the overall number of infections within the group of the ages 60 and above started to drastically decline, the

other age groups continued to rise.

And as a result, we also opened to ages 50 and above and 40 and above also in order to protect them. And what we find is that, only after opening to more age groups, the absolute percentage over all the population has started to decrease, and now this is from 7th of October to 2.6. Now, it's actually at about 1.5, much continued to decrease following the booster dose for more age groups and not just as a result of the age of 60 and above.

By the way, we're looking here at the percentage of positive tests and not just based on the number of cases, which we could also show you. And that is because there are effects from the high holidays that are taking part in Israel during September, and, therefore, this is a more robust way to analyze this.

Finally, looking at what's happened in terms of severe disease -- severe cases in Israel during that time period, we saw that following the administration within the time -- this was when the booster campaign

began -- you can see that in green here are the vaccinated people. And you can see that they were the majority, about two-thirds of the severe cases. The very severe cases that we had were those that were vaccinated. That was a combination of the waning and of the Delta variant. And we saw that it began after a delay. Roughly at two weeks, we started to see a stabilization and then a decrease as a result. As Dr. Preis was saying, about 90 something percent of those within those age groups had been taking the booster.

And there was a continued rise in the number of cases for the unvaccinated such that, even though they're only a small population of the people at risk from the adults -- less than 20 percent -- they were in charge of the vast majority of the severe cases in Israel ever since.

And we started to see a decrease of that in the same time that we started to see overall incidence in Israel declining after wide booster adoption in the ages 60 and above, which can be interpreted by the fact that, whilst you had the booster adopted by many age

groups, the overall incidence in Israel declined significantly, which is what I've just been talking about. It is now over 5-fold less than it used to be in terms of overall incidence in Israel.

And that also started to decrease the number of severe cases also among the unvaccinated in all age groups, including the elderly, as a result of the fact that the incidence is now much lower. And with that, I'll give it to Sharon.

DR. SHARON ALROY-PREIS: I'll take it from here. I just want to emphasize something that Ron said, but it was a question last time. And so I want to put a notice on it. The severe definition is the NIH definition. It's not something that is specific Israeli construction. It's something that we're using -- the NIH definition for severe case, and we have been using the same definition since July '20. So the change in the numbers that you're seeing is not because there was some change in definition midway.

The booster is important to see the vaccine effectiveness of the booster, but as important is to

see the safety data. And so now we have more data on the safety of the booster in younger age groups, and I will show you the data -- the rates of adverse events per million doses within 30 days post-vaccination. It's updated until four days ago. And for the youngest age groups, which is 16 and above, we have for 50 percent of them more than 30 days of follow up. So for about 50 percent of them, all the adverse events following vaccination would have happened by now.

There is a limitation to note. As we said last time, the reporting is based on passive surveillance, so we are looking for healthcare providers to report to us. But the myocarditis data we're proactively looking for, so we are calling hospitals and asking for the data. And so this is something that is more hands-on with myocarditis knowing that this is an adverse event that is connecting usually to the second dose of the vaccine in younger males.

So the data that you are seeing here is the rate of adverse events by category and age groups.

You're seeing on the left the first dose, the middle the second dose, and on the right the third dose. And you're seeing that at least we have the same amounts of adverse events, not more. Again, we are aware of the fact of the limitation that could be underreporting, but it's the same system for all three doses that we provided.

This is the rate of systemic adverse events by dose. Again, the third dose on the right is not higher rates of adverse events.

This is the rate of local adverse events, again, similar if not lower.

Neurologic adverse events in gray is the third dose, and I should have mentioned the number of cases. So, for the first dose, we have more than 6 million people -- 6 million vaccinees, for the second dose 5.6 million, and for the third dose 3.7 million. So it's big numbers, and you see on the gray the rate for neurologic adverse events.

Allergic adverse events, similar. We have to mention that between the first and the second, if

someone developed an allergic adverse event, usually they will not be given an additional dose, so part of it is those who were allergic to the medication were not given another one. We're not seeing huge amounts of allergic adverse events post the third dose. And what is more important to us is the serious adverse events. You can see here the definition of serious adverse events that result in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; result in a persistent or significant disability, incapacity, congenital abnormality; and other important medical events that required intervention.

This is a common serious adverse event definition, so we're not defining this in any other nationally accepted way. For 3.7 million booster doses administered, we had 44 serious adverse events reported. And, for those adverse events, we have a special committee that looks into each and every case, looks at the clinical data, and defines whether it's connected or possibly connected to the vaccine.

And here you have the results of that group. You see here for ages 16 to 59 on the green on the left, out of 2.5 million vaccinees, we had nine cases of myocarditis and eight cases of perimyocarditis, so altogether 17 cases of either myo- or perimyocarditis. And, in smaller rates other adverse events, some of them related like the allergic reactions, and some of them like the DVT that were deemed not connected to the vaccine.

And, on the left [sic], you see for age 60 and above, out of 1.2 million vaccinees, the adverse events that are seen here were deemed not connected to the vaccines. One of the cases is still under investigation, and, in one case, the causality is possible.

So myocarditis, which is the one adverse event that we found connected in Israel and other countries to the Pfizer vaccine usually after the second dose, what you see here in this table is the data for the first dose, the second dose, and the third dose. And it splits to female and male and splits by age groups.

So what we saw before is really a high number, increased rates of myocarditis among 16 to 19 and 20 to 29 males. This is from the prior vaccination campaign.

What we're seeing now with the third dose, you see here the number of cases. This is what I mentioned before. We have 17 cases of either myocarditis or perimyocarditis, and so we're not seeing an increased risk of those events following the booster dose. Same again for about half of the younger population. We don't have the full follow-up observation time. We do have them for roughly 50 percent.

So, in summary, the booster dose in Israel was effective and so far had a safety profile similar to the other doses. We have improved protection against confirmed infection for all ages, 16 and above. We have improved protection against severe disease in ages 40 and above, and I have to mention we are always talking about the fact that younger people have less tendency to go into severe and critical conditions and to die. But, as you saw in the slides that Ron showed before, we didn't have mortality and severe cases among

the younger age groups who were doubly vaccinated but did not get the booster dose. So it could impact even younger than 40 years old for severe and critical disease and mortality.

The booster dose adverse events are not more acute than the first or second dose, and their rates of occurrence is not higher. And I think that we can say when we're looking at all the data -- the epidemiological data in Israel so far is that the administration of the booster dose helped Israel dampen the infections and the severe cases in the fourth wave.

So we are now coming out of a fourth wave that, I believe, without the booster, would have dose put us in a worse place with really high burden on hospitals with severe and critical patients. And we were able to get out of this wave due to the booster dose. Thank you and we are more than happy to answer any questions that you might have.

Q&A SESSION

DR. ARNOLD MONTO: Thank you so very much, Dr. Preis, Professor Milo, for the presentations. A very good tag team of the two of you going over the material. Dr. Preis, you were very careful to say that the side effects of the third dose were no higher than that of the second dose, although some of your data suggested that they might be lower. Not going on record but just giving your personal opinion about this given the short time and selection that might have gone on, what do you really think about this?

DR. SHARON ALROY-PREIS: I think it's lower, but I want to be very careful about how I present this because there could be underreporting. And there could be a difference between the underreporting of a third dose compared to the first and second. With the new vaccination campaign, the awareness may be higher, and with the third dose may be lower, so I'm trying to be very careful about that. But I am very confident about the serious events. I think that the serious events are being reported to the Ministry of Health and especially the myocarditis cases, which we are actively

looking for. We're going out and doing active surveillance on, so we're very confident on those numbers.

DR. ARNOLD MONTO: Do you have a feeling that young males are holding back from getting vaccinated?

DR. SHARON ALROY-PREIS: I think that there is some concerns among younger males, even though the fact that the publication in the *New England Journal of Medicine* of both our data and (Inaudible) data that showed that most of the cases are mild and are resolved completely without sequala was important. So I think there could be some concern, but I think we are showing in the data that it's a really rare occurrence and mild in most cases.

DR. ARNOLD MONTO: Thank you. Dr. Gans.

DR. HAYLEY GANS: Thank you so much. I really appreciate you coming and sharing your data with us, and I just want to say it's really beautifully presented and very accessible.

I did have a couple of questions if that's okay. One question is in catching these, quote, cases,

I'm wondering if you have any mandatory testing? So is there a difference in the way that people are getting tested now? So, for instance, we have some businesses that require biweekly testing, and are we just catching people who aren't symptomatic? Or are most people just getting these tests because they're symptomatic?

So that's one question just to understand the data, but I think my overarching question -- because I think your data is very compelling in the lens that you bring to it. So we aborted this wave. I'm wondering if you could overlay -- because I'm sure you thought about this -- the idea that many countries show a similar pattern regardless of what they do with vaccination. So there's sort of this wave of epidemics that come and go, so I'm wondering if you could overlay what would have been the natural history of the disease with your data because it's very compelling?

And then lastly just so that I can throw these three out, do you have any immunologic data that you did sort of side by side with this so that you can start to understand these are the breakthroughs, here's

the immune part -- you know here's the immunity that we saw at that point so we can start understanding any immune correlates of protection? I realize that's sort of a side study.

DR. SHARON ALROY-PREIS: I'll start from the end and see if I can remember all the way through.

DR. ARNOLD MONTO: A lot of questions to answer. Go ahead, please.

DR. SHARON ALROY-PREIS: So first about the study, we are completing hopefully in the very really few weeks a family study in which we enrolled vaccinated family members of confirmed cases. We took at the beginning of the study serology and neutralizing antibodies and, for some of them, cell immunity tests and PCR at the beginning and PCR at the end. And the purpose of that study -- the goal -- is to try to see if there is some protection level. What is the correlate of protection?

We don't have the data yet. I can say that we are seeing breakthrough infections even when we have hundreds of titer -- a titer of hundred, 300, 400, 500

and people got infected. So we are completing the data now, and hopefully, that will be available soon because, for some people, it will be really important to know what is that correlate. So that was the second question.

The first question -- and I don't remember the middle one. But the first question was about the policy of testing. So, in Israel, the testing policy was -- after the vaccination campaign is that if you -- everyone who traveled abroad, when they come back, they needed to be tested when they enter Israel. So that's everyone, vaccinated and not vaccinated. So, in that population, which is not representative of all Israel obviously -- it's a very unique population, but many people in Israel travel -- we have everyone.

For the rest, the recommendation is to be tested when you are in contact of a confirmed case. You have to be tested. Again, it's not really mandatory. There's no mandatory except for travel abroad testing, but it's highly recommended to be tested when you are a contact of a confirmed case. And

if you are tested, it shortens your isolation period. So without testing, you need to be in quarantine for 14 days, and you can shorten this to seven days if you test at the beginning when you've just learned about the contact being the contact. And on day seven, if both tests are negative, you go out of quarantine. So that is the main reasons where people would be tested if they're asymptomatic.

Another specific population is the long-term care facility workers where we do constant testing every week. And, for that group of employees we're doing this for everyone, vaccinated and not vaccinated.

So what we saw is really a decrease in positive case. Especially what we can compare really nicely is when we are testing everyone in that population. So, for example, the testing when you come back from abroad or the testing among the long-term care facility employees, you can see the drop in confirmed cases with the booster dose.

So, before we implemented the booster dose coming from abroad, we had hundreds, up to 200 a day,

confirmed cases coming back and either being tested positive at the airport or in the seven days following their return, and this has dropped significantly with the booster dose. I saw Ron waving his hand.

DR. RON MILO: So maybe just to add a sentence on the answer regarding the issue of testing. So I think in that respect very informative is the alternative control group where you're looking at the same people but at days 3 to 7 versus days 12 and onward because this means it's the same people.

And I would also say that if they tend to do less -- just after the booster for some reason or another, that will just give you an underestimate. Okay. So together, I think that was a very good way to think about this, think about the same people which you're comparing in terms of the tendency to go and be tested.

DR. ARNOLD MONTO: Okay. Thank you.

DR. SHARON ALROY-PREIS: And if you can remind me the second question, I'll try to answer.

DR. ARNOLD MONTO: Let's move on so we --

let's move on so we can get some other people. We have a lot of hands raised and a limited period of time. I'm sure we'll get back to the same topics. Dr. Levy, one part question only, please, from now on.

DR. OFER LEVY: Okay. Thank you to the team in Israel at the Ministry of Health. This was a very informative and important presentation. We need to be mindful, of course, that Israel's a very different country in population than the U.S. and that we're talking about a vaccine that's different from the vaccine we're considering today. But nevertheless, it is a similar mRNA platform, so there is relevance there.

I had a question for Dr. Milo regarding his graph depicting the fold reduction in rates of COVID by age. The alternative control group was selected at, I forget, day three or so, but why not at day zero?

And I didn't understand why the day zero group already had a 5-fold reduction in risk. The data are very convincing in general, but that aspect I didn't understand. And the question to Dr. Alroy is simply

regarding the myocarditis, if I understand correctly, there is some additional risk after the third dose -- the booster dose, but the rate of risk isn't higher than the second dose if I understood that correctly? Thank you.

DR. SHARON ALROY-PREIS: So I'll let Ron answer.

DR. RON MILO: Thanks for pointing that out, and we also explained about that in detail in the *New England Journal* paper and in the medRxiv. But just briefly what we observed is that on day zero and day one, meaning just after you took the booster, it is very rare to also do a test on that day. There's a behavioral effect with people just as they're taking the booster, they usually don't go and perform the test as well. And therefore, you get an artificial protection. This is just assuming protection, and we observed that. And we have it in the supplementary material exactly the numbers, et cetera, is the reason.

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Dr. Preis, the myocarditis.

DR. SHARON ALROY-PREIS: As for the myocarditis, we've seen -- we've shown that myocarditis could be an adverse event following Pfizer vaccine, so we're not trying to say that after the third dose it's not connected. I'm sure it's connected, but the rate is really, really low compared to what you would have expected if it was the same rate as after the second dose.

And perhaps it's because we're giving this dose five months or more later, and so it doesn't have the same response as giving one dose and then after three weeks the second dose. In our workgroup, what we saw in Israel is that most cases were in a few days -- three to five days after the second dose among the younger males, and so maybe the fact that we're giving it months after is causing this rate to be actually lower.

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth.

DR. RON MILO: I just have a reminder that the second question was what would happen if there wouldn't

be a booster, and I would just mention in brief that our modeling analysis shows that the number of hospitalizations, severe cases, et cetera, would have continued to rise very significantly according to all the data that we have. We didn't get very detailed into it, but I just wanted to mention it briefly.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth.

DR. JAMES HILDRETH: Good morning. Thank you, Dr. Monto, and thank you, Dr. Alroy-Preis and Dr. Milo, for presenting the compelling data from Israel.

The most interesting part of your presentation for me was the fact that the cases began to drop among the unvaccinated once you achieved a large percentage of the population getting the third dose. So do you think that you've achieved herd immunity by getting so many of the people there boosted with a third shot? And part of my question is, what percent of those unvaccinated individuals had had COVID-19 and recovered? So could natural immunity be contributing to that group as well? Thank you.

DR. SHARON ALROY-PREIS: I'm sure the people

who have been infected with COVID-19 and recovered, we don't even know about them -- like the silent recovered individuals are there. When we're doing serology testing, among kids we find between 5 to 12 percent of the kids that did not know that they had COVID-19 were tested positive by serology depending on the sector. So we do know that there is this population of people who have been infected and don't know that, and they are definitely contributing to the population of the protected that leads us to herd immunity. For me, it's hard to actually say if we're in a herd immunity place at the moment. It's easier to say it when you look back in retrospect.

So, when I look back in retrospect on our third wave, we see that we got to herd immunity with the Alpha variant when we still had about a third of our population not vaccinated, mainly kids, and still the wave went down. And this for me is the answer -- like the perfect depiction of herd immunity, that you still have a third of your population not protected. And, if I go beyond my way and say some of them were

probably protected and we didn't know about that, 20 percent of the population is not protected, and still the wave is coming down.

So we're starting to see this trend now. I'm hoping we're in herd immunity now for the Delta strain, but I'm not sure we know it yet. But it seems like it's going in that direction.

DR. JAMES HILDRETH: Thank you very much.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. What I'm curious about is obviously the rationale for the booster because at least with regard to the breakthrough infections is the declining -- the rather brisk antibody decay rate for neutralizing titer. And I'm wondering if you have any evidence that the third boost -- the third dose -- the boost that you've provided, which some people have suggested may actually serve as a true boost in a prime-boost strategy -- is that actually impacting the antibody decay rate? Or do you have any evidence that the antibody drop off in neutralization titers is the same after the third dose

as it is after the second and you'll be back in another six months needing the boost again?

The other aspect of this is, do you know whether or not people who have suffered a breakthrough infection, do they need to be boosted?

DR. ARNOLD MONTO: Lots of speculation there.

DR. SHARON ALROY-PREIS: I'll get Ron to answer the second one because there was a lot of work done showing this. There was a lot of work done about the recurrent infection among recovered individuals and what is their risk, but I think what we're seeing in serology is that, when you give a third boost -- the booster dose, you see a rapid increase in the serology in the titers. And, to some extent, it's even higher in some studies than the highest level that people got from the second dose. I think what you asked is the million-dollar question that unfortunately I don't have the answer to. We're hoping that it's not a setting of every six months we need to be vaccinated.

We know from other diseases that sometimes you need in the protocols two doses a month apart and then

after six months another booster dose, and you're protected for years. I'm not yet sure what will be the answer here, but we'll definitely look carefully into that and hopefully see the decline or identify the decline earlier this time than we identified in the third wave.

DR. RON MILO: Regarding your other question, I will just say briefly that we're doing the analysis around the clock about the recovered, and where we're talking about breakthrough, meaning that they had at least one dose and then also got infected and then recovered, we see that they have a very good protection overall if they have this combination of being recovered and a single dose, similar to what they have if they have -- versus people who have a booster. And we hope to wrap all this up and put it on the medRxiv as soon as possible.

DR. ARNOLD MONTO: Dr. Pergam, please.

DR. STEVEN PERGAM: Thanks, Dr. Monto. Just a question about the pediatric population, since you present all adult data, 16 and older, I'm curious about

patterns you saw within the pediatric population with the booster and declining rates of disease within those under 16. And did you look at timing of when that occurred based on the ages of when boosters were given to the adult population? Thinking of course as parents and children in those typical age ranges, did you see shifts in those declines during the periods when those were given?

DR. RON MILO: So let me say the following. It's a bit complicated in the sense that we had our school year open in parallel. I mean they're not very different timing when the booster shots were administered. Therefore, it's not easy to disentangle what happened in the pediatrics in terms of this indirect effect of the protection that they got from the decreasing say from the booster to the parent and the fact that now they started to meet in classes.

So it's a complicated picture, but what I can say for certain is that we see that the overall incidence in Israel, as I said, declined about 4- to 5-fold and continued to decline 2-fold every ten days.

So it seems like this is also pertaining to the younger age groups -- the pediatric age groups, that they also see a reproduction number lower than one right now.

DR. ARNOLD MONTO: Thank you. Dr. Nelson.

DR. MICHAEL NELSON: Thank you, Dr. Monto and Dr. Alroy and Dr. Milo. Congratulations on your active surveillance for myocarditis and pericarditis, certainly a topic that will impact our deliberations today. The value of active surveillance was seen as we rolled out the smallpox vaccine to a large number of vaccine naïve individuals here in the U.S.

I wonder if you would expand a little bit on your surveillance itself and the ability specifically to detect pre-hospitalization myopericarditis and pericarditis as well as perhaps subclinical myocarditis and pericarditis. The outcomes of those individuals with less severe disease as well as those with severe disease in the long-term basis still is not yet settled upon, and I'm very interested in what case definitions you used for myocarditis and pericarditis as you call your hospitals and your ability to detect these milder

forms.

DR. SHARON ALROY-PREIS: I hope you can hear me because I lost the connection, but I'm still online with you.

DR. MICHAEL NELSON: I can.

DR. ARNOLD MONTO: We can hear you.

DR. SHARON ALROY-PREIS: Great. So we used a definition that is common based on suspected probable cases. It's in our *New England Journal of Medicine* publication. We have there two ways of defining criteria, and so we're classifying. We have a group of cardiologists and a rheumatologist who are defining each and every case based on pain, troponin level, EKG changes, ECHO findings, MRI findings, or biopsy findings. And so the combination of those four categories would lead to someone being defined as probable, suspected case, and most cases are probable in our group.

What we're doing is all healthcare providers know about the active surveillance that we have for hospitals which is where we would assume the severe

cases would go into. In Israel, myocarditis is a diagnosis that is recommended to be sent to the hospitals, sent for hospitalization for observation. So for the most part, if not all, cases should be in our hospitals, and we have communications with all hospitals in Israel in getting their results of hospitalization each and every week for myocarditis cases.

We also have IDF -- Israel Defense Force, our army -- cases that we reach out to them and make sure that we're not missing that young group that might develop myocarditis as well. And so the data from Israel is actually -- has the cases from the army as well in the total representation of myocarditis cases.

DR. ARNOLD MONTO: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, thank you very much for your presentations and the answers to the questions so far.

My question is around what impact behaviors in terms of the mitigation measures might have had on the epi curve that you showed. In other words, were there

mask mandates? Were there other mitigation measures, and was there a way to evaluate those and their impact? Because we know even pre-vaccination, we had these waves, and, as the cases would start to go up in the community, people would sort of self-quarantine or not be going out into big groups. And there was increased mask use, and that definitely had an impact on curbing some of those earlier waves. So are you able to disentangle that, the behavioral aspects, with the impact of the booster dose?

DR. SHARON ALROY-PREIS: So there are mask mandates since the beginning of our fourth wave. We reimplemented the mask mandates, and, except for the mask mandates, we started using a green pass, which means you need to go into certain places using your green pass that shows you're either vaccinated or recovered individual or has a negative corona test.

I have to say that there was no correlation between implementing mitigation steps and the decline in confirmed cases. So we started using the green pass at least a month and a half before we started to show a

decline. We would expect numbers to go down if that mitigation step would have worked efficiently.

We would have seen a drop in the reproductive number about two weeks after, and so I have to say that, shortly thereafter we implemented booster doses, we didn't see a huge decline with the implementation of the booster dose. But there was some mitigation steps that we took. There was no curfew that was put in place, and, until we started the booster regimen, we saw an exponential rise in cases.

Now, I remember the second question from before, whether this was some normal decline -- I think Ron answered this along the way -- in the pandemic wave. We don't think so. This was an exponential rise that continued to go up and up and up. Fifty to 60 percent of those infected in the fourth wave were actually doubly vaccinated. The effectiveness of their vaccine went down to 40 percent. And so they were part of this wave, some of them getting severely ill and dying.

And so there is no question in my mind that

the break of the curve now was due to the booster dose. There was nothing implemented at that period of time that got the curve to break. I don't know if there is a way to bring back Mike.

DR. ARNOLD MONTO: Let's move on to a final question from Dr. Meissner, and then we're done with this session.

DR. CODY MEISSNER: Thank you, Dr. Monto, and thank you for the presentations. The data that's come from Israel has been so interesting and I think helpful for other countries, particularly thinking about the two articles in the most recent *New England Journal* regarding myocarditis have been very, very interesting.

The question I have is this. In Israel, you've used just the Pfizer, I believe, and not the Moderna vaccine. So one question is how applicable -- would you have had a similar result you think if you had used the Moderna vaccine instead of the Pfizer vaccine? Because that's really the question we're thinking about today. And so along those lines, was there any attempt to measure cellular immunity? You

showed us a lot of data about antibodies. Do you have any sense of the role of cellular immunity and waning immunity? Thank you.

DR. SHARON ALROY-PREIS: So for the cellular immunity, we have this research that we hope to finalize shortly, and, in that group of family members with confirmed cases, we will have data on cell immunity. We don't have it on a national level. The data that we showed here -- or that Ron showed here -- is public health surveillance data. It's not connected to serology because we're not doing serology testing for all of the citizens. We do have a lot of research work from Israel by different groups showing the decline in serology and the effect of the booster dose. We are trying to get the data on cell immunity as well hopefully finalized soon so we'll have that answer.

DR. ARNOLD MONTO: And I'm going to park the question about how relevant --

DR. SHARON ALROY-PREIS: And the question about Moderna.

DR. ARNOLD MONTO: Yeah. I'm going to park

that question to later discussion because that's going to be something that we're going to have to discuss in terms of data that we get about the way the Moderna vaccine has behaved elsewhere.

So now we've got a break. I've eaten into the time for the break a bit, so we are going to come back in approximately 10 minutes. That will be at 10:45.

[BREAK]

SPONSOR PRESENTATION - SAFETY AND IMMUNOGENICITY OF A 50 MG BOOSTER DOSE OF mRNA-1273 (MODERNA COVID-19 VACCINE)

MR. MICHAEL KAWCZYNSKI: All right. It's still good morning or depending upon where you are in the country or the world. But welcome back to the FDA Center for Biologics Evaluation and Research meeting. This is the 169th VRBPAC meeting. We just had a quick break, and now I'd like to get it back to our chair, Dr. Monto. Dr. Monto, are you ready?

DR. ARNOLD MONTO: I am. It's my pleasure to introduce the sponsor presentation from Moderna, going to be given by Dr. Jacqueline Miller, ID Therapeutics Area Head. Dr. Miller?

DR. JACQUELINE MILLER: Yes. Thank you, Dr. Monto. Good morning. My name is Jacqueline Miller, as Dr. Monto just said, and I am the therapeutic area head for Infectious Diseases at Moderna. Thank you to the FDA and the VRBPAC for the opportunity to present our safety and immunogenicity data for a 50-microgram booster dose of mRNA-1273, our COVID-19 vaccine. Thank you for everything you're doing to help fight the pandemic.

Moderna has submitted a data package to the FDA for supporting use of a 50-microgram booster dose of mRNA-1273 for individuals 18 years of age and older. In alignment with recent FDA and CDC recommendations, we're (audio skip) emergency use authorization for all individuals 65 years of age and older and individuals aged 18 to 64 years at high risk of severe COVID-19, or with frequent institutional or occupational exposure to

SARS-CoV-2. This is aligned with the recommendations evaluated a few weeks ago.

How does the 50-microgram booster dose fit into the mRNA-1273 vaccination schedule? The first two doses are administered as a 100-microgram dose separated by one month. This was the emergency use authorization granted last December, and for which Moderna has filed a BLA, which is currently under review. Today, we're seeking your endorsement for a 50-microgram booster dose for the individuals I just described.

A second schedule is depicted on the bottom row. For significantly immunocompromised individuals, who do not always develop neutralizing antibody titers after two doses. A third 100-microgram dose administered at least one month after the second dose is needed to complete the primary series. This indication already has emergency use authorization and is not the focus of today's presentation.

This slide outlines the agenda for my presentation. I will start with why booster doses are

needed. This rationale is supported by the ongoing vaccine efficacy analysis and the pivotal Phase 3 Study 301, long-term evaluation of antibody persistence, and observations of breakthrough disease observed in vaccinated individuals which occurred in July and August of this year.

I'll then present data from Study 201B, which evaluated the 50-microgram booster dose, including the rationale for dose selection, study design, the safety profile, and immunogenicity data against both the original virus and the Delta variant.

So let's begin with a recap of the Phase 3 data and the use of mRNA-1273 since the EUA. When we met last year, I presented the primary analysis results from the Phase 3 Study 301, the pivotal safety, efficacy, and immunogenicity study. The study enrolled 30,375 subjects who were randomized one to one to receive the vaccine or saline placebo.

The two-dose primary series of mRNA-1273 was observed to have an acceptable safety profile and a vaccine efficacy of 94.1 percent after nine weeks of

median follow-up time. Based on these data, the emergency use authorization was granted on December 18th, 2020. Since that time, more than 190 million doses of mRNA-1273 have been distributed in the U.S., with nearly 70 million Americans being fully vaccinated. Additionally, according to the CDC, nearly 1.5 million Americans have received a third 100-microgram dose.

Now, I'd like to update the Committee on additional longer-term data from our Phase 3 Study 301. After Study 301 participants were unblinded, those randomized to the placebo group were offered the opportunity to receive mRNA-1273. We then continued to follow all subjects for signs of COVID-19 through weekly e-diary contacts and monthly phone calls.

If a subject reported disease symptoms, the site conducted a physical examination and PCR testing. At the end of the blinded phase of the study, an updated efficacy analysis was performed. This was the basis of Moderna's BLA submission.

This slide shows the Kaplan Meier Curve for

COVID-19 disease occurring at least 14 days after dose 2. This is after a median of 5.3 months of follow-up, and vaccine efficacy remained high and durable at 93.2 percent in the per-protocol cohort. Then this is the Kaplan Meier Curve for severe COVID-19 disease where vaccine efficacy also remained high at 98.2 percent.

So during this period of time, through the end of March 2021, primary SARS-CoV-2 strains detected in the study were the original virus with a D614G mutation and the Alpha variant. However, while the team was preparing the BLA submission, the Delta variant had emerged as a variant of concern in the United States. So, the team constructed an exploratory analysis in subjects who previously received two 100-microgram doses of mRNA-1273 in the Phase 2 Safety and Immunogenicity Study 201.

These were 20 subjects boosted with 50 micrograms of mRNA-1273 and neutralizing antibodies are measured against the original virus as well as the Beta, Gama, and Delta variants. Immunogenicity was first evaluated one-month post-dose 2 with a research

neutralization assay.

In this graph, the bars represent neutralizing antibody titers for the various strains, and the circles represent the individual subjects. The dotted line represents the limit of quantification of the assay. Subjects above the dotted line have antibody, which can be reliably quantified while subjects below the dotted line do not. All subjects evaluated at one-month post-dose 2 had neutralizing antibodies against the original virus. And most also had antibodies against the Beta and Gama variant, although at lower titers.

Six to eight months later, see that antibody titers have waned. Nonetheless, all but one subject retained quantifiable neutralizing antibody titers against the original virus. In contrast, approximately half of the subjects had lost neutralizing antibodies for the Beta, Gama, and Delta variants.

Now, as seen on the right, 14 days after the 50-microgram boost, all subjects had neutralizing antibodies stored to the original virus as well as to

the three variants of concern, including Delta. The increases for the pre-boost to post-booster ranged from 23-fold for the original strain, the 44-fold for Gama, and in particular, neutralizing antibody titers to Delta increased by 42-fold. This was the proof of concept that a fractional booster dose could restore neutralizing antibody even to variants not contained within the vaccine.

So, as we were learning more about the variants of concern, the Delta variant became the dominant circulating strain in the U.S. And we continue to follow the subjects enrolled in the Phase 3 Study 301 for breakthrough COVID disease.

In the slides that follow, you will see the incidence traced in the subjects who were originally randomized to receive mRNA-1273 compared to those originally randomized to receive placebo. For brevity, I will refer to these groups as the early group and the latter group respectively reflecting the time frame of their mRNA-1273 vaccination.

Now, this slide illustrates the time frames in

which the early and later groups were vaccinated. We performed an updated analysis of COVID-19 incidence rates in August of this year because we had observed an increase in the number of breakthrough cases of COVID-19 in the study population during July and August of 2021.

Prior to July, the maximum number of cases reported in mRNA-1273 recipients in a single month was 23. This increased to 81 cases in July and 169 cases in August with 97 percent of these cases due to the Delta variant. At the time of this analysis, subjects in the early group had a median of 13 months of follow-up after their first dose, while the latter group had only eight months. This enabled us to compare incidence rates in subjects who were vaccinated earlier versus subjects vaccinated later.

So, this is the comparison of incidence rates of COVID-19 in the July to August time frame. In light blue, you see the incidence rate in the early group, which was 77 per-thousand person-years as compared to the latter group in dark blue, which was 49 per-

thousand person-years. Therefore, we observed a 36.4 percent decrease in the incidence of cases in those who were vaccinated more recently as compared to those who were vaccinated at an earlier time.

Similar trends are seen when the data are stratified by age. In the younger cohort, 18 to 64 years of age, there was an observed reduction in rates of approximately 40 percent. The reduction was lower in people over 65 at approximately 17 percent.

Incidence rates overall were, therefore, higher in the group vaccinated earlier, and these findings are consistent with the waning antibodies I previously showed, particularly to the variants of concern. They're also consistent with the findings of several real-world evidence studies, which have documented reduced vaccine effectiveness to the Delta variant.

One way to increase antibody titers to the Delta variant could be to administer a booster dose of mRNA-1273. As part of the Phase 2 development program, we had evaluated the safety and immunogenicity of a 50-

microgram booster dose in the subjects who originally received active vaccine in Study 201. These data support our 50-microgram booster dose application.

We chose the 50-microgram dose for the booster because we believe we should vaccinate with the lowest amount of antigen needed to induce an immune response at least equal to that in Study 301, which was linked to vaccine efficacy of 93 percent, which was durable for a median of (audio skip) six months. This has become a successful strategy for other booster vaccines, such as Tdap because immune memory is reactivated. Reducing the booster dose to 50 micrograms would also increase the worldwide vaccine supply of mRNA-1273.

This study was an extension of the original Phase 2 Study 201, which investigated 50- and 100-microgram doses as a primary series. When this study was unblinded to allow cross-over vaccination of placebo recipients, subjects originally randomized to the two mRNA-1273 groups were offered a 50-microgram dose booster at least six months after their primary

series.

A total of 344 subjects received the 50-microgram booster dose, 173 after a 50-microgram primary series, and 171 after the 100-microgram primary series, which is the authorized series currently being administered. The co-primary endpoints were evaluated on the pooled dataset, which included both groups. We also analyzed the 50-microgram booster dose after the 100-microgram primary series because this reflects the schedule that people will receive under the EUA.

The 100-microgram primary series group is a subset of the pooled primary series group. This slide gives the demographic characteristics of the 100-microgram prime subgroup as well as the pooled primary series group. Demographics were similar between the subgroup and the pooled group. There were more females than males enrolled, and the mean age was 52 years. Most subjects were white and not Hispanic or Latin X.

Now, let's review the safety data. The total safety database for the 50-microgram booster dose is 344 subjects. In the slides that follow, I will focus

primarily on the 171 subjects who received the 100-microgram primary series, and I will compare these results to the safety data from Study 301, which is important to investigate potential increases in reactogenicity. Although the data are not shown for the 50-microgram primary series group, please note that the reported rates were numerically similar between the two primary series groups.

Safety data were captured similarly to Study 301. Subjects reported local and systemic adverse reactions for 7 days and unsolicited reactions for 28 days after booster vaccination. SAEs, medically attended AEs, subject deaths, and adverse events leading to discontinuation are being recorded for six months after booster vaccination.

This slide compares the reported rates of solicited local reactions within 7 days after the 50-microgram booster in Study 201B to those reported after the second 100-microgram primary series dose in Study 301. On the left-hand side of each panel is the booster dose. On the right-hand side is the second

dose of Study 301. Grade 1 events are in blue. Grade 2 are in green. Grade 3 are in orange. The reported rates of pain, erythema, and swelling were numerically similar between the groups with no increases in severity after the booster.

Axillary swelling and tenderness was the only solicited symptom reported more frequently after the booster. As with the primary series, the majority of events are mild to moderate in severity and lasted a median of three days or less. Overall, the rates of local reactions were generally similar between the booster dose and dose 2 of the primary series.

This slide shows the systemic solicited reactions. For all systemic reactions, reported rates after the booster dose were numerically lower than after dose 2 of the primary series of Study 301. Again, these reactions were mostly mild to moderate in severity with a median duration of two days or less.

So now let's review the safety data by age group in Study 201B. Here, the bars on the left represent individuals 18 to 64 years of age and on the

right, those over 65. Overall, subjects in the older age group tended to report lower rates in severity of local reactions. The sole exception was Grade 3 injection site swelling, which represented one subject reporting in the over 65 age group.

Now, we see a similar pattern by age for the solicited systemic symptoms. Most symptoms were mild to moderate in severity, and they were reported less frequently in the older adults.

Now, this slide, "Unsolicited Adverse Events," in Study 201B compared to those reported in Study 301. The first column shows the group boosted after the 100-microgram primary series, and the second column is the pooled groups after both doses of the primary series. The third column represents the data from Study 301. Reported rates in Study 201B were similar to those in Study 301. To date, there have been no vaccine-related SAEs or deaths in Study 201B. Overall, the observed safety profile of the 50-microgram booster dose is acceptable.

So now, let's review the immunogenicity of the

50-microgram booster dose, first against the original virus. We pre-specified two co-primary hypotheses to demonstrate the noninferiority of immune response against the original virus strain in Study 201B versus Study 301. The pre-specified cohorts for the primary endpoints was the pool's primary series group, which includes subjects who received either 50- or 100-microgram dose for their primary series. Post-booster immunogenicity was compared to post-dose 2 responses from a subset of the subject in Study 301.

The first hypothesis was based on the geometric mean ratio, or GMR, which was pre-specified to have a lower limit of the 95 percent confidence interval greater than 0.67 and a point estimate of 1 or greater.

The second hypothesis was based on group differences and seroresponse rates, or SRR, in a pre-specified lower limit of at least minus 10 percent. These criteria were selected to align with FDA guidance, and immunogenicity was also evaluated against the Delta variant.

Vaccine effectiveness of the 50-microgram booster was inferred by immunobridging of the pooled primary series groups in Study 301 data. This was done to ensure sufficient study power where evaluation of the statistical criteria recommended by the FDA since we had a fixed number of subjects originally enrolled in the Phase 2 study to boost and could not increase further at that time.

Our briefing book presented the pooled analysis as this was the pre-defined primary subset. Additional analyses were also performed on the 100-microgram primary series group, and I will also share these data in the following slides.

The first co-primary immunogenicity hypothesis regarding the geometric mean ratio of neutralizing antibodies to the original virus strain was met for the pooled dataset. The GMR was 1.7, and the lower limit of the 95 percent confidence interval was 1.5. Because the 95 percent confidence interval excluded the value 1, we conclude that the GMTs post-booster are statistically significantly higher than the GMT post-

primary series.

Now, this slide shows the same analysis for the GMR evaluated in the groups that received the 100-microgram primary series. The results were very similar. The GMR was 1.8 with a lower bound of 1.5, and therefore, the first co-primary immunogenicity hypothesis was also met for the 100-microgram primary series group. The post-booster neutralizing antibody tigers were statistically significantly higher as compared to the post-dose 2 titers in the Phase 3 Study 301.

Our second pre-specified hypothesis compared seroresponse rates, which we initially defined as a 3.3-fold rise from pre-booster titers. This definition was based on the variability characteristics of this specific neutralization assay. Using this definition, the seroresponse rate was 94 percent in the Study 201B group, compared to 99 percent in the Study 301 group with a lower limit for the group difference of minus 8.8 percent each point, which exceeded minus 10.

Thus, the second pre-specified endpoint

against the original virus strain was met for the pooled study group using the original seroresponse definition. And this is notable especially because the pre-booster GMTs in the 201B group were so much higher at 126 than the pre-dose 1 titers in the Study 301 subjects, who were seronegative at the time of enrollment. The higher pre-booster titers make it much harder to reach the same fold rise as in the seronegative subjects.

The FDA requested that we evaluate a different definition for seroresponse, which I will evaluate and then present in the slides that follow. This panel contains the data we just reviewed. So the light blue bar represents the seroresponse rate defined by a 3.3-fold rise in Study 201B in the pooled group, and the dark blue bar represents Study 301. These bars represent the same study populations using a 4-fold rise as the seroresponse definition. Because a higher fold rise is required, the seroresponse rates are lower for both groups than with the first definition.

We also noted that the VRBPAC Committee

reviewed a third definition at the prior meeting. This last analysis is a within subject comparison of those who achieved a 4-fold rise increase in titers from pre-dose 1 at either the post-booster time point or the post-dose 2 time point in Study 201.

Using this definition, numerically higher response rates are observed after the booster dose than after the dose 2 primary series in the same subjects. Importantly, regardless of the definition used, at least 90 percent of the subjects in the pooled groups achieved a seroresponse rate post-booster.

So, the FDA also asked us to evaluate a seroresponse rate definition of a 4-fold rise only in the population that received a 100-microgram primary series. This is the inferential analysis highlighted in the FDA briefing book. In this instance, the statistical criterion was not met.

Nonetheless, the seroresponse rate was 88 percent, like the fact that pre-booster titers were 150, which were 15 times higher than the pre-dose 1 titers in Study 301. It should be noted that the post-

booster GMTs at 1,952 were nearly twice as high as the post-dose 2 titers of 1,081 in Study 301 which were associated with vaccine efficacy.

Now, let's further examine the subjects in Study 201B who did not achieve a 4-fold rise. In subjects who failed to achieve a 4-fold rise, pre-booster GMTs were 492, which was more than 4 times higher than subjects who met the definition with baseline titers of 108. Subjects in both categories achieved post-booster titers well above the level of Study 301 at 1,081. Therefore, subjects who did not meet the 4-fold rise definition are still deriving substantial benefit from the 50-microgram booster dose.

One of the key populations proposed for booster vaccination are adults over the age of 65 because of their increased risk from severe complications of COVID-19. Therefore, we performed an analysis comparing GMTs by age group. This slide presents the pre-booster and post-booster GMTs in subjects 18 to 64 years of age, those over 65, and the overall population who received the 100-microgram

primary series, so the subgroup. Again, all post-booster GMTs are above the level at Study 301 with adults over 65 achieving an 18-fold rise.

Similarly, we performed an evaluation of seroresponse rates by age based on the 4-fold rise definition in the 100-microgram primary series group. Post-booster vaccination, 88 percent of younger adults and 89 percent of older adults achieved a 4-fold rise indicating no reduction in the over 65 age group. We also tested the serum samples from Study 201B for neutralizing antibodies to the Delta variant as this is currently the variant of greatest concern.

This slide shows the pre- and post-booster titers against the Delta variant in subjects 18 to 64 years of age, over 65, and overall, for the group that received the 100-microgram primary series. In the younger cohort, antibodies increased 16-fold after the booster dose, and they increased 22-fold in the older cohorts.

These data suggest that the neutralizing capacity against the Delta variant can be substantially

enhanced by administration of a 50-microgram booster of mRNA-1273, which would help address the current breakthrough cases due to the highly transmissible Delta variant.

So here, we see the seroresponse rates to Delta variant by age group and overall, in the 100-microgram primary series group. The younger age cohort had an 88 percent response rate, which increased to 95 percent in the older cohort. This analysis supports the robust immunogenicity to the Delta variant of the 50-microgram booster.

Now, I'd like to summarize our safety and immunogenicity data of the 50-microgram booster dose of mRNA-1273. The safety profile of the 50-microgram booster was comparable to dose 2 of the 100-microgram primary series in Study 301. Injection site pain was the most common local solicited reaction and headache, fatigue, and myalgia were the most commonly reported systemic adverse reactions.

As with the primary series, most adverse reactions were mild to moderate in severity. Axillary

swelling and tenderness was the only solicited symptom reported more frequently after the booster dose and in Study 301. And all other symptoms were numerically lower post-booster. No vaccine-related SAEs or deaths were reported during this study period.

So, to summarize immunogenicity, the co-primary hypothesis on the GMR was met for both the pooled dataset, as well as the 100-microgram primary series. The pre-specified hypothesis on seroresponse rate in terms of a 3.3-fold rise on the pooled dataset was met. This criterion was not met for the 4-fold rise analysis in either the pooled or 100-microgram primary series population.

Nonetheless, 88 percent of subjects achieved a 4-fold rise. The subjects who did not meet the 4-fold rise had pre-booster antibody titers more than four times higher than those who did have a seroresponse. A 13-fold rise from pre-booster titers was observed to the original virus, and the Delta variant antibody titers increased by 17-fold overall.

A substantial increase in neutralizing

antibody titers against both strains in both the younger and the older age group. Taken together, these data suggest that a 50-microgram booster of mRNA-1273 will result in higher antibody responses and observed after dose 2 in Study 301 in which efficacy was demonstrated at 93 percent.

This booster has the potential to address waning antibody titers and to reduce breakthrough disease due to the highly transmissible Delta variant. And the data that I have now presented for the 50-microgram booster dose and at least 6 months after completion of the primary series.

The proposed use is for individuals who are 65 years of age and older, 18 to 64 years of age at high risk of severe COVID-19, and those who are at increased risk because of institutional or occupational exposure to SARS-CoV-2 aligned with the Committee's previous vote.

We would like to thank our collaborators at the NIH, the COVID-19 Prevention Network, BARDA, the Montefiori Laboratory at Duke University, and the

investigators and site personnel, and most especially, we would like to thank the study participants. This concludes my presentation. Thank you.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Miller. Given the fact that you have finished a bit early, we have time for a few questions from the members. I see Dr. Pergam.

DR. STEVEN PERGAM: Thanks for that presentation. I appreciate Moderna's efforts in putting that together.

I had a question about how the drug is going to be put together and labeled specifically for the differing booster versus the primary vaccine, particularly when addressing the different populations who are getting boosters.

Since the immunosuppressed population will be getting the 100 milligram and the rest of the population will be getting 50, how is Moderna putting

that together to make it clear? Because I could see issues coming with inappropriate dosing being given to specific populations. Can you discuss how Moderna is going to be organizing that specifically?

DR. JACQUELINE MILLER: Yes, absolutely. So the current presentation is a multidose vial. So healthcare providers pull a 0.5 mL dose, which is the 100-microgram dose from a multidose vial to administer. That same vial can be utilized to administer a 0.25 mL dose, and that 0.25 mL dose being lower is actually consistent with some other vaccines, particularly during the H1N1 pandemic where lower doses of a multidose vial were administered to some populations.

We recognized that this will require some education and enforcement, and so we are preparing to send a "dear healthcare provider" letter explaining how the doses are to be administered. In addition, our fact sheet is going to contain detailed information, and we have a 24-hour call center to support healthcare providers in their administration efforts.

There are additional resources that will be

available on the Moderna website, and then finally, our team that engages with primary care physicians is going to be going out and doing additional training to make sure that people understand the differences between the two doses.

I think the important emphasis is that the 50 microgram is a booster. The 100 microgram that immunocompromised subjects are receiving is really a different indication. These are subjects, who in multiple studies, did not respond as well to the second dose and really need that third dose to reliably induce neutralizing antibody titers.

DR. ARNOLD MONTO: Thank you. Dr. Lee?

DR. JEANNETTE LEE: So one question I have is you noted, obviously, that with the criteria for immunobridging success, which included a seroresponse defined by a 4-fold increase entire was not met and that was in the report. In your presentation, you looked at a different threshold with 3.3. Can you sort of indicate why you chose that particular level as opposed to -- I mean, we see what you had before, but

where does a 3.3 come from?

DR. JACQUELINE MILLER: Yes. Thank you. The 3.3-fold rise is actually based on the inherent variability of the assay. So, the assay itself has discriminating capabilities and the statistical analysis you see in both booster titers during the validation of that assay indicated that you could reliably discriminate between levels of titers at the 3.3 threshold.

I'll point out that there are some other vaccines particularly the meningococcal B vaccine that also uses a different definition for fold rises, so, the 5-fold rise in that case. But we accept the feedback that the 4-fold rise is going to be applied across companies, which is why we have also calculated using the 4-fold rise.

DR. JEANNETTE LEE: Thank you.

DR. ARNOLD MONTO: Dr. Gans? Muted. Can't hear you.

MR. MICHAEL KAWCZYNSKI: You're muted on your phone, Dr. Gans.

DR. HAYLEY GANS: Okay.

MR. MICHAEL KAWCZYNSKI: There you go.

DR. HAYLEY GANS: Can you hear me now? Okay.

DR. ARNOLD MONTO: Yes.

DR. HAYLEY GANS: Thank you. Thank you, Dr. Miller, for that, for you and your team putting that together for us.

I have a real question about really trying to identify the 18 to 64 age group because we're trying to really parse out their susceptibility for needing a booster.

So, you talk a lot about -- you showed the breakthrough disease within that cohort, and it's actually quite high. We didn't see any outcomes for those breakthrough diseases, so hospitalizations or severe disease, which is what we're trying to parse out.

You also show the geometric mean titers pre-booster. They're pretty much the same as they are for that age group as they are for the greater than 65 age group. So, I'm really trying to understand what we

should be thinking about in terms of that age group and whether or not we really need to think about their also waning immunity.

You don't seem to parse out the age groups when you're looking at the overall wane and antibody. I think that was Slide 14, that you show against all the different variants. So, we don't really know that per age group. And so I'm wondering if you could parse that out a little bit more for us and talk about what those levels actually mean for that particular age group.

DR. JACQUELINE MILLER: Yes. I am actually going to show some additional data from that breakthrough analysis. So, Panel B, please. I would like to show you first the cases of severe COVID-19 between the more recently vaccinated participants and the later vaccinated participants by age groups.

So what you see on this slide is that all subjects are on the left-hand side of the panel. In the middle are the 18 to 64 years of age. On the right are the greater than 65 years of age. And so what you

can see here is that amongst all subjects, there was a 46 percentage point difference between the earlier and later group overall, with 30.9 percent in the 18 to 64 group with only 11 cases.

So, this is the severe cases. And then over 65, a 64-percentage point difference. Then can we go to Panel A, please, because Dr. Gans also asked about the characteristics of severe cases and hospitalizations. Just to show you that the severe cases comprised 7.6 percent of the breakthrough cases. There were 19 of them overall.

Notably, three hospitalizations and two subject deaths occurred in the earlier vaccinated group. Both of those deaths occurred in males over 70 years of age. Both of them had underlying COPD and other medical complications.

Then, Dr. Gans, your second question was with respect to antibody titers by age after the primary series, and I'm going to show you the original strain. So, can we put up Panel B, please? This is going to be after the 50-microgram booster for the 100-microgram

series. What you see -- this time I'm going to reverse it a bit and move over to the right-hand side first.

You see most to the right are GMTs from Study 301, and overall, the GMTs for the pooled age group. Then on the left-hand panel, you see 18 to 64 years of age and 65 years of age. The antibody persistence -- can we please pull up a slide that shows the GMT ratios by age group, please? The comparison of GMT ratios is actually higher in the older age group and the antibody persistence was higher in the younger age group. I'm just going to wait for the slide to come up to show you.

You know what? I will show that slide at the next Q&A and provide you with those stats.

DR. ARNOLD MONTO: Right. Which helps me move to say that the next Q&A is going to be after lunch, so we will have some additional time to ask questions of Dr. Miller.

We'll move now to the FDA presentation of the data, and we're going to have two speakers. Tina Morgan Mongeau and Hui-Lee Wong with Dr. Richard

Forshee ready in the background to answer additional questions. Let's move ahead to the FDA presentations.

FDA PRESENTATION - FDA REVIEW OF EFFECTIVENESS AND SAFETY OF MODERNA COVID-19 VACCINE (mRNA-1273) BOOSTER DOSE EMERGENCY USE AUTHORIZATION AMENDMENT

DR. TINA MONGEAU: Good morning. My name is Dr. Tina Mongeau. I am the medical officer in the Office of Vaccines Research and Review within the Division of Vaccines and Related Products Applications at the FDA. I will present FDA's review of the effectiveness and safety data following a booster dose of Moderna COVID-19 vaccine as submitted by Moderna under an emergency use authorization amendment.

I'd like to start off by acknowledging the contributions of many of my colleagues within the Center for Biologics Evaluation and Research. My presentation is a reflection of all of their contributions.

So my presentation will begin with background

information, followed by an overview of the booster dose and two-dose series studies, the immunogenicity and safety results, and then I'll conclude with an overall summary.

So Moderna COVID-19 vaccine, also known as mRNA-1273, has been available under emergency use authorization since December 18th, 2020. It is authorized for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 18 years of age and older. The authorized regimen is a two-dose series administered one month apart with each 0.5 mL dose containing 100 micrograms of mRNA.

A third 0.5 mL dose is authorized for administration at least 28 days following the second dose in individuals with certain immunocompromising conditions. Moderna has submitted an amendment to their EUA to support authorization for booster administration of Moderna COVID-19 vaccine at 50 micrograms, 0.25 mL dose, at least six months following a two-dose series for the following populations: individuals 65 years of age and older, individuals 18

through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19, including severe COVID-19.

Regulatory background for this submission dates back to May 28th, 2020, with initiation of Phase 2 Study P201 Part A, which I'll refer to as P201A, evaluating two dose levels of the two-dose series of mRNA-1273.

On July 27th, 2020, the Phase 3 randomized placebo-controlled safety and efficacy study, P301, was initiated.

On December 18th, 2020, FDA issued an EUA for a two-dose series of Moderna COVID-19 vaccine in individuals 18 years of age and older.

On January 28th, 2021, the booster dose phase of Study P201, which I'll refer to as P201B, was initiated.

On August 12th, 2021, the Moderna COVID-19 vaccine EUA was reissued to include a third dose for

immunocompromised individuals 18 years of age and older.

The next part of my presentation will provide an overview of the design of the booster dose and two-dose series. So, Study P301 is an ongoing randomized observer-blinded, placebo-controlled study conducted in over 30,000 participants 18 years of age and older. Participants were stratified by both age and risk for progression to severe COVID-19 into one of three groups shown on this slide here and randomized one to one to receive two injections 28 days apart either mRNA-1273 at 100 micrograms or a placebo-controlled.

Data from Study P301 supported the EUA for the two-dose series of mRNA-1273 at the 100-microgram dose in adults 18 years of age and older. The 15,184 recipients of the 100-microgram mRNA two-dose series were used as a comparator group for overall safety following the booster dose. The 1,080 participants who were randomly selected as an immunogenicity sub cohort in P301 were used as a comparator group in booster dose immunogenicity analyses.

In the context of this EUA submission, Study P201 is an ongoing two-part study. Part A is the observer-blinded randomized placebo-controlled two-dose series phase, and Part B is the open-label booster dose phase of the study.

Part A was conducted in a total of 600 participants without preexisting conditions that would place them at risk of severe COVID-19. Participants were stratified by age into two cohorts and randomized according to a one to one to one ratio to receive two injections 28 days apart of mRNA-1273 at either a 50-microgram dose or a 100-microgram dose or a placebo-control.

At the conclusion of Part A, all participants were offered a 50-microgram booster dose at least six months after completion of the two-dose series during the booster phase of the study. Of the participants who completed Part A, 344 agreed to and actually received an open-label booster dose in Part B of the study.

This included 173 participants in the 50-

microgram primed group and 171 participants in the 100-microgram group. Only the 171 booster dose participants primed with the 100-microgram series, shown in bolded text on the slide, contributed to our analyses of the immunogenicity analyses.

In addition, these participants contributed the main safety data for the booster dose safety analyses. Median interval between completion of the 100-microgram two-dose series and the booster dose was approximately 7.2 months, ranging between 5.9 and 8.6 months.

Booster dose effectiveness is being inferred by immunobridging analyses comparing two immunogenicity endpoints. Geometric mean neutralizing antibody titers, or GMTs, and seroresponse rate against a pseudovirus expressing the SARS-CoV-2 spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, which I'll refer to from this point forward as the D614G strain.

Immunogenicity analyses compared each co-primary endpoint at 28 days after the booster dose in

study P201B to the corresponding endpoint 28 days after dose 2, which would be Study Day 57 in the P301 random immunogenicity subset is the reference study population in whom vaccine efficacy was demonstrated. Just to note, neutralizing antibody titers were 50 percent inhibitory dose ID50 titers measured with a validated pseudovirus neutralization assay against the D614G strain by Duke University Medical Center.

This slide summarizes the immunogenicity analysis of the GMT co-primary endpoint against the D614G strain. The primary analysis evaluated the ratio of GMTs after the booster dose in Study P201B to the corresponding GMTs after dose 2 in Study P301. The immunobridging success criteria required that for the GMT ratio, a lower limit of the 95 percent confidence interval not to be greater than 0.67, a 1.5-fold margin, and that the point estimate of the GMT ratio not to be greater than 1.0.

This slide summarizes the immunogenicity analysis of the seroresponse co-primary endpoint against the D614G strain. Seroresponse for an

individual participant is defined as the 4-fold or greater rise of neutralizing antibody titers from baseline to 28 days post-vaccination against the D614G strain where baseline titers that were less than the assay's lower limit of quantitation or LLOQ, were set to the LLOQ.

For P201B booster dose recipients, baseline was defined as the titers prior to the booster dose on the day of booster vaccination. For P301 two-dose recipients, baseline was defined as prior to dose 1. For the immunobridging analysis, the percentage difference was calculated between the seroresponse rate at 28 days post-booster dose in P201 and the seroresponse rate 28 days after dose 2 in P301.

The immunobridging success criterion required a lower limit of the 95 percent confidence interval for the difference in seroresponse rates to be greater than or equal to negative 10 percent.

P201B statistical analysis plan also pre-specified immunobridging analyses with hypothesis testing for the B.1.617.2 or Delta variant. These

analyses are not yet available because the assay for the Delta variant is not yet validated. We will, however, present descriptive analyses submitted by Moderna using an exploratory assay for the Delta variant.

At this point, I'll move on to review the booster dose study results starting with immunogenicity data. In Study P201B, of the 171 participants who were administered a booster dose, 149 were included in the per-protocol set, which is the primary analysis population for immunobridging comparisons. A total of 15 participants were excluded from the full analysis set due to the lack of baseline or post-baseline immunogenicity data.

An additional seven subjects were excluded from the per protocol set due to SARS-CoV-2 infection or a major protocol violation involving incorrect dosing at the booster dose visit. Of note, one 100-microgram prime booster dose participant who did not receive dose 2 was included in the per-protocol population as P201B participants were not required to

receive both doses of the two-dose series to be included in the per-protocol set.

In Study P301, of the 1,080 participants randomly selected for inclusion in the immunogenicity sub cohort, a total of 1,055 participants were included in the per-protocol set for the primary immunobridging analyses. Exclusion from the P301 per-protocol set was most commonly due to HIV infection followed by errors in the administration of dose 2 and one participant with other protocol deviation.

This slide presents the demographics of the per-protocol immunogenicity subset for Studies P201B and P301. Compared to Study P301, participants in Study P201B were less racially and ethnically diverse, had a lower percentage of males, a lower median BMI, and a lower percentage of participants who were in the category of obese with a BMI 30 or greater.

MR. MICHAEL KAWCZYNSKI: Your audio feed (audio skip). I just want to make sure we're good. All right. You can continue.

DR. TINA MONGEAU: Thank you very much. So

this slide shows the results for the GMT co-primary endpoints, again, for the D614G strain. And we see neutralizing antibody titers against the D614G strain at 28 days after the booster dose in P201B -- that's in this column here -- and 28 days after completion of the two-dose series in P301.

The GMT ratio of Study P201B over P301 was 1.8 with a 95 percent confidence interval ranging from 1.5 to 2.1, which met the pre-specified success criteria of a lower limit of the 95 percent confidence interval being greater than 0.67 and the GMT ratio point estimate being greater than 1.

This slide presents the results for the seroresponse co-primary endpoint for the D614G strain. The difference in seroresponse rates between the booster dose recipients in P201B and two-dose series recipients in P301 was negative 10.5 with a lower limit of 16.7 percent. I'm missing the pre-specified immunobridging success criterion of a lower limit of the 95 percent confidence interval greater than or equal to 10 percent.

In post hoc analyses, participants with lower pre-booster neutralizing antibody titers appear to be more likely to achieve a 4-fold or greater rise in titers after the booster dose compared to participants with higher pre-booster titers. For instance, P201B participants who met the 4-fold rise in titers had a baseline GMT of 109, whereas those who did not meet the 4-fold rise in titers had a baseline GMT of 492.

Seroresponse rates in baseline GMTs and P201B participants by age subgroups also appear to be consistent with this observation. Participants who were 65 years of age and older had a lower baseline GMT but a higher seroresponse rate compared to participants 18 through 64, less than 65 years of age.

This slide shows the exploratory descriptive analyses of neutralizing GMTs against the Delta variant after the booster dose in Study P201B among the 100-microgram prime booster dose participants and after dose 2 in Study P301 participants who received 100-microgram two-dose series. These data suggest numerically higher GMTs were achieved one month after

the booster dose (audio skip) data with some caution because they are limited by the use of a non-validated assay against the Delta variant.

Assessment of the incidence of SARS-CoV-2 infection in Study P201B was an exploratory endpoint. SARS-CoV-2 infection was detected by virologic or serologic evidence at scheduled visits or for potential SARS-CoV-2 exposure and/or symptoms. Through the August 16, 2021, cut-off date, a total of 38 booster dose participants had positive tests, 20 in the 50-microgram primed group, and 18 in the 100-microgram primed group.

All participants who tested positive did so at pre-planned study visits. Of the 18 booster dose participants who were primed with the 100-microgram two-dose series and who tested positive, two occurred prior to when a maximum antibody response would have been anticipated after the booster dose, both being positive on day 8 after (audio skip). The remaining 16 infections were identified at day 29 or later. Only one of the 18 participants was symptomatic, and no

SARS-CoV-2 infections were reported as severe.

Limitations of this analysis include the exploratory nature and the lack of a controlled group. Case definitions for COVID-19 were not pre-specified and were not provided to study sites, nor used in the analyses, and information related to COVID-19 cases was not really collected systematically.

Responding to an FDA request, Moderna performed a post hoc analysis of protocol-specified COVID-19 cases in the ongoing P301 efficacy study, which accrued during the period between July 1st and August 27th, 2021, corresponding to the Delta variant surge. The analysis compared rates of COVID-19 among participants originally randomized to mRNA-1273 and those who completed the two-dose series early in the study versus those who were originally randomized to placebo and then crossed over to mRNA-1273, and thus, completed the two-dose series later in the study.

Study participants who were included in the analyses were those who remained at risk for first occurrence of COVID-19 following receipt of the two-

dose series. Although not independently verified by FDA, the post hoc analyses appeared to indicate that the incidence of SARS-CoV-2 during the analysis period among participants who completed the two-dose series early in the study was 77.1 cases per 1,000 person-years versus 49 cases per 1,000 person-years among participants who completed the two-dose series study.

The median duration of follow-up was 13 months post-dose 2 among those who completed the two-dose series early in the study, and 7.9 months post-dose 2 among those who completed the two-dose series later in the study. Nineteen severe COVID-19 cases were reported during the analysis period; 13 of which occurred among participants originally randomized to mRNA-1273 giving an incidence of 6.2 per 1,000 person-years, and six occurred among participants originally randomized to placebo with an incidence of 3.3 per 1,000 person-years.

Overall, 15 of these 19 severe cases occurred among participants who were 65 years of age or older and/or who had a risk factor for severe COVID-19. The

four remaining cases occurred in participants between 42 and 64 years of age and who were not at risk of severe disease. Of those four, three out of the four were originally randomized to the mRNA-1273 group.

We'll now move on to review safety results. This slide shows the median length of safety follow-up after the booster dose and all P201B participants through an August 16, 2021, cut-off date. Among the 100-microgram prime booster dose participants in the middle column here, we see that the median duration of follow-up was 5.7 months ranging from 3.1 to 6.4.

So our review of safety results, we'll start with the immediate reactogenicity defined as reactions occurring within approximately 30 minutes after (audio skip) injection. Results are shown for P201A and P301 participants who received a 100-microgram two-dose series of mRNA-1273 and 100-microgram prime booster dose participants in Study P201B.

Overall, immediate reactions were reported by a numerically higher proportion of P201B participants at 13.2 percent compared to P201A participants at 5.1

percent. The rate in P201B is notably similar to that in P301, which had a rate of 9.9 percent. A total of 22 participants in the P201 group reported any immediate adverse reaction. Of these, one was reported as severe. One case of severe injection site pain.

Breaking down these reactions by local versus systemic, 10.2 percent of participants reported immediate local reactions, which consisted mostly of injection site pain followed by erythema and axillary (audio skip) and 4.8 percent of participants reported immediate systemic reactions, which consisted of headache, fatigue, arthralgia, myalgia, (audio skip).

This slide shows the rates of solicited local reactogenicity by age group within seven days after dose 2, among the 100-microgram two-dose series recipients in P201A, and within seven days after a booster dose, following a 100-microgram two-dose series in P201B.

The most frequent local adverse reaction reported in both age groups was injection site pain in which this was reported by a similar proportion after

the booster dose versus (audio skip) dose 2. Among participants 18 to less than 65 years of age, rates of axillary swelling or tenderness of the vaccination arm, which were mostly mild in severity and transient, were higher after the booster dose at 24.8 percent compared to dose 2, 11.6 percent.

When comparing the rate of axillary swelling or tenderness after the booster dose, for the corresponding rate after dose 2 in the larger P301 population of 18- to less than 65-years-old, the rates were more similar, 24.8 percent versus 16 (audio skip).

In participants 65 years of age and older, there were no notable trends in the frequency of local reactogenicity after the booster dose compared to after dose 2. Rates of local reactogenicity were generally lower in participants 65 years of age and older compared to those 18 through 64. Across both age groups, severe local reactions after the booster dose were reported by 0 to 5.3 percent. No Grade 4 solicited local reactions were reported in either group after the booster dose in either age group. Are you

still able to see my slide?

MR. MICHAEL KAWCZYNSKI: Yeah. Hold on a second. Somebody moved the slides here. I'll put it back on yours. Give me a second here. There you go, Dr. Mongeau. There you go.

DR. TINA MONGEAU: So yeah. Rates of local reactogenicity were generally lower in those 65 years and older compared to (audio skip). I think I was going over the -- yeah, the severe reactions -- and overall, the median day of onset of local reactions was generally between day 1 and day 3, and the median duration of local reactions was generally no longer than three days in both age groups.

We'll move on to review this slide, which shows the rates of solicited systemic reactogenicity. Again, shown by age group within seven days after dose 2 among those who got the 100-microgram two-dose series in Study P201A, and within seven days after a booster dose among those who received the 100-microgram two-dose series in P201B.

The most frequent systemic adverse reaction

reported in both age groups was fatigue followed by either headache or myalgia and then arthralgia and chills. In participants 65 years of age and older, which had a relatively small denominator, the rates of myalgia and arthralgia were numerically higher after the booster dose compared to after dose 2.

However, the rates of myalgia and arthralgia after the booster dose were notably similar to the corresponding rates after dose 2 in the larger P301 population 65 years of age and older. Across both age groups, severe reactions were reported by 0 to 7.9 percent, and there were no Grade 4 reactions reported after the booster dose. Overall, the median day of onset for systemic reactions was day 2, and the duration of these reactions was generally no longer than two days in both (audio skip).

This slide provides an overview of the unsolicited adverse events and serious adverse events reported in Study P201B. Through the August 16, 2021, cut-off date, there were no unsolicited adverse events that were not already captured as solicited local and

systemic reactions and which were not considered causally related to Moderna COVID-19 vaccine.

A total of 20 subjects or 11.7 percent reported unsolicited adverse events through 28 days after the booster dose. The most common unsolicited adverse events included headed and fatigue. One case of Bell's palsy was reported and considered unlikely to be related based on temporal implausibility that that occurred five hours after booster dose.

There were no serious adverse events reported within 28 days after booster vaccination. As of the August 16, 2021, cut-off date, five SAEs were reported in four participants with time to onset more than 30 days following the booster dose. That included one case of tendon rupture, one case of spontaneous abortion, one case involving deep vein thrombosis and pulmonary embolism, and one case of pericarditis.

None of these SAEs were considered likely to be related to the vaccine because the timing of the events in relation to the vaccination did not suggest a causal relationship and/or a more likely alternative

etiology was identified, and no participants were withdrawn due to adverse events.

So, I will now conclude with a summary of P201 immunogenicity and safety data. In terms of immunogenicity, immunobridging analyses against the D614G strain met the pre-specified success criteria for the GMT ratio but not for seroresponse rates.

In post hoc analyses, participants with lower pre-booster neutralizing antibody titers were more likely to achieve a 4-fold or greater rise in neutralizing antibody titers after booster vaccination compared to participants with higher pre-booster neutralizing antibody titers.

Immunogenicity data to support effectiveness of the booster dose against the Delta variant are limited to exploratory analyses using a non-validated assay. In terms of safety, there was no evidence of increased reactogenicity following a booster dose relative to dose 2, with the exception of axillary swelling or tenderness of the vaccination arm in participants 18 to less than 65 years of age.

Unsolicited adverse events did not reflect any new safety concerns.

Through the August 16, 2021, cut-off date, there were no death or SAEs considered causally related to Moderna COVID-19 vaccine. That concludes my presentation. Thank you.

FDA PRESENTATION - SURVEILLANCE UPDATES OF MYOCARDITIS/PERICARDITIS AND mRNA COVID-19 VACCINATION IN THE FDA BEST SYSTEM

DR. HUI-LEE WONG: Good morning. I'm Hui-Lee Wong, Associate Director for Innovation Development, Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research. On behalf of our multiple collaborators in the FDA BEST system, today I'll present the preliminary results on post-market data of myocarditis and pericarditis following mRNA COVID-19 vaccination in the FDA BEST system.

Information on myocarditis and pericarditis has an update to the fact sheet for COVID-19 vaccines

for Moderna. Post marketing adverse reports have indicated and suggested risk around within seven days following the second dose, highest in males 18 through 24 years of age. We evaluated this in the FDA active surveillance system, the Biologics and Effectiveness Safety System, or BEST.

The FDA CBER active surveillance program through multiple partners as illustrated here on this slide where it actively monitors the safety and effectiveness of biologics, including COVID-19 vaccines. The (inaudible) surveillance of COVID-19 vaccines, the BEST system works with the -- in this case, the four large nationwide health plans seen here in the yellow circles.

So collectively, the four BEST medical claims databases here contain data from every state in the United States, in this case, claims databases and covering approximate around 80 million enrollees per year. For analysis that I'll be showing here today, that is around 21 million vaccine doses; that's 12.6 million doses for Pfizer and 8.5 million for Moderna.

In this presentation, when I state myocarditis and pericarditis, we do find that BEST myocarditis and/or pericarditis identifies that using diagnosis codes for reimbursement and the risk interval is one to seven days after each dose. We estimated the incidence rates and compared incidence rates between Moderna and Pfizer.

So, for incidence rates, we estimated this in the Moderna and in Pfizer vaccine brand, by groups, by sex, and by dose. In dose, that will be any dose post-dose 1, post-dose 2, on post-on regression. It adjusted for age, sex, and by sample size permits, week of vaccination, history of prior COVID-19, and urban/rural status.

This slide shows you the number of events, seen here, the first one through seven days of receipt of any dose in the FDA BEST system. You can actually see here that it's actually the highest in the younger age group at 18 to 25. It's also the highest in males and not shown here is actually also the highest after the second dose. So that would be males 18 to 25 years

of age.

This slide here illustrates, graphically summarizes the incidence rates of myocarditis and pericarditis in the first one to seven days of receipt of any dose of mRNA COVID-19 vaccines for the four databases. So, the vertical axis here is by age, so the upper most there is the youngest age group, 18 to 25. The horizontal axis here is the incidence rate, and that it's per-million person per days.

Overall, as you can see here, you see colored dots and whiskers and that denotes the incidence rate and the corresponding 95 percent confidence interval for each of the databases here. In general, we can see that the incidence rates vary across the four databases, a wide confidence interval.

As you can also see, the highest actually is in 18 to 25 years of age. In our analysis, we saw that the highest risk is actually in the 18 to 25 years, male, post-dose 2. With that, one thing also to note that these events here are not -- have not yet been confirmed with medical charts and medical chart

confirmation is underway.

The highest risk of -- sorry, for highest incidence rates of myocarditis and pericarditis, we're looking at the age group of 18 to 25 males after dose 2 (inaudible) that the dose here actually -- for this post-dose 2, the incidence rates here vary across these four databases, and this actually went from 5 to 37 per-million person-days.

We compared between Moderna and Pfizer this incidence rate. We used a retrospective comparative cohort study design, and what we did was that we compared the post-vaccination rates in the first one to seven days of each dose. We also adjusted for the (inaudible) that the BEST sample size permits that we used in the incidence rates.

Among the males 18 to 25, there's a total of 1.16 million mRNA vaccine doses of which 750,000 Pfizer, 410,000 is Moderna. For this analysis, there's a total of 68 events that we see here. As you can tell, most of the events are actually in dose 2 (inaudible) analysis by dose. The conclusions are

somewhat actually similar for any dose in dose 2, so, in my next slide, I'll be showing you results for any dose. In this case, this will be comparing between Pfizer and Moderna incidence rates.

This slide shows you the incidence rates ratio of myocarditis and pericarditis comparing Moderna versus Pfizer and that will be the reference. This is for as much and the highest group. The group at the highest risk is male, 18 to 25 years, any dose. What you see here actually on the horizontal axis is the incidence rate ratio, and that once again is -- that compares between Moderna and Pfizer.

The dotted line here actually denotes the rate ratio of one that indicates that that's no difference in risk between Pfizer and Moderna. So, the incidence rate ratio is on the right of this dotted line, then represents a high incidence rate ratio for Moderna and, on the left, a high incidence rate ratio for Pfizer.

As you can see here, the top -- well, actually, the first top four is incidence rate ratio estimates in our four databases here that (inaudible)

among those. In three of these, actually, the (inaudible) now. So there was no (inaudible) elevated risk here. One of these here, the data pack number 4, there's an elevated risk and it's based on 20 events.

BEST also evaluated a data system, which means that we were able to take advantage of (inaudible) protocol and common data elements combined these estimates, and this is particularly helpful for rare outcomes in -- for example in myocarditis/pericarditis.

So, we summarized these incidence rate ratios and this is represented in the rate or dot with the whiskers here in random-effects meta-analysis. Here, we see that there isn't a significant elevated risk. However, this could be as low as 0.56 and as high as 2.6.

In summary, in our year-study of four large client databases covering 18 million persons annually with 21 million mRNA vaccine doses, our preliminary results have shown that incidence rates is highest in males at 18 to 25 post-dose 2. However, as you can tell there is a wide range of incidence rates among

these four databases with wide confidence intervals.

For incidence rate ratios, estimates this compares between the Moderna and Pfizer, the current preliminary results do not support a significant difference for males 18 to 25 years. We do want to note that these estimates have very large uncertainty. As you can tell, this is due to small numbers of observed events for this rare outcome, and we also partially adjust -- well, we adjusted for some potential confounders. So we cannot exclude that these estimates may actually be biased.

It has come to our attention and we -- and our understanding that maybe some results are from other surveillance systems. As of this meeting, we are involved in communication with some of them, we have not actually independently reviewed, verified the underlying data for the conclusions.

We do want to note that our understanding is that the results that we just shared with you, it probably comes from the largest studies in terms of -- for this very rare outcome, actually. Also, the

(inaudible) just shared with you, it takes into context of the various limitations that I actually summarized during this result interpretation.

I'd like to thank all the multiple and various collaborators who contribute to this work and who has worked with us: the FDA BEST coordinating center Acumen and our data partners who contributed to the analysis, CVSHealth, Optum, IQVIA/HealthCore, Blue Health Intelligence, all of our FDA colleagues and federal partners. This concludes my presentation. Thank you.

Q&A SESSION

DR. ARNOLD MONTO: Thank you both very much. The presentations were very clear and helpful. We have a very few minutes now for questions, but we have a much longer time after lunch for more broad questions of both the sponsor and the FDA presentations. I'd like to restrict the few minutes we have now for questions concerning the most recent presentation, the myocarditis/pericarditis presentation. So, if you

aren't asking about those, please lower your hands. Keep them up if you want to ask about this most recent presentation, and then we'll get back to it later.

Dr. Moore?

DR. PATRICK MOORE: I believe this is about the myocarditis issue because the data is being presented on the 206 study is really quite complicated to me.

First, I want to say thank you so much to the FDA for their analysis of the Moderna data. I think it may be just me, but perhaps other members of the Committee are confused as well.

I found that the FDA's clarification made a great deal of sense of the data that's being presented, but much of the data that was presented was on a vaccine that we have not authorized, and no one is actually receiving and will not receive a booster, and that is two 50-milligram doses followed by a 50-milligram booster. That's not EUA approved.

What is approved is two 100-milligram doses followed by a 50-milligram dose. The reason why I say

that that may be related to the myocarditis issue is because, if we're looking at any serious adverse effects and we're mixing all those people together, we're going to be underestimating because, if there's a dose-response effect on myocarditis, who's going to be less if you're mixing a lower-dose vaccine that is not being used together with the remaining data.

Similarly, for immunogenicity, with a lower dose vaccine, you are going to have a lower, one assumes, basal reactivity and a boost will obviously increase the relative amount of immunogenicity compared to the vaccine that's currently being given.

While the FDA personnel are here, I just want to know, am I confused, or did I more or less describe the data as it was presented and what is being seen? We should just be looking at the 149 people in the 206 study that had 100 milligrams of vaccine for their primary series.

DR. ARNOLD MONTO: Yeah. Could we have some clarification? Dr. Fink?

DR. DORAN FINK: I can clarify that the

primary analyses that FDA considered in its review of the Moderna submission was the cohort of study participants who were vaccinated with the two-dose series of 100 micrograms each followed by a 50-microgram booster dose, which is what Moderna is requesting for emergency use authorization.

We additionally considered safety data namely in terms of serious adverse events for the additional cohort of subjects who received a 50-microgram two-dose series prior to a 50-microgram booster. I would mention that really the sample size is sufficient for characterizing common adverse reactions, but in order to assess for rare adverse reactions such as myocarditis, one would really need a significantly larger safety database by orders of magnitude and that is really for post-authorization surveillance to address.

DR. ARNOLD MONTO: Dr. Fink, the materials that Dr. Wong presented was the authorized dose, correct?

DR. DORAN FINK: That is correct. The

material that Dr. Wong presented was from BEST analyses of the 100-microgram two-dose series as used in the U.S. under emergency use authorization.

DR. ARNOLD MONTO: Thank you. Final question before lunch break from Dr. Rubin.

DR. ERIC RUBIN: Thanks for the nice presentation. Just a quick question. Do you have an idea of the specificity of the diagnosis from the diagnostic codes? In previous work, we're looked at diagnostic codes.

DR. HUI-LEE WONG: Thank you. Currently, we're doing chart review for that, but we do not have that currently right now.

DR. ARNOLD MONTO: Okay. We have a full 45 minutes after lunch and the public presentations to get back to all these. So, note your questions, and we'll take them on the 45 minutes for robust discussion. So we break now for lunch, and also for the open public hearing. The full meeting, other than the open public hearing, resumes at 2:00 p.m. Eastern.

MR. MICHAEL KAWCZYNSKI: All right. I'm going

to take us to lunch. So, thank you while we get set for lunch.

[LUNCH BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: Okay. Welcome back from our little lunch break to the 169th VRBPAC meeting. Dr. Monto, if you're ready, take it away. Hold on second. Somebody unmuted somebody. All right. Dr. Monto, take it away.

DR. ARNOLD MONTO: Okay. Welcome to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open

public hearing speaker, who at the beginning of your written or oral statement advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Over to you, Prabha.

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Can you all hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can.

DR. PRABHAKARA ATREYA: Okay. Thank you. Before I begin calling upon the registered speakers, I would like to add the following additional information for the record.

FDA encourages participation from all public

stakeholders in the decision-making process. The FDA Advisory Committee meeting includes an open public hearing session, during which interested persons may present relevant information or their views.

Participants during the OPH session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. These statements made during this open public hearing session reflect the viewpoints of individual speakers or their organizations and are not meant to indicate Agency agreement with the statements made.

With this guidance, I would like to now state that each speaker has five minutes to make his or her remarks. The first two speakers will utilize PowerPoint slides, while others simply make oral remarks. Thank you and the first speaker is Benjamin Newton. Can we have his slides and his presentation, please?

MR. BENJAMIN NEWTON: Hi. Thank you. My name is Ben Newton. I'm here to speak today about how we

can save the most lives. We should approve boosters, heterologous boosters, and vaccines for children.

Slide 2. What could we have done? We could've authorized tests as soon as they were developed. Instead, we sent cease and desist letters to the first people detecting community spread. We could have authorized vaccines in July of 2020 based upon safety data in Phase 1 and 2 studies and animal trials. Instead, we waited months after 90 percent efficacy was demonstrated.

We could've authorized micro doses so that 100 times as many people could've been protected at any given time. Instead, even though we knew that a 50-microgram dose of mRNA-1273 elicited the same antibody response with fewer side effects, we insisted on a 100-microgram dose, killing tens or hundreds of thousands who couldn't be vaccinated. We could've lived in an alternate universe where Delta never developed, but we chose to be precisely wrong instead of approximately correct.

Slide 3. As you all know, the FDA has an

animal rule. It is possible to approve vaccines without full-scale human testing of efficacy by using human safety data and animal efficacy data. We chose not to use this rule for COVID-19, which cost tens or hundreds of thousands of American lives.

Slide 4. In July of 2020, animal challenge trials had already made its way to *New England Journal's Medical*. It was widely known that vaccines equaled faster viral clearance.

Slide 5. In August of 2020, we saw a nature that micro doses protected animals. So, one 100 dose would provide significant protection against severe disease. There was no risk of vaccine-enhanced respiratory disease. We could significantly decrease dosing safely for children because there was not a Goldilocks zone. Any tiny dose was better than no dose.

Slide 6. We looked at the Moderna and Pfizer data from their original EUA filings and saw a 90 percent efficacy 14 days after the first dose. Once the DSMB had this data, they likely contacted the FDA

to ask for a pause of the trial and the FDA said no. How many additional people died because of that single decision?

Slide 7. When was 90 percent efficacy reached? About August of 2020, you can see from trial enrollment. To know for sure, you would have to FOIA the underlying data. So the FDA refused my request for the data.

Slide 8. Merck developed an antiviral drug, and the FDA paused the trial once 50 percent efficacy was reached. Vaccines reached 50 percent efficacy in Phase 1 or 2 trials by matching participants to the general population. In endemic respiratory disease, there was a 100 percent chance of catching it, which means that the standards for treatments and vaccines approval should be identical.

Slide 9. Adenovirus vaccines require heterologous boosting. All the regulators knew this and encouraged heterologous boosting months ago, even for heads of state.

Slide 10. Since April, we have had a very

helpful rubric. Once you know the amount of antibody increase from a boost, you can accurately predict the change in efficacy.

Slide 11. Chinese regulators on June 4th approved vaccines for children aged 3 and older. The American Academy of Pediatrics on August 5th recommended that we approve pediatric vaccines, based upon sero-bridging data. Pfizer, on September 20th, released data suggesting vaccines for children were safe and effective. DSMBs have already seen everything necessary to prove children's vaccines. Just because we have not seen the data, doesn't mean the data doesn't exist. Pulling less hard on a syringe does not require anything complex from an approval standpoint.

Slide 12. Everyone here went into medicine to save lives, but today, we are killing people. Not by our actions, but by our inactions. If you withhold care from someone who needs it, that is no different than providing bad care. We falsely believe that it is safe to wait when waiting kills and maims thousands of people each day. Is there any potential that vaccines

could be more dangerous than COVID? No.

In fact, the most significant risk associated with vaccinations not even acknowledged by the FDA is the risk of driving your car to get vaccinated. Today, the FDA is preventing J&J recipients from receiving heterologous boosts. The people who took that vaccine acted in good faith and took whatever was available when we all knew that the Moderna vaccine was the best one from Phase 1 data alone.

The FDA is preventing many Moderna and Pfizer recipients from receiving boosts, and the FDA is preventing children from being vaccinated. We are failing to protect those too weak to protect themselves. Today, a child died because the FDA prevented her from being vaccinated. One father, just like me or you, lost his daughter because he wanted to send her to school. I thank you for your time.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is James Rios.

MR. JAMES RIOS: Hi, my name is James Rios. I have no financial relationships to disclose. I'm

pursuing my master's at --

DR. PRABHAKARA ATREYA: Go ahead, James.

MR. JAMES RIOS: Okay. I'm pursuing my Master's in Economics at Florida International University, and I'm currently in the midst of an internship with the Vaccine Considerations Project. While the Vaccine Considerations Project has encouraged and supported me, in applying for and preparing for this presentation opportunity, all the assessments and recommendations I'll be sharing are my own and may be different from the neutral stance of the Vaccine Considerations Project.

All the peer-reviewed research papers and other reference materials that I used to create this presentation are available live on vaccineconsiderations.com right now. If you have the ability, I encourage you to follow along on vaccineconsiderations.com right now.

Next slide, please. My intention is to open a discussion that will address the need to increase trust in new vaccines. States across the country are

encountering hesitancy and resistance to getting vaccinated among their populous. The overall success of new vaccines will rely on more than the public fully accepting these vaccines into their everyday lives. It is critical that the FDA and these new vaccines producers create communication guidelines in order to identify, clarify, and explain potential risks.

Here are a few of the suggestions from the 2019 CDRH communication guides. One, further expand the reach of communications. Two, clarify the FDA's role. Three, constant outreach and accurate information to promote understanding, trust, and adaptation. I encourage a full mechanism to be developed moving forward.

Focusing on increasing trust and credibility through mechanisms and systems that produce consistent and scientifically accurate information regarding the vaccine will reduce uncertainty regarding the vaccine. This will hold long-term implications as people learn to trust the information they consume through these systems. Next slide, please.

Even before the pandemic, it was common for patients to seek information about health conditions and treatment options from health-related sites and sources of information on the internet. As the pandemic began to spread, individuals once again turned to the internet for information. According to many experts, including Dr. Akpan, the effect of the lagging responses by government and public health agencies to prioritize the dissemination of information about the coronavirus outbreak drove many back to the sources they were familiar with.

The vacuum and the supply of information regarding COVID-19 was then filled by popular media producers, on social network platforms, news platforms, websites, and blogs with unsubstantiated, incorrect data, or misinformation. To understand consumer perspectives, recent studies have employed an epidemiology approach or method, which is designed to measure and track health information, demand, and supply by analyzing search queries, or social network communications.

Other studies have focused directly on patient education and intervention or internet technology application. The overarching conclusion in these studies is the individual is becoming a savvy patient consumer. A savvy consumer is a consumer who is media literate, knowledgeable about marketing and targeting, as well as cynical about advertising, and can see through the traditional sales pitch. Next slide, please.

In trying times, some have come to expect extreme solutions is the only methods for progress. However, I do not believe we're at such a point. This Committee and others like it are charged with putting the patient consumer first above all else. I implore you to continue to do so by making it a priority to build trust and credibility parallel to addressing efficacy and safety and concerns.

Increasing levels of trust and credibility should become an iterative process at every level through business development, regulatory approval, and finally communications with the patient consumer. This

is why I encourage the Committee to continue these events and increase its focus on the mechanisms and systems most efficient at taking on the tremendous task of organizing consistent and scientifically accurate information regarding the vaccine.

Taking these steps now could prevent future hesitancy with new medical technology as patient consumers begin to trust these reputable sources. Next slide, please.

As a reminder, all the peer-reviewed research papers and other reference material that I used to create this presentation are available live on vaccineconsiderations.com right now. I encourage you to dig deeper. Thank you to the Committee and thank you all for your time.

DR. PRABHAKARA ATREYA: Thank you, Mr. Rios. The next speaker is Karen Azarian.

MS. KAREN AZARIAN: Hello. My name is Karen Azarian. I have no financial relationships with the sponsor, its products, or any competitors.

The Committee's decision whether to recommend

the Moderna booster for each of the three populations and your question today will require making a single risk-benefit assessment for different groups of people within each population.

One of those groups is a community of people who have intellectual and/or developmental disabilities. I'd like to highlight the high risk of severe COVID, the high exposure, low vaccination rates, and current lack of requirements for vaccines and rapid testing among people with IDD and the people who support them -- the factors that should be considered when weighing the risks and benefits of a booster.

I respectfully ask the Committee to consider the public health impact of your decision, specifically for people with IDD, and, if you decide not to recommend emergency authorization for the broader populations at this time, to recommend it for people with IDD who received the Moderna vaccine more than six months ago and for those who support them.

People with IDD are at high risk of being infected with and dying from COVID and are often

included in high-risk groups as a result. As Jonathan Gleason and others wrote in the *New England Journal of Medicine Catalyst*, March 5th, 2021, a cross-sectional study of over 64 million patients across 547 healthcare organizations, quote, "Reveals that having an intellectual disability was the strongest independent risk factor for presenting with the COVID-19 diagnosis, and the strongest independent risk factor other than age for COVID-19 mortality."

A person with IDD, who's been fully vaccinated and who lives in a certified group home in New York, for example, is supported by staff who have a statewide vaccination rate with at least one dose of 36.3 percent. They may attend a day program where the staff have a vaccination rate of 34.4 percent, and where they interact with peers who have a vaccination rate of 47.7 percent.

There are currently no vaccine or rapid testing requirements that apply to either staff or individuals with IDD in New York, other than in state-run homes. All figures are from New York's Office of

People with Developmental Disabilities as of September 10th, 2021.

As you decide whether to wait for more data or how to balance competing public health interests, I ask you to consider that in New York, the case fatality rate for people with IDD for COVID is 7.7 percent. Even mild cases can have a disproportionate impact on the system of supports. And, as the pandemic takes its course, a person who has IDD often can't avoid exposure or maintain social distancing in their home.

Many of the people with IDD in New York who completed the Moderna series did so in January and February, more than eight months ago. The Committee may question whether the data sufficiently demonstrates the need for, or the effectiveness, of a Moderna booster. Nevertheless, I ask the Committee to consider the factors I outlined for people with IDD and those who support them.

I believe they support recommending an emergency authorization of a booster for this Committee whether homologous or heterologous as was done last

month for people who are immunocompromised, if not for each of the broader populations. Thank you for the opportunity to speak and for your work.

DR. PRABHAKARA ATREYA: Thank you, Ms. Azarian. The next speaker is Mr. Burton Eller.

MR. BURTON ELLER: Good afternoon. My name is Burton Eller, and I am the (audio skip) from the National Grange in the advocacy arena. I'm the director of policy and advocacy. The National Grange is America's oldest agricultural, rural life, and small citizen advocacy organization. An important factor impacting the health of rural Americans is a significant number of disparities that increase our vulnerability to certain conditions and, at the same time, impede our access to care and treatment.

Here are a few examples. Since 2015, 181 rural hospitals have permanently closed depriving surrounding populations with timely access to everything from emergency care to disease management and prevention. Despite recent advances, 20 percent of our population still cannot access high-speed

broadband, which essentially eliminates their access to virtual clinical care.

In comparison to urban and suburban areas, there are far fewer providers of rural health and their resources. Moreover, rural patients often have to drive significant distances to reach those that are available. The COVID-19 pandemic has brought new challenges to the importance and urgency of addressing these disparities.

Throughout its existence, the National Grange and its state and local chapters have advocated for educational outreach, sound public policy, and adequate resources to protect in advance of rural health. That has not changed, nor will it. Today, as the expansion of protection through boosters is being considered, we want to thank the FDA for its work and leadership.

We respectfully ask that the Committee keep in mind during its deliberations the access challenges that face the population we are proud to serve and the frontline healthcare workers who care for us. As we represent rural Americans across all generations, we

look forward to FDA's upcoming assessment of COVID-19 vaccines for our younger children as well.

We welcome the actions of FDA in this and all matters so important to our health. Thank you for the ongoing commitment to protecting Americans against COVID-19.

DR. PRABHAKARA ATREYA: Thank you, Mr. Eller. The next speaker is Thair Phillips.

MR. THAIR PHILLIPS: Thank you. Good afternoon. My name is Thair Phillips of Seniors Speak Out. I have no financial relationship to disclose.

For the 20 years before I became eligible for Medicare and the eight years since, I have been an advocate for the concerns of older American. As a military veteran, I have a special interest in all our veterans. I want to start by thanking this Committee for your unending commitment to ensuring the COVID-19 vaccines are safe and effective for as broad a population of Americans as possible.

From the early days of the pandemic, it was clear that the threat of COVID-19 was particularly high

for people 65 years and older due to our weakened immune responses and increased likelihood of chronic conditions. Ensuring these most vulnerable members of our society had access to effective and safe vaccines to prevent the onset of serious respiratory illness was a critical first step toward slowing the spread and impact of this deadly virus.

While some chose to ignore the science-based recommendations, it quickly became apparent that these vaccines were the right medicine to concur this deadly virus. For our part, older Americans have stepped up to the plate and take an action to protect both ourselves and our families from COVID-19. Older Americans leave the country in protecting ourselves from COVID as those 65 and older have the highest rate of vaccination among all age groups with 89 percent having received at least one dose compared with 68 percent for people ages 18 to 64.

Now, we once again look to the FDA for guidance on how to continue to take the appropriate steps to provide ourselves with the strongest

protection possible against COVID-19 with the booster vaccine.

We are encouraged by the current vaccine's ability to greatly reduce the risk of hospitalization and deaths from COVID-19 and know the lives of thousands of seniors have been saved as a result. As the science continues to evolve, we believe ensuring broad access to the booster dose will provide an added layer of protection so that we as a nation can continue to watch the rate of COVID cases declining.

We know that we are not only taking this action to protect ourselves, but also to help stop the spread and impact on younger generations who are not yet eligible for the vaccines. We are grandparents, aunts, uncles, teachers, mentors, and friends who are eager to see all generations obtain protection from this virus.

Just as you have worked diligently to ensure safe and effective vaccines are available to a broad population of Americans, we look forward to seeing the youngest generation have access to needed protections

as well. I thank you for this opportunity to speak on this important issue.

DR. PRABHAKARA ATREYA: Thank you, Mr. Phillips. The next speaker is Ms. Lynda Dee.

MS. LYNDA DEE: Hi, yeah. Good afternoon. My name is Lynda Dee. I have been an AIDS activist for 35 years and have served as the community representative on many feeder antiviral advisory committee hearings. I have no conflicts.

I usually address scientific and regulatory issues at VRBPAC meetings. Today, I intend to shine a light on Moderna's failure to provide mRNA-1273 vaccines to low- and middle-income countries with few exceptions. Unless we begin vaccinating the entire world in earnest, SARS-CoV-2 mutations will continue to develop. We will continue to need boosters and the pandemic will never end. It will certainly not be over by next year.

International variants have continued to plague us, including variants from the United Kingdom, Brazil, South Africa, and now the Delta variant from

India, which is the most transmissible and virulent to date. If anything, international travel has steadily been increasing with no signs of decreasing.

Messenger RNA vaccine technology was developed by U.S. government researchers. According to *The New York Times*, our government contributed $300 billion to Moderna in research and clinical trial support and another 1.5 billion for pre-ordered, unproven vaccines. Taxpayer dollars also pay Moderna 15 to 16.50 per U.S. dose. Moderna's 2019 revenue was 60 billion. Their projected income for 2021 is 20 billion with approximately 14 billion in profits. Moderna's market value has tripled and is now about 120 billion.

Forbes lists two Moderna founders among the 400 richest people in the United States. Yet, Moderna has provided its vaccine to wealthy countries to the exclusion of low- and middle-income countries more than any other vaccine manufacturer. Moderna has provided eight times less vaccines than Pfizer and 25 times less than Johnson & Johnson to World Bank classified low-income countries.

The few middle-income countries that do have contracts with Moderna are paying more per dose than both the United States and the European Union. The Biden Administration has expressed dismay about Moderna's international vaccine allocations and has called for Moderna to produce more vaccine for international donation and to license their technologies to overseas manufacturers that are able to produce the vaccine for international use.

Licensing their technology would be the quickest way to begin vaccinating the rest of the world, but it would also mean Moderna might lose potential profits from the development of mRNA vaccines for other diseases such as cancer and HIV. VRBPAC recommending the authorization of a 50-microgram booster dose of 1273 will also increase the availability of vaccine doses.

While Pfizer has agreed to sell low-cost vaccine doses to the U.S. for overseas donation, Moderna has not. Meanwhile, only 10 percent of people in Africa and the Middle East have been vaccinated.

Moderna has stated that low- and middle-income countries will receive vaccines after its commitment to developed countries have been fulfilled. Moderna has not delivered any of the 34 million vaccine doses promised to the United Nation's COVAX program or the 500,000 doses promised to Botswana.

Other international shipments are not slated until next year. If we are going to successfully combat COVID-19 and prevent the possibility of our current vaccines from eventually being overtaken by even more virulent variants, we must ensure that the entire world has vaccine access.

It is not only the right thing to do; it is also the scientifically sound thing to do to end the pandemic by reducing continuous viral replication and possibly even reducing the necessity of continuous administration of boosters in the future. Thank you for the opportunity to comment and for your dedicated service.

DR. PRABHAKARA ATREYA: Thank you, Ms. Dee. The next speaker is Dr. Michael Carome.

DR. MICHAEL CAROME: Good afternoon. I'm Dr. Michael Carome, Director of Public Citizen's Health Research Group. I have no financial conflicts of interest.

Public Citizen's supported the initial emergency use authorization of the primary two-dose series of the Moderna COVID-19 vaccine because clinical trial data demonstrated that the vaccine was highly effective and safe. Importantly, data from observational studies summarized by the CDC at the September 2021 meeting of VRBPAC indicated that the primary series of the Moderna COVID-19 vaccine continued to afford robust protection against severe COVID-19 disease and death in the U.S.

Although there may be a role for a booster or a third dose of the Moderna vaccine in certain populations, such as individuals 65 years of age or older, who are at least six months post-completion of the primary series, we want to highlight three limitations regarding the data submitted in support of Moderna's request for an EUA for such booster doses.

First, the efficacy of booster doses of a vaccine against symptomatic or severe COVID-19 disease was not evaluated in the Phase 2 clinical trials of the booster. Second, the subject population enrolled in the Phase 2 clinical trial was not representative of the racial and ethnic diversity of the U.S. population. Specifically, with regards to race, the subject population was 95.3 percent white, only 2.3 percent black or African American, 0.9 percent Asian, 0.6 percent American Indian or Alaska native, and 0.3 percent native Hawaiian or other pacific islander. Then with regards to ethnicity with 93.8 percent not Hispanic or Latino and only 7.6 percent Hispanic or Latino.

In contrast, the U.S. population, according to the 2020 U.S. Census is 61.6 percent white, 12.4 percent black or African American, 6 percent Asian, 1.1 percent American Indian or Alaska native, and 0.2 percent Native Hawaiian or other pacific islander, and any 1.3 percent not Hispanic or Latino versus 18.7 percent Hispanic or Latino.

So, significant overrepresentation of white and not Hispanic or Latino populations and underrepresentation of black or African Americans, Asians, American Indians, and Hispanic or Latino populations raises concerns about the generalizability of the clinical trial findings to a large proportion of the U.S. population.

Moreover, the lack of diversity in the enrolled subject population indicates a failure of Moderna and the trial investigators to ensure that selection of subjects was equitable and satisfied the basic ethical principle of justice articulated in the 1979 Belmont report that upon which human subject protection regulations are founded.

Third, although no serious safety signals were identified during the clinical trial of the proposed 50-microgram booster dose of the Moderna vaccine, the safety database for this booster dose is very small, and including only 171 subjects who received a 50-microgram booster dose administered at least six months after completion of a primary series of two 100-

microgram doses, the authorized doses under the initial EUA granted by the FDA, and 173 subjects who received a 50-microgram booster dose administered at least six months after completion of a primary series of two 50-microgram doses, a dose not authorized under the EUA. For the former subject group, median follow-up was just 5.7 months and a range of 3.1 to 6.4 months.

Finally, while the U.S. already is implementing widespread distribution of COVID-19 vaccine boosters, the vast majority of people and low- and middle-income countries have had no access to any COVID-19 vaccine, let alone the highly effective mRNA vaccines.

The world continues to suffer from an artificial scarcity of high-quality COVID-19 vaccines because governments are permitting drug corporations to maintain monopolies. It is ethically imperative that the U.S. government move to rapidly ramp up global vaccine manufacturing so that every person on our planet can be vaccinated. Thank you for your attention.

DR. PRABHAKARA ATREYA: Thank you, Dr. Carome. Thank you all for your comments, and this concludes the OPH session, open public hearing session. Now, I hand the meeting back over to Dr. Monto. Dr. Monto, take it away.

DR. ARNOLD MONTO: We are at the end of the open public hearing. It would be great if we could start the question and answer session at 1:45 Eastern. Prabha and Kathleen, do you think that's going to be feasible?

DR. PRABHAKARA ATREYA: Dr. Monto, it is now 1:20 p.m. in Eastern time. So, if you take a ten-minute break, we could start earlier, then, maybe around 1:30.

DR. ARNOLD MONTO: And the Committee members are online?

DR. PRABHAKARA ATREYA: They are.

DR. ARNOLD MONTO: They know to start?

MR. MICHAEL KAWCZYNSKI: They are.

DR. ARNOLD MONTO: That's the thing that worries me.

MS. KATHLEEN HAYES: They're online.

MR. MICHAEL KAWCZYNSKI: They're all online, sir.

DR. ARNOLD MONTO: Okay. 1:30 start. Wonderful. Just a ten-minute break right now.

[BREAK]

ADDITIONAL Q&A REGARDING SPONSOR AND FDA PRESENTATIONS

MR. MICHAEL KAWCZYNSKI: Welcome back from that real quick short break. Dr. Monto, are you ready to kick off this last leg of today's meeting?

DR. ARNOLD MONTO: I am and I want to thank the staff for expediting this return to our deliberations. We've got a long day, and moving things forward is always very helpful. So now we've got the question and answer session. It's questions and answers for both FDA and for the sponsor, who are all back online. So, Dr. Kurilla, you are leading us off.

DR. MICHAEL KURILLA: Thank you, Arnold.

Yeah, I have a question for Moderna. I don't know if Jacqueline is back in the hot seat. She is. Okay. Thank you. Yes, so with regard to your immunobridging analysis, it seems that that is predicated on the assumption that the protection is mediated exclusively by antibody response, specifically neutralizing titer. And it's clear that, even when your neutralizing titer levels drop, you're still seeing some degree of protection. And that's not surprising, particularly for severe disease because we would expect that there would be hopefully some good cellular memory responses that would be kicking in.

And so my question really gets to the heart of -- at a lower dose, what is the impact on all of those other protective effects? You're predicating everything just on the neutralizing titer dose. So one aspect is, are you actually going to be impacting the decay kinetics of the antibody response, which seems to be why you get breakthrough infections in the six to eight months? So is it going to come sooner?

Secondly, what's the potential impact on the

waning immunity with regards to more severe disease, hospitalizations, and death?

DR. TINA MONGEAU: Yes. Dr, Kurilla, that is a very interesting and relevant question. If I implied that neutralizing antibody, that I believe that's the only element of protection that the vaccine's inducing, then I apologize. I misspoke. We have Phase 1 data demonstrating the induction of both CD4 and CD8 cells. There clearly is some T cell work that is induced. The other point, in collaboration with the CoVPN, where we looked at correlates of risk, there was an estimate that at least 40 percent or so of protection in our recent publication is likely due to T cells.

There's one final line of evidence that there's T cell immunity, and it comes a bit from the exploratory analysis I showed you in the core deck where you saw the increase in neutralizing responses not only to the original strain but also to Beta, Gamma and Delta. Those samples were actually taken at day 15. In the CoV study, we really didn't see full neutralizing antibody titer until two weeks after the

second dose. After the first dose, even one month afterwards did not see neutralizing antibody titers in about half of the subjects.

That brisk return is certainly an indication that immune memory has been established. That said, we are still concerned about the breakthrough disease that we've been observing in the participants in the CoV trial and particularly the breakthrough cases that we're starting to see in severe disease in the older adults, which is why these data that we've investigated earlier in the year we now have submitted for emergency use to enable booster vaccination. We are going to investigate immune memory further. We have an ongoing collaboration with Washington University.

And as we continue to study the impact of booster doses and the possibility in the future of variant booster doses, one of our ongoing studies is actually going to be looking at germinal centers, memory B and memory T cells.

In summary, I think you're right, that T cell immunity is contributing here. But nonetheless, we

continue to see breakthrough cases.

DR. MICHAEL KURILLA: One follow on, do you have any evidence or experience with, perhaps, other mRNA-based vaccines that you've worked with that would suggest that a six-month boost is likely to lead to better durability than what you've seen with what is likely a suboptimal dosing interval of one month?

DR. TINA MONGEAU: We have ongoing vaccine programs in CMV. CMV is the most advanced program that's in a multidose usage. Subjects in Phase 1 and Phase 2 clinical trials have been vaccinated at dose 1, then two months later for dose 2, and then six months after dose 1, four months after dose 2 for dose 3. In CMV, we have also observed the induction of T cells. We have antibody persistence data out to six months after that third dose. We see persistence, but again this is smaller sample sizes. I think that question will probably be answered better in the Phase 3 trial that we're about to launch.

DR. MICHAEL KURILLA: Thank you. Dr. Gans?

DR. HAYLEY GANS: Thank you very much. It's

wonderful for this opportunity to ask a question. I did have a question about breakthrough disease. Arnold, one question now, and then I'll come back around if I have another question. Is that a good idea?

DR. ARNOLD MONTO: Thank you. Appreciate that.

DR. HAYLEY GANS: I guess my question, then, right now will relate to safety. We've seen a lot of data on the original safety for the two dose, but there has been 1.5 million doses of the Moderna. We've seen other data related to Pfizer. I'm wondering if someone can give us any follow-up on safety data in the (inaudible) people (inaudible). I realize they're immunocompromised or whatever I know are not necessarily relevant by the group (audio skip) hearing today, but I'd like (audio skip).

DR. ARNOLD MONTO: Dr. Miller, can you answer that, or should we refer that also to FDA?

DR. JACQUELINE MILLER: No, I'll be happy at least start. I'll share with you the data that we're

aware of. So we have had the emergency use authorization for the third dose in immunocompromised population since about the middle of August. In that subset, we have been reported to our pharmacovigilance database 355 total events. The most commonly reported adverse events that we have heard about really aligned with the symptoms that we solicit as part of the clinical trial process.

Fever was the most commonly reported event, and it followed by headache, arthralgia, chills, and myalgia. Overall, I think it's been a bit of a short time period for us to really have data in that regard. We are generating additional data in immunocompromised patients, so we have an ongoing study in 240 renal and liver transplant patients. We are offering all of those patients a third dose, so we will be reporting the safety data from that clinical trial as well.

Dr. Gans, if I may, you had asked me a question before the break, and I was able to pull up the slide showing the geometric mean ratios by age with the immuno-persistence.

Panel 8 please. Thank you. What you see in the top row of the table are the antibody persistence results in the 18- to 64-year-olds in the left column and the greater than 65-year-olds in the right column. The Study 301 is pre-vaccination, and that's why the titers are so low at 9 and 10. But in the older adults, the pre-booster titers were 91. In the younger cohort, they were 177. You see the post-vaccination titers on the slide. It resulted actually in very comparable geometric mean increases, so 1.7 for the younger cohort, 1.9 for the older cohort. Thank you.

DR. ARNOLD MONTO: Dr. Hawkins.

DR. RANDY HAWKINS: Thank you very much, Dr. Miller and to all the presenters. I'm a consumer representative and a physician, private practice.

Can you respond to the criticism often levied against Moderna, include today in the open public hearing section? What is Moderna's commitment to CoVAX and other steps it will take to help control the pandemic in countries suffering disproportionately, and can you give specifics?

DR. JACQUELINE MILLER: Yes, I'd be happy to address that question. I'm actually going to refer you to an open public letter that was published by our CEO where he laid out a five-pronged strategy to address COVID-19 disease in the developing world. The first element refers to our announcement in October 2020 that we were not going to pursue patent enforcement of our mRNA technology for the duration of the pandemic. The second has to do with the 50 million doses of a vaccine that we've delivered to CoVAX through September of 2021. That was made possible by our pursuit of the emergency use authorization letter from the WHO.

We've been meeting with the WHO and the SAGE working group throughout our development. We have an agreement to supply doses to CoVAX, 500 million doses to CoVAX, in 2022. We have just announced that we will be building a manufacturing facility in Africa. This is important because it will be a localized manufacturing facility in Africa for Africans.

We also have plans to distribute one billion doses to low-income countries in 2022. Even though it

includes greater complexity, we're reducing the dose to 50 micrograms in order to try to make more vaccine available for the world, so that frees up a billion extra doses if we can have a booster dose.

DR. RANDY HAWKINS: Thank you very much for that. Do you have a timeline on that manufacturing plant in Africa?

DR. JACQUELINE MILLER: My sincere apologies. I'm in the R&D group, so I'd have to check back with other colleagues to be able to answer to that.

DR. RANDY HAWKINS: Thank you very much.

DR. ARNOLD MONTO: Thank you. Dr. Perlman.

DR. STANLEY PERLMAN: I just had a question about the myocarditis. I don't think we understand why that occurs and the fact that it seemed like it might have been occurring less after the third dose and the second dose. I don't know if that's true, but it seemed like that was the case. Does that give you any insight into possible mechanisms because, of course, the concern is, if you had immune response to the vehicle or the product of the RNA, that that would get

worse potentially with repeated immunizations. But it seems like it's not. Does that tell us anything? Does Moderna know anything about possible mechanisms there?

DR. JACQUELINE MILLER: The mechanism of action in question is one that's really important to us as well because patient safety is of the utmost importance. After the third dose, I think you mentioned we don't have a lot of cases yet. I would say we also don't have a lot of exposure yet. I wanted to mention that, for that reason, we actually are offering the 50-microgram booster to all of those subjects in CoV or the Phase 3 Study 301. The reason to do that is to investigate the vaccine in a larger safety database as well as to generate additional immunogenicity.

As part of that effort, we have enhanced the clinical trial procedures to detect myocarditis. For example, we're now screening subjects for myocarditis-specific symptoms after vaccination. We are collecting serum samples that we're banking in case a subject should develop symptoms later and we need to test

troponins and compare to a baseline. We've convened an adjudication committee composed of cardiologists independent from the company who will be evaluating these patients and advising us on what we should be doing to investigate further.

The part of your question about the mechanism is action though because in 25,000 subjects we are probably not going to be able to tell too much about myocarditis since this is such a rare event. We believe that understanding the immune response that's actually induced by the vaccine is really a critical component. In addition to the mechanistic study that I described in collaboration with Washington University, we're also looking to do a mechanism of action study comparing multiple antigens in our mRNA technology and then looking at system serology afterwards. Hopefully, as we continue to generate these data, we'll be able to elucidate a greater understanding.

DR. STANLEY PERLMAN: Okay. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Levy.

DR. OFER LEVY: Thank you. I have a question

that's actually both for FDA and for Moderna. It has to do with the data that's being presented today on antibody responses to the mRNA vaccine, to the booster dose. That makes a lot of sense to look at because we have a lot of evidence in animal models and some evidence emerging in humans that an antibody response is relevant to protecting us against Coronavirus infection and disease. That said, what's being presented is very specific types of analysis, 4-fold rises and other types of cutoffs to judge a quote seroresponse.

All of this kind of begs the question of do we know the correlative protection. There was already a question about antibody responses versus cell-mediated responses. I appreciated the response from Moderna on that. I'm taking a step back and asking both FDA and Moderna what is their best estimate of the antibody response level that protects against infection and against severe disease? I know research is ongoing, but we're talking about a lot of very specific data on antibody responses. We need a context to contextualize

those data. I'm wondering if FDA and Moderna could comment on that. Thanks.

DR. JACQUELINE MILLER: I'm happy to start, but then I will hand over to the FDA. Dr. Levy, your question I think allows me maybe to expand a bit further on the publication I spoke about earlier. As part of the Study 301 and in our collaboration with the COVID-19 Prevention Network, we utilize the immunogenicity subset and examined, actually, correlate of protection. We had baseline results in all subjects. We made sure to sample subjects once they had a case of COVID-19.

And we had a subset of immunogenicity in patients that were non-cases and were able to analyze antibody titers looking at individuals who received placebo that got infected, individuals who had placebo that did not get infected, and importantly mRNA recipients who had breakthrough disease versus the rest of the pool of mRNA recipients. We've published that work on the medRx (phonetic) server, and it has been submitted for peer-review publication.

But what we found was that for 50.8 percent of the subjects the vaccine efficacy compared to individuals that were vaccinated and unvaccinated with messenger RNA was 50.8 percent if the antibody titer in the breakthrough case was undetectable.

It was 90.7 percent for an antibody titer of 100. It was 96.1 percent for a titer of 1,000. While this is not at all a validated correlate of protection -- the data would need to be submitted to FDA and undergo additional statistical review -- we believe that that thousand benchmark really represents a reasonable threshold that we should be targeting. It also aligns nicely with the GMT that we saw post-vaccination in the CoV study.

DR. OFER LEVY: Also to the comments from Dr. Alroy in Israel, so that's a different product; it's a Pfizer product. Again, they're not there yet to announce an exact correlate. She talked about breakthrough when the titers were in the hundreds. Does FDA have a comment on this?

DR. DORAN FINK: I can comment. I wish I

could tell you what FDA thinks is the correlate of protection. That would make all of our lives so much easier, wouldn't it? But at this point, FDA's position is that we don't have enough information to understand what specific threshold of any immune response is fully predictive of protection. In the meantime, we're tasked with evaluating data and taking action to address public health needs.

To do that, we are relying upon established regulatory science and precedent, in which we use an immunobridging approach based on an immune marker which, although it may not be scientifically established to predict protection at a given threshold, we have reasonable enough confidence in the clinical relevance. We use that immune marker to bridge back to a dosing regimen in the population in which efficacy has been demonstrated.

DR. OFER LEVY: Has the FDA made an estimate of this number and is not free to talk about it? Is that the situation?

DR. DORAN FINK: No. We are continuing to

await traditional data that are both from vaccine manufacturers as well as U.S. government partners and elsewhere.

DR. OFER LEVY: Okay. To recap, this 4-fold - -

DR. ARNOLD MONTO: Thank you. Let's go on to some other questioners. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: My question is actually for Dr. Miller. I believe that you presented data that the booster dose is less prominent in those participants who had a higher pre-booster antibody level compared to those had lower pre-booster antibody levels. Do you have any kind of an explanation for that because, when I think about those data, I think about, okay, this is not the live virus. This doesn't need to replicate. So why are we seeing this difference in people who had higher pre-boost antibody levels versus those who had lower pre-boost antibody levels?

DR. JACQUELINE MILLER: Yes, Dr. Chatterjee. Thanks for that question. I think it might help if we

put the slide back up. Could we please put up Panel 8? Thank you. I believe this is the slide you were referring to, where we showed that the subjects who did not achieve the 4-fold rise had a pre-booster titer of 492. With respect to the reason why subjects may not have responded as well, I'm going to start, but I'm also going to ask for my colleague, Dr. Darin Edwards in the research group, to contribute as well to the response.

Overall, when there are preexisting antibodies, our technology works through expression of the protein antigen on the cell surface. Preexisting antibodies can, I believe, bind to that cell surface protein. I'm going to ask Dr. Edwards to come up and explain further.

DR. DARIN EDWARDS: Thank you, Dr. Miller. My name is Darin Edwards. I'm the director of immunology within the Infectious Disease group at Moderna. As Dr. Miller alluded to, the mechanism of action of our vaccine is to deliver the spike protein mRNA to cells where it is translated into protein and inserted into

the cell membrane of the expressing cell. That protein, while present not only in the injection site but also in the draining lymph node, is able to activate the immune system.

However, it can be impacted by the presence of preexisting antibody. That is a potential reason why in the group that had a high baseline we see a lower neutralizing antibody level after the booster.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: As we go forward, I just want to remind the Committee that the discussion question we're going to be asked later on -- and we are going to have a chance to do a question and answer with the sponsor at that point -- about other ages going down in the discussion topic to 18. Let's keep that in mind as we ask our questions. Dr. Moore.

DR. PATRICK MOORE: Hi. Clearly, this is not an amazing new thing -- is that this epidemic won't end until we end transmission, regardless of how effective on an individual basis a vaccine is. What we saw was that the FDA reported that Moderna had 18 cases post-

booster that were PCR or antigen positive. We don't have a control group, so we don't have a vaccine efficacy for asymptomatic or pre-symptomatic infection and the protection against that. That's a really, really, really critical thing for the ending of this epidemic.

Do we have an idea of what it would take to be able to shift to a Delta booster because people have already had two, if I understand it correctly, Wuhan-1 sequence injections. Now they're getting a third Wuhan-1 sequence. If you did shift to a variant of concern booster, would you anticipate that you would have increased protection against asymptomatic infection or pre-symptomatic infection since those are our best guess of inhibiting transmission?

DR. JACQUELINE MILLER: Yes. I think your question maybe gives me the opportunity to review some data first from an ongoing vaccine effectiveness study because we take your point that, because all of the placebo subjects have received vaccine, it's not a true efficacy study anymore. But we are currently working

with Kaiser Southern California in a large-scale vaccine effectiveness study where we're able to compare vaccinated versus unvaccinated individuals. As was noted earlier this morning, this kind of analysis has some limitations because unvaccinated individuals don't necessarily have the same behaviors as vaccinated individuals. But it still, I think, provides at least a value in understanding the data that we're seeing.

May we please show Panel 8? While we're waiting for the slide to show up, I'll just say that we have been following vaccine effectiveness in approximately 1.1 million Kaiser numbers. The effectiveness has been estimated not only overall but also by variants of concern. So the slide that you see now in the orange includes vaccine effectiveness against all PCR samples that have been detected that were not of the Delta variant.

I guess I should note here that, unlike most effectiveness studies, we actually are sequencing every subject that is a case in this observational study and will be continuing this study into the period should

the booster dose be authorized. In green, you see the vaccine effectiveness against the Delta variant. As you can see, the vaccine effectiveness is still high, but the Delta variant is clearly lower.

The other, I think, important point about the Delta variant is, after initial vaccination, the vaccine effectiveness actually was much higher. Delta effectiveness was 94.1 percent between 14 and 60 days after vaccination.

This declined to 80 percent 151 to 180 days after vaccination. The waning of that effectiveness was less pronounced for the other variants, indicating that as the antibody titers wane, we are seeing also a concurrent waning in vaccine effectiveness.

I'm sorry. Could you please remind me of the second part of your question?

DR. PATRICK MOORE: The question is that, obviously, if you have -- right now we're in the middle of a Delta epidemic. So, if you have a better antigenically fit booster, people were not really -- at least I'm not terribly worried that we're shaping the

immune response such that it will not recognize earlier variants because people have already seen those earlier variants spike proteins because they've had two doses of the Wuhan vaccine that has roughly 95 percent vaccine efficacy. So, if they get a new booster with a new antigen that is shaped towards Delta, then it seems like your efficacy will be much better.

Now, the Kaiser study, if remember correctly, had a 72 percent estimated vaccine efficacy against asymptomatic infection. You got 18 people out of 149 that are point positive at some point after booster. Maybe it was 16. I'm sorry. There may have been two people that were early on that have not really reached full antibody response after booster. But nonetheless, it's about 10, 12 percent of those people are (audio skip) positive for SARS-CoV-2. (Audio skip) group. I'm sorry.

If you don't have a comparison group (audio skip), but if you invert a ratio -- if we had a hypothetical comparison group, then that would be an attack rate in that group of 30, 40 percent during a

comparable period I would think. That seems just really, really high. And that's the reason why I think the efficacy looks somewhat low in protecting from asymptomatic carriage.

DR. JACQUELINE MILLER: Yeah, thank you so much for reminding me of the question. You're correct, but I want to emphasize that the 18 cases that were detected, these were primarily cases that were found from the nasal swabs that we conduct routinely at dose 1 and dose 29. You're absolutely right that they were contributing to asymptomatic infection.

The other part of your question was with respect to variant-specific boosters. We actually are investigating the possibility to further boost individuals with variant sequences. We think that this is really important, even if we don't administer booster doses for quite some time, to understand whether the messenger RNA sequence can be replaced out with a comparable profile to what was observed in the large-scale study. Can you put up Panel B, please, because it gives me a chance to speak a bit about the

ongoing work we have with boosters.

DR. ARNOLD MONTO: Let's not spend too much time on it, though. We're getting short. Go ahead, please.

DR. JACQUELINE MILLER: Okay. Well, Dr. Monto, I'll summarize by saying that we agree that it's absolutely important to understand if a Beta or a Delta sequence could better protect against the variants of concern. That's why we've committed to studying it.

DR. ARNOLD MONTO: Thank you very much. Dr. Offit.

DR. PAUL OFFIT: Thank you. A question for Dr. Miller. Jacky, Tony Fauci has said that, were this not a pandemic, this would have been a three-dose vaccine. The reason he said that is that he likens this vaccine to the inactivated viral vaccines, like the inactivated polio vaccine, the Hepatitis B vaccine, or Hepatitis A vaccine, where you need to have an interval of four months plus in order to get decent frequencies of memory cells because that's going to allow you to have protection against serious illness

and to have durable protection. The question is, is this that vaccine? Because, as you said, it's not quite an inactivated viral vaccine.

You have viral proteins that are being made in the cytoplasm, which likens, more frankly, to a live attenuated viral vaccine where a single dose can induce long-lived memory responses. The thing you said earlier that I think is really important is that, when you do this third dose and you're looking at the effect of the third dose, I think it's really important to look at the memory B cell response to answer the question, do you really boost memory B cells? Because, if you look at the data by John Wherry and Shane Crotty in La Jolla, John Wherry at Penn, what they find is that, six months after your two-dose vaccine, you have reasonably high frequencies of memory B cell, which if anything increase over time suggesting long-lived immunity induced by two doses.

So it may never have really been a three-dose vaccine. If the goal is to try and protect against the unfortunately-named breakthrough infections of

asymptomatic infection and mildly symptomatic infection -- which I wish we'd never use that term because it implies failure, and that's not a failure -- then we're going to be talking about giving frequent boosters, which I don't think is a reasonable strategy for this vaccine. I think it's really important to look at can you boost memory with that third dose?

DR. JACQUELINE MILLER: Thank you for that, Dr. Offit. We agree, which is why we are engaging in that particular mechanism of action study. I'll just mention that we're also utilizing a bivalent vaccine in that study. So we are looking at the Beta-Delta in a combination vaccine to also understand, if you give a different antigen, what does the memory B cell look like to that variant of concern. I think to your question about what we call the schedule, I mean, I take your point that one person's primary series and another person's booster series I suspect that there's a continuum of improvement and protection and immunogenicity with every dose.

I guess what I would say about longer-term

boosters is that I'm not sure that a booster that you give in the middle of a continuing pandemic that's due to a lot of different factors necessarily will determine what will happen in the future. The dataset we're bringing here today is really to address a specific problem, which is the breakthrough severe disease that we're beginning to see in the patients that have been (audio skip).

DR. ARNOLD MONTO: Thank you. Dr. Lee.

DR. JEANNETTE LEE: Dr. Miller, this is something of a follow on to Dr. Chatterjee's comment about the fact that your seroresponse seems to be greatest among those that had the lowest pre-booster levels. I guess one of the questions I have is whether you actually looked at the association between time from their last second dose to when that happened.

What I'm leading up to is the fact that maybe six months -- we've drawn a line in the sand of six months which is completely arbitrary -- whether or not it would be optimal for people to wait longer to get the boosters, et cetera, because the waning hasn't

occurred as much in some and they don't benefit that much about it. I'm interested in your comments on that observation. Thank you.

DR. JACQUELINE MILLER: Yeah, that's a great question. Unfortunately, in this Phase 2 trial, subjects were really vaccinated in a relatively narrow time window, so six to eight months. That particular analysis will not be as helpful.

What I would say is that's why we think that investigating the booster dose in the Phase 3 study, CoV, is so important because, by that time, subjects will have been in the earlier group. Now, it's even later than July and August, so closer to 14 and 15 months past their initial vaccination, while subjects who were originally in the latter group, originally allocated to placebo group, are going to be about 9 to 10 months after vaccination.

I think all of those data together may build a picture. I think you'll see some data tomorrow presented by colleagues at DMID regarding a booster dose within the 4- to 12-week window. Hopefully, that

will also help inform the discussion.

DR. JEANNETTE LEE: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. Dr. Miller, I would like to ask you a question about sterilizing immunity. I think, as you just said, it's so important to look at breakthrough disease or disease that occurs in people who are fully vaccinated rather than just an infection from whom one can get a positive PCR or recover virus. It seems to me that it's going to be very difficult with the mRNA vaccines to achieve that objective, that is asymptomatic infections in someone who had preexisting immunity because these viruses are mostly simulating IgG and circulating immunity. Have you looked at IgA?

I guess there's no reason to think that there would be secretory IgA made, but is it reasonable to expect that these vaccines would prevent essentially colonization that results in asymptomatic disease in someone who's immune?

DR. JACQUELINE MILLER: Dr. Meissner, I'm

going to turn your question back over to Dr. Edwards in just a minute. But I will tell you that, in the Phase 3 study -- and again, this is a different moment in time. So it was when the original Wuhan strain and the Alpha variant were circulating. But, at the very end of the placebo-controlled period, so when subjects were in the process of crossing over, they had a final visit. That was the final efficacy that I described to you and, in the interest of time, did not speak to the asymptomatic infection rates.

We had an efficacy of about 60 percent against asymptotic infection. I think that question about sterilizing immunity and IgA is best addressed by Dr. Edwards. Thank you.

DR. DARIN EDWARDS: Thank you, Dr. Miller. I think some of the best evidence that we have on the ability of our vaccines to elicit secretory IgA and the mucosal tissues is from our nonhuman primate studies that we have run with our wonderful collaborators at the NIH.

Several of those studies have been published.

Amongst the observations that we've made is the presence of IgA in the nose and in the BAL in the lung samples that we've collected. Now, more recently we are now looking at nonhuman primates over the course of an entire year to look at the durability of protection during that time period and the immunogenicity that's observed during that time period.

We don't yet have specific IgA measurements over that time period, but the results should be available in the near future, at which time, it will be published. It will be interesting to look not only acutely after vaccination the presence of IgA but what levels are present over a long period of time.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gans.

DR. HAYLEY GANS: Thanks for allowing me to come back on. It's so great to hear from my colleagues because they had a lot of questions answered. Anyway, I think there's a lot of evidence that we're now seeing that, despite our desire to see this memory response, I think we are starting to see a signal that is

suggesting to us that despite what we (audio skip) what might be the role of this virus (audio skip) breakthrough of serious disease. I take Dr. Offit's point, that we're not trying to (audio skip) disease that we can see by PCR. However, that is important for role of transmission.

Anyway, I did want to understand more because we are starting to see a signal in (audio skip) individuals, and it is different from what we were seeing previously. I think, unfortunately, for the Moderna, I know that the breakthrough is only 19 cases, so (audio skip) have a low number. But the pool of people we were looking at was very low too. So the 4 individuals who were not accounted for by age greater than 65 or those under 65 who had preexisting conditions, which I think would be taken care of by the people that you've listed for your extended EUA.

The four individuals who don't fall into any of those categories, would they actually perhaps fall into a category (audio skip)? I'm wondering if you know anything more about those individuals that could

help us under- (audio skip) they too would have been protected by being provided (audio skip) considering occupations that (audio skip) high exposure (audio skip) we do know (audio skip) correlate of (audio skip).

DR. JACQUELINE MILLER: Yes, Dr. Gans. I think you're right that we don't have a sufficient number of cases in this particular analysis to be able to refine our analysis to that level of degree. I think the Phase 3 study has larger sample sizes of those kinds of populations.

I think I'll clarify that our intention in our labeling information is to say that the booster dose is indicated for those 18 years of age and above. There's no reason to necessarily exclude someone that either FDA or particularly CDC, who make the vaccine recommendations for which population should be vaccinated -- we want to give them the ability to recommend the vaccine booster for who they think needs it.

DR. ARNOLD MONTO: Thank you. Let's go on to

Dr. Nelson.

DR. MICHAEL NELSON: Thank you. This question's also for the sponsor.

DR. ARNOLD MONTO: There will be two more questioners before we move on, so Dr. Nelson and then two more.

DR. MICHAEL NELSON: Great. This is indeed a question for the sponsor. Dr. Miller, thank you again for enlightening us this afternoon.

This has to do with the relationship between preexisting immunity and the risk for adverse events by a booster dose. My understanding of the data presented earlier was the reactogenicity is measured by common adverse events, and the combined data set for the 300 recipients of the 50-microgram dose doesn't appear to be significantly different than after dose 2 compared to the primary series. So what was found was that the risk of myocarditis and pericarditis does appear to be increased after dose.

It's unclear to me probably most whether the level of current humoral and cellular immunity at the

time of boosting is directly related to this risk or the risk of any other (audio skip).

What I didn't see in the briefing material -- this isn't a criticism; it's a question -- is is there data that stratify the risk for systemic adverse events by pre-event titer? Data of this type will help us do the risk-benefit analysis for broader populations who are largely immunocompetent, such as the third population will fit as being we're asked to address today, that is the 18 to 64 at higher risk for institutional occupational exposure.

The premise being, with the immunocompetent possibly having a higher baseline cellular and humoral memory response from the two doses, are they at significantly higher risk for a booster dose?

DR. JACQUELINE MILLER: Yes, thank you for that question. Unfortunately, we don't have that analysis. It's a really excellent suggestion. Again, thanks.

DR. ARNOLD MONTO: Thank you.

MR. MICHAEL KAWCZYNSKI: Dr. Fuller, are you

there? I unmuted you. There we go. Go ahead.

DR. OVETA FULLER: Yes, I am. Something happened to my phone. Yes, thank you.

Dr. Miller, this question has to do with messaging for vaccine boost. I remember, I believe, that in your first application for EUA, that those people who had recovered from COVID had slightly more robust side effects. I have heard from a number of people who'd gotten the Pfizer third dose that those who had had COVID have a bit more severe side effects.

In terms of messaging for people to know what to expect, can you tease out or have you any evidence that folks who'd had COVID and now are in the third boost or in the boost for Moderna have slightly more severe side effects? If so, is there a plan for messaging about that so people know what to expect? I think it's relevant to uptake and what gets said to other people.

DR. JACQUELINE MILLER: Yes, Dr. Fuller. Thanks for that question. Maybe just a clarification. I think in our Phase 3 dataset, overall, we saw a lower

reported rate in people who were initially seropositive. I need to qualify that because we did enroll people. Again, this was initially an efficacy study, so we wanted seronegative people to be able to follow breakthrough cases that would be captured. But, in people whose baseline swabs or who had baseline evidence of previous infection, they actually tended to report overall that they had lower reactogenicity, although some specific elicited symptoms. So the individual symptoms, some of them were higher.

I think we will learn a lot more about the third dose and lot more than we did in the original iterations of Phase 3 when we give this 50-microgram booster because there certainly was a lot of breakthrough disease in the original placebo group. They've actually now continued, potentially, in the study, and we'll be vaccinating them with this additional dose.

In terms of education of people, though, I think regardless of whether they had COVID before or they did not, it's important that patients understand

what to expect before they get the vaccine. That's why we really invested in looking in the comparison to the Phase 3 data. The Phase 3 data are the data that are currently represented in our vaccine fact sheet. I think going through that fact sheet, letting people know what they might experience, let them know that, at least in our initial studies, has been similar to what they saw after dose 2 is probably the best guidance we can give them.

DR. ARNOLD MONTO: Thank you.

DR. OVETA FULLER: Thank you.

DR. ARNOLD MONTO: Dr. Rubin.

DR. ERIC RUBIN: Thanks, Dr. Monto. I'm honored to get the last question if that's really the case.

DR. ARNOLD MONTO: It is before we have more comments.

DR. ERIC RUBIN: The presentation today included presentations from our Israeli colleagues about their Pfizer vax results. In fact, when Pfizer's vaccine came up for consideration, the fact that there

was widespread news and some efficacy data from Israel, I think, influenced many of us to think that this was a reasonable idea. Now we have more of those data, but they're Pfizer data.

So I want to ask Dr. Miller a totally unfair question. Do you think we can generalize from data from this other vaccine to what you might see in Moderna? Because I will say that the safety data, in particular, are very dim.

As was pointed out in the public comments, there are really only 170-ish people who got the same dose that we will be giving if we approve a third dose.

DR. JACQUELINE MILLER: Yes. Dr. Rubin, we don't have real-world data similar to those that were generated in Israel. I will say, I guess, we're indebted that Israel decided to be the frontrunner so that we have those data to review today.

What I will say is I think the 1.5 million Americans who have already been vaccinated with 100 micrograms as a third dose -- and these are admittedly immunocompromised but also medically vulnerable

individuals -- contributes to at least some of the understanding of the safety profile.

That safety profile is in a different population but reasonably conservative given that they got twice the dose. We're going to continue to follow the subjects that I described in the Kaiser study if they are offered their third dose, and that will be another way in which we can continue to evaluate what happens in terms of vaccine effectiveness. Then, certainly from a safety perspective, all of the ongoing pharmacovigilance activities that are currently underway will continue and include subjects who have received a third dose.

I would say I think the data, much as they did with the original messenger RNA submission, where we had 30,000 subjects' worth of data but now we have over 190 million doses worth, will grow the database in the similar fashion.

DR. ARNOLD MONTO: Thank you very much. We are going to terminate the question and answer session right now because, in reality, we do not have only our

voting topic. We will have after our voting topic a discussion which may be a rather robust discussion of steps forward for all of the vaccine. We will go into our Committee discussion. This discussion will be focused on our voting question. So can we get the voting question up so that we can at least focus our discussion on this?

COMMITTEE DISCUSSION AND VOTING

MR. MICHAEL KAWCZYNSKI: There you go.

DR. ARNOLD MONTO: There is our voting question. What we're going to do now is discuss this, have the vote, have any explanations of votes afterwards by those who want to explain their vote, and then go onto the discussion topic which is not going to have a vote. And that's going to be trying to harmonize any recommendations across the board in terms of different age groups and things of this sort. So reserve your broad thinking to the discussion, and let's focus now on the question that we've got in front

of us, which we will vote on. Okay. Dr. Nelson.

MR. MICHAEL KAWCZYNSKI: He put his hand down.

DR. ARNOLD MONTO: Okay. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I would like to ask a question about the third bullet, going back to something I mentioned earlier. Are there data to indicate that individuals who have occupational exposure to SARS-CoV-2 are at a high risk of severe COVID-19? For example, for healthcare workers, are they at increased risk of severe infection? My only point being, I think we have to be sure that we can justify everything we're saying. I'm not aware of data to support that. I need to be educated.

DR. ARNOLD MONTO: This mirrors the approval that we gave for the Pfizer vaccine.

DR. CODY MEISSNER: I understand.

DR. ARNOLD MONTO: So anybody at FDA or elsewhere ready to answer that question? Dr. Fink.

DR. DORAN FINK: Let me try to explain a little bit about how FDA arrived at this authorization statement for Pfizer. You're right that, when we held

the VRBPAC on September 17th and, when we constructed this authorization statement, there were not specific data nor do I think there are specific data now that speak to the risk of severe COVID among individuals with increased exposure in institutional or occupational settings. But I think it's important to highlight a couple of principles.

First of all, this third bullet includes the words "severe COVID," but it also includes "serious complications of COVID." As Peter Marks explained earlier in the day, there are sequelae of COVID, including long COVID, thromboembolic events, and other sequelae that may not meet someone's definition of severe COVID and yet would be considered serious conditions that would be applicable to the statutory criteria for emergency use authorization. I think it's also worth mentioning that, at the time (audio skip) COVID following primary vaccination, one can hypothesize that it might be the same group as would be at high risk of severe COVID prior to the primary series. But we don't know this for sure. We didn't

have data, yet such groups may exist.

And so really, the intent of structuring the authorization in this way is to provide a regulatory allowance for groups that could reasonably be considered at risk of serious complications of COVID for which there would be benefit to a booster dose being made available under emergency use authorization.

The point of emergency use authorization is that it is intended to address a current emergency situation. It can be changed as circumstances evolve. And, furthermore, ACIP can evaluate data to make recommendations for use of the vaccine that had been made available under EUA, and those recommendations can change as circumstances evolve.

And so really, this authorization was designed to allow for flexibility in making the vaccine available under EUA to individuals for whom it could provide a benefit and where the benefit would outweigh the risks.

DR. CODY MEISSNER: Thank you very much.

DR. ARNOLD MONTO: Thank you.

DR. CODY MEISSNER: Can I have a follow-up?

DR. ARNOLD MONTO: Yeah. Go ahead.

DR. CODY MEISSNER: Thank you, Doctor, and thank you Dr. Fink for that thoughtful answer. I appreciate it.

The only point I'd like to say is that I think it's so important that these recommendations are evidence-based. And I agree it's the ACIP which will make this decision. It's so important because this is such a controversial issue. If we can't defend these recommendations based on evidence, I think it's going to further complicate getting this vaccine into every single adult American, and that's really what we want to do.

DR. ARNOLD MONTO: Thank you, Dr. Meissner. Dr. Lee.

DR. JEANNETTE LEE: I think one of the questions I'm a little bit troubled by is that, as Dr. Moore pointed out, the data we have that have the individuals that have the full dose of Moderna followed by the booster is really only limited to about 149

patients, which is a fairly limited group, and also only meets one out of the two criteria that were prespecified for the emergency use. So I guess one of my questions I have -- as you can see, I have a little bit of hesitation -- maybe for Dr. Fink is would the requirements for full authorization of the booster mimic the ones that we have now for the EUA?

Or would they be more stringent? Have they been formulated, or what is sort of the thought at FDA? Were we to grab that EUA, what would be the requirement for them to get a full authorization for the booster?

DR. DORAN FINK: I had to unmute myself there. Thank you for that question.

I would really like the Committee to focus on the question as it pertains to emergency use authorization. It is an entirely valid question to ask, where we are ultimately going. We've heard discussion today about what the appropriate regimen would ultimately be, perhaps, under different circumstances when we're not in the middle of an active pandemic. I really would like the Committee to focus

on considerations for emergency use authorization right at this moment in time.

DR. ARNOLD MONTO: Thank you.

DR. JEANNETTE LEE: But it's actually (inaudible). That's what I'm getting at. Thanks.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth.

DR. JAMES HILDRETH: Okay. Thank you, Dr. Monto. I want to go back to Dr. Meissner's comment about bullet number three and that is that, oftentimes, individuals who have occupational exposure are brown and black people who work under conditions where they're exposed. And as we know, they're more likely to have underlying conditions that predispose them to severe COVID-19. So, as far as I'm concerned, that's the only justification needed for bullet number three, the higher percentage of people with underlying conditions who have occupational exposure. So, for me, bullet number three is very important and should remain a part of this voting question. Thank you.

DR. ARNOLD MONTO: Dr. Sawyer.

DR. MARK SAWYER: Mine is more of a comment.

I don't really have a question. I've been listening to all of the discussion and the excellent questions that have been raised. I'm of the opinion that we need boosters.

I find the Israeli data compelling as well as the breakthrough cases we're identifying in the United States. I agree that the amount of safety data presented specifically from the company was very minimal, but I do think that we can take some reassurance from the 1.5 million U.S. citizens who have already received this vaccine at a higher dose and without -- and we have good surveillance systems in place to have detected any new or unusual side effects.

I also think we can probably extrapolate from the Pfizer data in Israel and the experience in Israel in that, in all other ways, these two vaccines are quite similar.

Lastly, I think that, since I'm of the opinion that we need these boosters to be available for use in some populations, I think it's best to put it in the hands of ACIP to determine exactly who should get it

and under what circumstances. I'm not wild about a bunch of 20-year-olds running out and getting a booster dose unless they're at increased risk of either exposure or severe outcome.

DR. ARNOLD MONTO: Thank you. Dr. Gans.

DR. HAYLEY GANS: Hi. Thank you. I just wanted to make the comment alongside of my colleagues how important I think it is to act. We use vaccines protective. I'm not sure that we want to allow (audio skip) signals to be (audio skip). I couldn't agree more that the Israeli data that related to a messenger RNA vaccine that we're also considering here today is very compelling. They've done a really good job of showing us that it (audio skip) are in fact (audio skip) and actually impacts severe disease.

Their hospitalizations did fill up with (audio skip) were outside of ones that were considered necessarily in the first round to be at risk for hospitalization and severe disease. So I think we need to be careful about that.

I couldn't agree more with my other

colleagues, also, about exposure and really protecting those people who are on our frontlines as well as those who are in industries that are bringing them at higher risk. I think that Dr. Fink's comment about what was happening pre-vaccine is very important.

There were healthcare providers who were getting sick outside of those age groups and without underlying conditions probably because of, again, an inoculum effect and how much they were being exposed. We do have PPE now, and we do have masks. However, some individuals are just in situations where the conditions are such that these are (audio skip). I also find it very important, the need to include this in recommendations (audio skip) way.

I couldn't also agree more with Dr. Fink to say we are in the middle of a pandemic (audio skip) better so stopping this virus from (audio skip) is also important. We're starting to see, once again, our hospitals filling up with children who've been exposed through community transmission. Another way of protecting them (audio skip) this (audio skip).

There's a lot of evidence that the level of action, whatever it's going to be, is not being met over time with the regimen. There's also a lot of data to suggest that two doses without a boost is not really a regimen that (audio skip) us. I'm in favor of this, and probably the broader discussion (audio skip).

DR. ARNOLD MONTO: Thank you, Dr. Gans. Dr. Marks, I see you have your hand up.

DR. ARNOLD MONTO: You're muted.

DR. PETER MARKS: Sorry about that. I just wanted to remind the Committee that, for emergency use authorization, ideally this Committee will try to be relatively specific about what they would like to see so that we can put into place the correct wording on our authorization. And that has to do with some of the legal liability issues and how that works. It helps avoid some of the issues that can come up, then, when CDC, if they were a need to, to change that language. Bottom line is, what I'm saying is that some of the deference that we are able to give to the ACIP when we do biologics license application approvals is a little

more complicated here.

It's not to say that ACIP will not decide to further manipulate these recommendations, but to the extent that we can try to come to a place that we think will be acceptable for ACIP, that will be appreciated.

DR. ARNOLD MONTO: Thank you, Dr. Marks. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thanks, Dr. Monto. I'd like to make three points. The first is I agree with several of my colleagues with that bullet number three on the vote in question. I do think that, besides the individual risk, which is what we are assessing here obviously, but there is also the societal risk, particularly for healthcare workers, for frontline essential workers, who, as Dr. Hildreth pointed out, have individual risks as well.

I think this was part of our discussion a month ago, that having a lot of these folks come down with disease, whether it is mild or more severe, is still a problem because, even if they were still asymptomatic but they were detected, that could take

them out of the workforce. That certainly is a concern for us, as well.

The second point I want to make is about the inclusion of racial and ethnic minorities in these studies. This was a point made by, I believe, one of the open public hearing speakers, that Moderna should look at those populations and their risk and their safety with regard to the booster doses because there are very, very limited data. There are limited data overall, but particularly in those populations, the data are very, very small.

Then the final point I'd like to make is about the Israeli data. I, too, am impressed with the work that they're doing. The point I'd like to make is that what they're seeing in Israel isn't necessarily what we're seeing here in the United States. They have shown very compelling data that the booster dose clearly disrupted the third wave of their pandemic. Our numbers are going down before very large proportions of our population have received the booster dose. I think when we extrapolate data, we have to be

very mindful of what the epidemiology is in individual countries and even in local areas.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Just a couple of comments. One is that I certainly recognize the desire for the FDA to put out an EUA for the Moderna boost that essentially mirrors what was done for the Pfizer. And I'm certainly comfortable with that. I think that the same reasons with the waning of immunity, particularly the antibody decay rates that these people are experiencing, place particularly those populations -- especially the elderly and the high risk of severe COVID disease are the ones who are most at risk. They're relying extensively on their neutralizing titers to really prevent infections. They have much more limited capacity to prevent the severe disease complications.

That being said, I have some degree of reservation about the Moderna booster, the 50 microgram because, as was demonstrated by Dr. Miller, even in the absence of neutralizing titer, they are still

manifesting more than 50 percent protection, which means there's things other than neutralizing titers that are doing something. I don't know if the FDA has any sense of how that will change going from 100 to 50. So that is a little bit of an unknown, and that may actually have a tremendous impact on the durability.

The other thing I would say, both with regards to the mRNA vaccine, is that the durability of both of these has been adequately demonstrated in terms of very limited durability, anywhere from four to six months or six to eight months. Whether that is a consequence of a suboptimal dosing interval, whether that is a dose of the vaccine itself, or whether that is a fundamental inherent issue with the mRNA platform, I think is unknown. It's going to be very critical to understand whether or not a six-month boost actually does change the trajectory of the antibody response and provides some better durability than simply anywhere from about four to eight months of the antibody responses. That's all we tend to see.

I think it's going to be very critical going

forward to be monitoring this ever so closely because I'm not convinced that we have actually identified the optimal primary vaccination regimens for these vaccines. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Kurilla. Dr. Moore.

DR. PATRICK MOORE: There's one point that I'd like to make and that's the beauty of the mRNA vaccine is obviously because you change based as you make vaccines. So you could, in theory, with making a new 50 milligram, which there's no formulation right now ready for public distribution presumably, at least theoretically -- I haven't done it, obviously, but theoretically, you could change the sequence.

The real question that I have is to Drs. Marks and Fink -- is that, approving this EUA, does that give you more flexibility administratively to be able to request or demand that booster doses are addressing the variant of concern? That's one thing.

Two, I don't quite understand why this is not Delta because that's what we're facing right now.

And three, we've got to remember that Israeli does really, really quite clear. I was unconvinced by the data, including the early and late vaccination. I can talk about that more, but I don't want to waste the Committee's time. I'll talk individually about that, why that's not convincing to me. But the Pfizer data is quite convincing in Israel, but they're different vaccines since, as Dr. Perlman reminded me, there's about three times as much mRNA in the Moderna vaccine as there is in the Pfizer vaccine.

So the question is to Dr. Fink and Dr. Marks. Approving this EUA, does this somehow give you value added in terms of the public health response to be able to quickly respond to variants of concern with a booster?

DR. ARNOLD MONTO: Dr. Fink, Dr. Marks?

DR. PETER MARKS: Thank you. So I think we have -- in our guidance for emergency use authorization, Appendix 2 discusses how we would deal with variants of concern. Additionally, the World Health Organization is now convening on how to try to

decide globally how we'll deal with variants of concern. I think that I would make the decision on this based on what you think the benefit to the patient would be and not our ability to move forward with further variants because I think we do have a reasonable procedure in place for moving through to variants.

Some of the sponsors, in fact, I think all the ones I can think of, are working with one or the other of the variants of concern to show that they can make a vaccine that will generate an immune response.

Now, I think the other question you asked, which somebody else can chime in if they think I've gotten it wrong -- the reason for going with the prototype vaccine here rather than moving to Delta was that the neutralization with these prototype vaccines against Delta are quite good. The feeling was not to move to a new vaccine if you could neutralize equally well with the response to this variant.

Again, it's less churn and burn on the manufacturing also less exposure of people to

potentially antigens that they may not need to see. It looks like someone from Moderna might also want to speak up here.

DR. ARNOLD MONTO: Yes. Dr. Miller.

DR. JACQUELINE MILLER: Yes. Dr. Marks, you actually do have it right, but I just wanted to add some other historical context to how we got here. We actually made the decision in February of 2021 to begin manufacturing and studying variants of concern. That was really based on data that we observed with the Beta variant, actually some of the data that you saw in one of the slides I presented where we noted a 6.9-fold decrease in neutralizing antibody titers relative to the Wuhan strain. But it takes some time to swap out the sequence, make GMP manufacture, move forward with clinical trials.

The exploratory analysis was actually a Phase 1 to then be able to move into Phase 2. The data you're reviewing today really came from the population that we had available at that time to vaccinate, and that was the Phase 2 study. So they really are the

only population, other than the much smaller cohort in Phase 1, that were available to be boosted. The mRNA-1273 vaccine was the only one that we had available for use in clinical trials. We're pleased to see that there is cross-protection to the other variants.

To the question that's been asked, yes, I mean, I think we need to see what happens in terms of the epidemiology and constantly reflect on what the next steps need to be. That's why we are investigating variants of concern. This submission is really the start of our evaluation. Maybe, if you'll indulge me since I have the floor, I'll just say completely agree that we need additional data. Completely agree that we need data in more diverse populations. That is why we are continuing to vaccinate individuals from the CoV study who are now further out from their primary vaccination. And CoV, if you'll recall, had a much greater degree of diversity.

The final point I want to make is that, for these variant vaccines that we're investigating, we also are boosting subjects from CoV and moving forward

employing the same diversity and inclusion of initiatives that we did in the Phase 3 study. Thank you for the opportunity to comment.

DR. ARNOLD MONTO: Dr. Marks, to close off this part of the discussion.

DR. PETER MARKS: Dr. Moore, one other thing, and you might know this already, but Israel's data were obtained pretty much in the setting of 99 percent Delta variant over this past summer. The real-world evidence study there from their boosters is largely from a Delta variant that was boosted with their prototype vaccine.

DR. ARNOLD MONTO: Okay. Dr. Perlman.

MR. MICHAEL KAWCZYNSKI: Dr. Perlman, you there?

DR. STANLEY PERLMAN: Yeah. I just wanted to make a couple of points. One is I think that it would be great if Moderna actually could do investigations of dosing intervals and mucosal vaccine. That's what we talked a lot about in the last bit of time. I don't know what they're doing with that, but that's just a small comment.

The second thing is in support of the notion of this 18- to 64-year-olds vaccination for people who have institutional or occupational exposure. I think another issue that we were thinking about when we approved this for Pfizer was that we can't afford to have healthcare workers, even if not sick, be positive and infected and have to stay home from work because there's parts of the country where there's just a shortage of healthcare workers and there's burnout everywhere. That was, I think, another part that's not quite in the statement but I think within the thinking of some of us anyway.

The other thing was that one thing I have had trouble trying to put together is the Moderna vaccine was actually a little more efficacious than the Pfizer vaccine, yet we're talking about the same six-month interval. I'm not sure that that's really necessary because the vaccine does seem to be a little more efficacious. It's hard for me to put that together mathematically to know what the best way to do that.

The final thing was, I think from the

pragmatic point of view, even with what I just said, some ways I support this EUA because we've already approved it for Pfizer. And I don't see how we can possibly not approve it for Moderna and not have most U.S. folks be completely confused. I know that's not really part of what we're supposed to think about, but I think it's a pragmatic issue. That's all.

DR. ARNOLD MONTO: Thank you. Dr. Nelson.

DR. MICHAEL NELSON: Thank you, Dr. Monto. Just a few comments and one technical question regarding this vote. I'm, one, very reassured that it's not a new preparation, actually half a dose of an existing formulation. I know it'll be very reassuring to the public. Two, I agree with our colleagues about the many unknowns regarding the durability of response and specifically, Dr. Kurilla's comments: does the lower dose have an implication for durability after this booster dose?

Next, I do remain concerned about the sluggishness with which we are acquiring knowledge about the risk factors for some of these adverse

events, the systemic adverse events. Communicating with the NIH and sponsors to assist in rapidly identifying these risk factors will make these decisions a lot easier in the future.

Finally, very supportive of this EUA intent of making the vaccine available to these very three valued and determined at-risk populations. And, with respect to the wording, I'm very happy to see the specific wording of at least six months. It allows some discretionary use with respect to the timing of this booster dose given some of the issues we've discussed today.

Then my last comment, or really a question, is a technical one. Before any EUA was authorized last year as a part of this Committee, we were informed that the data that we were to review to provide that EUA was to be based on individuals who were studied. So I was struck by the lack of under-represented minorities in the dataset of these 300 plus for this specific vaccine. I just wanted confirmation from the FDA that we're allowed to use the bridge data from the initial

primary series as part of our deliberations and not have to factor in the absence of these under-represented minorities. I appreciate the sponsor's commitment to acquire that data going forward.

DR. DORAN FINK: Thank you, for that question. I, of course, agree that ideally, we would have more diverse representation in all of the data that we have available to evaluate to make regulatory decisions. That being said, we do have fairly robust data from the primary series that does not suggest any significant differences between racial and ethnic groups or genders with regard to vaccine efficacy or vaccine safety. I do think it's fair, and it is the FDA's viewpoint as well, to rely heavily on those observations from the studies with the two-dose series in understanding how a booster dose would be effective and also safety across diverse populations.

DR. MICHAEL NELSON: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you very much, and I appreciate all the comments before.

I'm a physician caring for adults that are primarily African American and Hispanics in Los Angeles, California. I've been in practice for 35 years. I believe the results presented today will be encouraging for the many patients who have received available vaccines. They look forward to recommended boosters.

I also hope the presentation will result in and will be encouraging and instill more trust in including areas of safety and efficacy in hesitant citizens. I still have a substantial number of those. Physicians and medical groups are following CDC vaccination strategies, and overall acceptance has improved. However, challenges still persist. I think that approval will help us along the way. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Rubin. You're muted.

MS. KATHLEEN HAYES: It's your individual phone, Dr. Rubin.

MR. MICHAEL KAWCZYNSKI: Got it, sir? Dr. Rubin, just unmute you're regular phone, sir. Okay.

Let's go to someone else.

DR. ARNOLD MONTO: Okay. Let's go on to Dr. Hawkins.

DR. RANDY HAWKINS: I've already spoken.

DR. ARNOLD MONTO: Okay. Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Arnold. I think one thing that everybody's been talking about is this third group. I want to reiterate that I'm very supportive of that third group being part of this. Specifically, to Dr. Perlman's comment that the healthcare workers -- I think it's critical that we prevent infection as much as we can. If there is a benefit to that booster in preventing primary infection, then that will be critical at protecting healthcare institutions from outbreaks, et cetera.

I also want to comment as a side note that there was some concern that the number of groups here would suggest a large population of the United States would be eligible for boosters. One difference between the Israeli data and the United States data, so far at least, has been the uptick of boosters. At least what

I've seen that's been published by the CDC so far, only about 10 percent of those 65 and older have received boosters to date, and only about 4 percent in the United States have received boosters. It has not been as some had expected that large numbers would be going to go get boosters. I think one thing that I think would be important is really, if we are going to be making boosters available, to increase efforts to get these to specific communities at risk.

DR. ARNOLD MONTO: Thank you, Dr. Pergam. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I just wanted to clarify my comments because I'm not sure I was clear. I certainly agree that healthcare workers and institutionalized individuals should be eligible for a booster. My issue was that the statement says their employment or their living situation puts them at high risk of serious complications. I was just asking. I don't think there are any data that say that, for example, a healthcare worker has a higher risk of serious complications just because of his or her

employment. So it's the wording that troubles me, not the intent. I think it puts them at increased risk of COVID infection. I think that's fine.

The second point is I agree with the comment that people are getting Moderna's booster in a number of different places. I have a little bit of trouble with saying, yes, you can get it if you got the Pfizer the first time for the first primary series, but you can't get it if you got the Moderna for the primary series. I don't think that's really fair.

DR. ARNOLD MONTO: Thank you. Any comments from FDA about Dr. Meissner's concern about the wording? The problem is that's the wording we approved last time, correct?

DR. CODY MEISSNER: Yes.

DR. ARNOLD MONTO: In terms of amending --

DR. PETER MARKS: Dr. Monto, that's correct. I think when you come to your next question, we'd like to give you lots of latitude to make comments on how we could improve that.

DR. ARNOLD MONTO: Thank you. Dr. Rubin.

DR. ERIC RUBIN: Check and try. Working this time?

DR. ARNOLD MONTO: It is.

DR. ERIC RUBIN: Excellent. Thank you. I would echo what many people said and I'm not going to repeat. The data are not perfect, but these are extraordinary times, and we have to work with imperfect data.

I just want it to be said once here as it was said in the public meeting that the effect of the booster is much less than the effect of vaccinating unvaccinated individuals. That means both here and abroad. So I think that we want to clearly send the message or include the message that, if we're going to get out of this thing, we have to be vaccinating the unvaccinated.

DR. ARNOLD MONTO: Thank you. I think that message has been reiterated. Whether they're listening is the problem. Okay. We do not have any more hands raised. Are we ready to call the question, Kathleen?

MS. KATHLEEN HAYES: I believe so. Let me

just provide some instruction. Mike, are you back and able to pull up the questions? Okay. Great. Thank you, Dr. Monto. We have 19 voting members and 1 nonvoting industry representative attending today's meeting. Only these 19 voting members, excluding the industry representative as seen on this slide, should vote in today's meeting. If you are not an official voting member, please refrain from voting as your vote will not be counted.

In regard to the voting process, Dr. Monto will read the final question aloud for the record. Afterwards, all members and temporary voting members will cast their votes by selecting yes, no, or abstain. You'll have two minutes to cast your vote. After the question is read, we will broadcast the results and read the votes aloud for the record. Please note that, once you've cast your vote, you may change it within the two-minute timeframe. However, once the poll has closed, all votes are considered final. So unless anyone has any questions related to the voting process, we'll have Dr. Monto read the voting question aloud for

the record.

DR. ARNOLD MONTO: Okay. "Do available data support the safety and effectiveness of Moderna COVID-19 vaccine for use under EUA as a booster dose, 50 micrograms mRNA-1273, at least 6 months after completion of a primary series in the following populations: individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19?"

MS. KATHLEEN HAYES: Thank you, Dr. Monto. Mike, if we could pull up the voting pod. Great. Go ahead and cast your vote if you are an official voting member at this time.

DR. JEANNETTE LEE: Is the voting pod up?

DR. ARNOLD MONTO: It is.

MS. KATHLEEN HAYES: The voting pod is up. It should say Voting Question One, Yes, No, or Abstain.

Let me just look at the results here. Okay. I believe that we have all of the results in for all 19 voting members, and I will read them aloud for the record. Dr. Randy Hawkins voted yes. Dr. Cohn voted yes. Dr. Pergam voted yes. Dr. Nelson voted yes. Dr. Moore voted yes. Dr. Fuller voted yes. Dr. Levy voted yes. Dr. Wharton voted yes. Dr. Hildreth voted yes. Dr. Sawyer voted yes. Dr. Kurilla voted yes. Dr. Monto voted yes. Dr. Perlman voted yes. Dr. Lee voted yes. Dr. Meissner voted yes. Dr. Gans voted yes. Dr. Offit voted yes. Dr. Chatterjee voted yes. Dr. Rubin voted yes.

So we do have a unanimous 19 out of 19 yes votes. That concludes the voting portion. We can close this out, and I will hand it back to Dr. Monto. Thank you.

DR. ARNOLD MONTO: Thank you very much. If anybody wants to explain their vote, raise their hands. What we're going to do after that is we're going to take a merciful five-minute break before we go on to the discussion topic. We'll have a few minutes to

stretch between any explanation of votes and the discussion topic. Dr. Moore.

DR. PATRICK MOORE: I think that it's kind of clear that I've got some real issues with this vote. But nonetheless, I just want to explain. Why I voted yes on it is more gut feeling rather than based on really, truly serious data. I think that it's very important for companies that are coming to VRBPAC on dealing with this EUA that they really take seriously the idea that we need to see good solid data. And it needs to be explained well, which to be honest with you this submission was, to me at least -- and perhaps it's just because I'm old and befuddled -- but it was not explained well until I read the FDA review, the second half.

That, on the other hand, had a clarity and a crystal precision to it that really made it clear what the issues are. The data itself is not strong, but it is certainly going in a direction that is supportive of this vote.

DR. ARNOLD MONTO: Thank you, Dr. Moore.

We're going to break until 3:20 Eastern. Then, at that point, Mike, you'll put up the discussion question. Break for about six or seven minutes.

MR. MICHAEL KAWCZYNSKI: All right. Just a short break for seven minutes. Let me put the timer up.

BREAK

MR. MICHAEL KAWCZYNSKI: Welcome back from that quick break. Dr. Monto, you ready to take us into the discussion topic and get towards the end of the day?

DR. ARNOLD MONTO: I am. Remember this is not a voting topic. As Dr. Marks told us, we have free reign to say whatever we want to. We can be a little less focused than we were during the discussion of the voting questions. I won't just read this to you because you all can read the PowerPoint. What we're going to be doing is talking about how comfortable we would be in extending some of these booster

recommendations to age groups down to 18, not including anyone at this point under 18 years of age. This reflects some of the requests that have actually been made to FDA from the manufacturer. Dr. Chatterjee's got her hand raised. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you. We discussed this a little bit at the last meeting when Pfizer's vaccine was up for discussion. I think the concern I have -- there were a couple of concerns I had. One is that I am not convinced that the epidemiology of the pandemic at the moment in the U.S. supports this request. We are seeing cases going down without booster doses. Yet, in this population, the people who are vaccinated appear to be protected.

The disease primarily seems to be occurring, especially in its more severe form, in those who are unvaccinated. The comment was made earlier today that that is really the group that we need to focus on getting them vaccinated. That's the first point I want to make.

The second point is with regard to the

robustness of the data. The numbers of participants in the booster trial, the booster study, are very, very small. We're talking about basing a decision that will impact tens if not hundreds of millions of people based on data that have been provided by both the companies. If you add them together, they don't come up to 500 people. So I am very concerned about the paucity of data on which this decision will be made.

DR. ARNOLD MONTO: Thank you, Dr. Chatterjee. Dr. Offit.

DR. PAUL OFFIT: Yeah, I'd just like to agree completely with Dr. Chatterjee. I feel like we're sort of going down the line here of booster dosing based largely on data generated from Israel. Although I think the data generated in Israel certainly was clear of the 70- to 79-year-olds, I am just less impressed with who I'd put, frankly, in the same category as an immune incompetent host.

I am less impressed with the data regarding the younger person. There's just too many variables in there that I think may not have been considered, not

the least of which, as Dr. Chatterjee said, we're seeing a decline in this country right now, too, and it's certainly not because of booster dosing. We can claim that. I do worry about this broad use now of boosters. Certainly, I don't agree with doing this down to 18 years of age at all. Maybe at 30, I would feel a little better because the 18- to 29-year-old is at higher risk of myocarditis with any clear evidence of benefit.

I'm impressed by the fact that we continue to have excellent protection against moderate to severe disease in this country through Delta and for all age groups. I just think that we continue to send wrong messages out there by using terms like "breakthrough" and by making people feel that they're not protected unless they've gotten a third dose.

As Dr. Rubin said so accurately, the problem in this country is vaccinating the unvaccinated. I can tell you at the HUP, the Hospital of the University of Pennsylvania, CHOP and those over 12, the people who are in the ICU aren't there because they haven't gotten

a third dose. They're there because they haven't gotten any dose. I just worry that we haven't clearly defined what the goal of this vaccine is because, if the goal of this vaccine is to prevent asymptomatic or mildly symptomatic infection, that is a goal for which we have set no other vaccine.

If we're trying to prevent what is inevitable, which is a decline in neutralizing antibodies and an erosion of protection against mild or asymptomatic infections, that is a high bar to which we hold no other vaccine. I understand we're in a pandemic. I understand that we may need somewhat less shedding. I think if you really want to control shedding, we just have to vaccinate the unvaccinated. I'm uncomfortable with how we sort of trip down the line here regarding, now, the thought of universal booster dosing, which I just think is wrong. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Rubin.

DR. ERIC RUBIN: Thank you. Am I on?

DR. ARNOLD MONTO: You are.

DR. ERIC RUBIN: Oh, thanks. Sometimes it

talks to me, and sometimes it doesn't.

So I agree entirely with Dr. Offit. I guess I'd phrase it slightly differently which is -- and Dr. Chatterjee. I think that I'd phrase it slightly differently which is that, in order to demonstrate, we should be giving vaccine to much younger patients who are not otherwise at risk. We need to have some sort of risk-benefit analysis done. That risk-benefit analysis could include the fact that the vaccine inhibits transmission and therefore can break the cycle of transmission. That would be at least one factor to consider.

We don't have that. We don't really have a good idea of the benefit of boosters for this group. There's a good reason to think that there isn't much benefit. We know that there are some (audio skip) signal, and I'm not sure that we want to just explore it willy nilly by giving it to a lot of people.

DR. ARNOLD MONTO: Thank you. Dr. Gans.

DR. HAYLEY GANS: I want to thank my colleagues for bringing forward some really great

thoughts about (audio skip). I would argue that I don't think that we have to do (audio skip) talking about (audio skip) --

DR. ARNOLD MONTO: Dr. Gans, you're breaking up.

MR. MICHAEL KAWCZYNSKI: Dr. Gans, we're not hearing you right now. Yeah, Dr. Gans, we're not hearing you. So let's go to somebody else. I think her headset unplugged.

DR. ARNOLD MONTO: Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah, I agree with my colleagues. As I've expressed previously, I think that, in my mind, the need for the booster is primarily in those individuals who are at high risk for serious disease, which overlaps pretty well with individuals who don't respond very well with adequate cellular immune responses, which I think is most important for protecting against severe disease. For the younger population, they seem to be responding not only quite well to these vaccines, but they're actually holding up. So I don't necessarily see the

need for a sort of "let it rip" campaign for boosters for everyone who's ever been vaccinated.

I'll respectfully disagree with several of my colleagues. I was not as impressed with the Israeli data as a justification. They may be attributing their profile of their third wave to the introduction of boosters, but I think, if you look at their first and second waves, which was pre-vaccine, they qualitatively looked very similar. In fact, if you look at the Delta wave that went through India, which had less than 20 percent of fully vaccinated people and was very similar to what we're seeing here, the Delta wave seems to have entered into a population. It goes through and then it moves on. It's just been a wave moving throughout the country.

So I don't think that the boosters really should be the -- I guess the question I'm really getting at is, what do we want the boosters to do? As Dr. Offit was saying, if the intention here is to actually have an impact on the transmission with some sort of aspirational sterilizing immunity-type of

function, I don't think these vaccines are really demonstrating that. What they are very good at is preventing severe disease.

I think that if we can actually migrate the pandemic down from being a very severe case situation to something that is more akin to influenza, I think that the vaccines will have done what we really need for them to do which is to prevent the overwhelming of the healthcare system and to protect the people who are most at risk of serious disease.

The younger populations don't seem to have as much of a problem, and I'm not as really worried even if they are not boosted from the standpoint of -- the other factor we're not paying attention to is, as this pandemic evolves, we are looking currently as if people are vaccinated or unvaccinated.

But there's also people who have been infected. No one has really talked about whether breakthrough infections -- I know that some people don't like that term. But having been vaccinated and then having experienced an infection because of waning

immunity, what sort of immunological responses does that manifest and is that the equivalent of being boosted?

Those are questions that I think are going to become more critical because, eventually, everyone is either going to have been vaccinated or had been priorly infected or both. Really understanding what their immunological status is across the age spectrum and across the healthcare spectrum, I think, is going to be very important. We can't just look at this as boost people every six months. It's not going to work.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I completely concur with everything that's been stated up to this point in terms of younger adolescents and children. If we look at the CDC hospitalization rate for COVID-19 associated hospitalization in children under 18 years, it's less than 1 per 100,000. The rates of myocarditis are variable depending on the study but probably at least 5 to 10 per 100,000. So, before we recommend a vaccine for young children and

adolescents, I think we really need to know exactly what Dr. Rubin said, what is the risk-benefit ratio?

I think giving a booster without a large number of participants and subjects I think may not be the best thing to do. Thank you.

DR. ARNOLD MONTO: Dr. Levy.

DR. OFER LEVY: Thank you. I think there are four elements here I'd want to know more about before a decision on recommending boosters all the way down to 18 years of age. We've talked a lot about risks to young individuals, particularly young males, vis-á-vis myocarditis, in relation to the risk of COVID symptoms. What we haven't said too much about is if a vaccine helps reduce transmission of coronavirus from a young individual to their parents or grandparents. There are both indirect and maybe direct benefits to that individual as well. That calculus gets more complicated and should be considered and analyzed.

Is it possible that boosters in the right context could help us get to herd immunity? Several of the other Committee members brought that up. The

Israeli data spoke to that possibility. That's intriguing. Another unknown in my mind is solid studies about long COVID in children. Does it exist? What is it like? How frequent is it? Do we have phenomena where children initially don't have many symptoms, but then there are longer-term effects? To my knowledge, the literature is still muddled on this, and there's a lack of rigorous studies. We would look forward to information from CDC and FDA for their national analysis on that.

Finally, we're asked to consider these questions without regard often to whether recommending something would become making it available to a particular age group versus its turning into a mandate. That's not really the purview of our Committee because that goes to CDC, and then states in our federal system implement their approach to all of this. But nevertheless, it would impact my view of it in terms of the public health impact.

So those are four areas I think should be considered and explicitly analyzed and discussed ahead

of any such vote by this Committee. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gans.

DR. HAYLEY GANS: Apologies for being booted off last time. I don't know how much you got, but I really agree and want to thank my colleagues for this discussion.

As the question is stated, it's really asking if we have the current data. I think we need more, but I would add to the amount of data that we need because I think it's very important to get this question right. The fact that other vaccines are used. We don't call it a boost; just say a series. We really have to get right, what is a series for this? And so we really have to understand these breakthroughs to really understand the disease long-term ramifications.

We need immunologic data on these breakthroughs that we keep hearing we're going to get. We've been actually hearing that for quite some time. So it sounded like there were some preprint information. We need that to move forward. We need both the information not only around humoral immunity.

Everyone has brought up that we have to understand what actually is humoral immunity. We Really need to appeal to our colleagues looking at this to really understand it.

The other piece of information that I think is going to be really important, again, as the Delta variant is actually causing a different distribution as well as different severity of (audio skip) and we need to understand -- we're not going to have long-term data, but we need to understand the indications. Even if you have mild disease, whatever that is, what does that actually do? (audio skip) because allowing people to get infected because we can't achieve sterilization is different than affording them the ability not to have damaged tissues from infection, as mild as it is.

I think we need several points that we're all asking for and battling with so that we can make sure that we understand this. I think it's very important for us not to ignore signals that are out there. It's true that Delta's dropping, but it's also true that there's a different disease form and we are seeing

people hospitalized who don't necessarily meet the risk factors that we understood with the original. I think it's very important not to ignore signals early so that we can cause prevention.

I think that's what this question is asking. Did we hit it right first, and (audio skip) end it? That's what I think we need. But I also would say -- and I don't know if this was something that I said before and was heard -- but this question does not need to be answered in an and-or question. We can immunize people who are not vaccinated and still (audio skip). And then we need to also consider the protection of the very youngest people in our study who (audio skip).

DR. ARNOLD MONTO: Thank you, Dr. Gans. As we go forward in our discussion, I think we should not think about this as one enormous population group down to age 18. The risk-benefit may vary in some of the older -- still young but let's say down to age 40 -- as compared to the 40- to 18-year-olds. We are seeing breakthrough, to use an unwelcome term. We are seeing infections with hospitalization in those age groups.

We will be getting data as the boosters are rolled out in the older populations. Let's keep that in mind and not look at this as a single question but perhaps a question that can be broken into stages. Going further to Dr. Cohn.

CAPT. AMANDA COHN: Thanks, Dr. Monto. That is actually one of the points I was going to bring up as well. I'd really like to bring up the age group of 50 and older. One of the topics that came up during the ACIP meeting where this was discussed is that 65 is really a construct for being older or not. Given the incredible impact that COVID has had on many older communities of color, it's even especially important that we protect older persons of color who may not actually meet that 65-age cutoff.

I would like to consider, at least, moving down to age 50, where the risk for myocarditis after one dose and two dose and in the third dose from Israel, is back to baseline.

DR. ARNOLD MONTO: Dr. Hildreth.

DR. JAMES HILDRETH: Thank you, Dr. Monto. I

want to reference a point made by Dr. Gans. I said this last time. What would be really helpful would be to have some objective measure to know when boosters are needed, an immune correlate. It could be a certain neutralizing antibody titer or a certain T cell response. That way we could know when boosters are needed regardless of the risk factors because, after all, the first problem to be solved is keeping people protected from infection. To know when the antibody levels are high enough to protect them would be very helpful.

I don't understand how after hundreds of millions of people infected and almost a thousand trials that we don't have that information yet. I think an immune correlate would be really helpful in all of this. Thank you.

DR. ARNOLD MONTO: Dr. Moore.

DR. PATRICK MOORE: (Audio gap) change an adenovirus vaccine where something like 1 out of 50,000 to 100,000 young men will be affected apparently by the RNA vaccines. One way to approach that, of course, is

to restrict or at least suggest restricting the use of each class of vaccine to those that have the highest risk of severe adverse effects from it.

DR. ARNOLD MONTO: Thank you. We don't have any hands raised. Dr. Marks, would you like to make some comments before I try to summarize the discussion?

DR. PETER MARKS: Thanks very much to the Committee members. I think we heard pretty loud and clearly that there was not a lot of appetite for moving down the age range very significantly if at all. I think we'll go back and try to understand what might make the most sense, if anything, based on your feedback. If anyone wants to chime in on anything else in that regard, we're happy to hear that. I think that's the summary that we would take from this. We do hear very loud and clear this need for benefit-risk considerations here.

It is a very challenging pandemic. Having been doing this now for about two years, the problem here is that we don't know what we don't know. And making any predictions about what's going to happen in

the next month is very challenging. There are models that predict that we could potentially have another wave of COVID-19 as people go inside this winter, and we have either the current variants or one other one come up. That is part of what is going into our minds here about being prepared. I think we can't simply look right now at what's going on with the pandemic's curve and just call it a day.

We have to be able to think about what might happen. I would encourage people to look at anyone -- there were several very good modeling groups, academic as well as from the CDC, which are concerned that we could see another wave. That's part of what's going into our thinking here is that we do have to think ahead. But we're very, very grateful for the Committees. I think it seems pretty uniformed feedback here.

DR. ARNOLD MONTO: Dr. Pergam, I see that you have your hand raised. I may have missed it.

DR. STEVEN PERGAM: That's okay, Dr. Monto. This is more just a question of how the process works.

Maybe this is for Dr. Marks. Currently, the FDA guidance is that it's these particular groups that would be eligible. If the ACIP decided to change the age range, would that be a decision that they would make independently, or did they need our group to vote to make those changes first to allow them to drop to those lower levels? Are they only allowed to vote on sort of what we've approved from this Committee? I just wanted clarification on that.

DR. PETER MARKS: I'm going to actually defer part of this to Dr. Cohn. It's nice to have her on the line to be able to -- but, in general, the idea here is that ACIP for these emergency use authorizations could potentially -- there are a lot of options. They could potentially narrow. There's another vehicle they could use called "Emergency Use Instructions," which could work differently. Ideally, what we have would be something that would be broad, and they would potentially narrow or refine further. Dr. Cohn, do you want to try to refine what I said a little bit?

CAPT. AMANDA COHN: Sure. I'll confirm that

ACIP -- under the constrictions of the EUA, unlike a BLA, ACIP really can't expand or be broader than FDA conditions of use. However, we can be more narrow. For example, FDA could go down on age, and ACIP would not have to. But, if FDA does not change and go down on age, ACIP could not address it.

DR. ARNOLD MONTO: Thank you. I think that's pretty clear. What I would suggest, Dr. Marks, as we go forward -- and I'm not looking for more meetings. These are quite tiring and time consuming for all of us. I think we need to develop some rationale for going down in age groups. As we gain experience with the booster doses in an older and other populations at high risk, which will include younger individuals, I think part of the problem is, basically, one of risk-benefit. And I don't know that the benefit has been sufficiently defined.

As we go down in age and gain experience in terms of the risk and the, to a lesser extent, benefit because we may not see that if in fact the wave that we're currently getting out of does not return, then we

can revisit the topic and try to refine it in terms of different age groups and what might happen in the older of the young and the younger of the young, not going below 18 years of age. I think that would be my summary.

The concern that I have is that we don't want to wait until we see more severe infections in the under 65-year-old general population because getting this vaccine out takes time and requires extreme logistic efforts.

That's my summary. At this point, thank you all. Thank you to the staff of FDA. Thanks to members of the Committee. I'll turn this over to Prabha for the official closing, until tomorrow, that is.

MS. PRABHAKARA ATREYA: Thank you, Dr. Monto. Thank you, everyone, all the members and consultants and the meeting participants and speakers. Thank you for a very productive meeting. We are actually closing earlier than anticipated. We will be ready for our (inaudible) tomorrow morning on another topic. Thank you and the meeting is adjourned now at 3:50 p.m.

Eastern time. Thank you.

[MEETING ADJOURNED FOR THE DAY]

OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 169th meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. I am Mike Kawczynski, and I will be moderating today's activities throughout the day. That means you may see me pop in every once in a while to address any technical issues or -- so if that does happen, we may have to take an unscheduled break, but not to worry, we will get it back up and running really quickly after that.

So this is day two, so, with that being said, of the 169th meeting, so Dr. Monto, are you there? I'll have you turn your camera on. Dr. Monto is our chair for today. Dr. Monto, did you mute your -- there we go. That's all right, we'll wait for you. Can't

start the meeting without you.

DR. ARNOLD MONTO: I'm trying to get the camera to work.

MR. MICHAEL KAWCZYNSKI: All right, we'll wait a second.

DR. ARNOLD MONTO: It's behaving -- you're going to have to deal with me for the introductions without my picture for a moment.

MR. MICHAEL KAWCZYNSKI: All right.

DR. ARNOLD MONTO: I'd like to welcome you all to the continuation of the 169th Meeting of the Vaccines and Related Biologics Products Advisory Committee. This is day two, and the major topic for today, not the only topic, is the Committee will meet in open session to discuss the EUA of the Janssen Biotech, Incorporated COVID-19 vaccine for the administration of a booster dose to individuals 18 years of age and older.

Prabha Atreya, our Designated Federal Officer, will be introducing the members of the Committee and going over housekeeping details as usual, and read all

the appropriate statements that need to be handled. So, over to you, Prabha. Good luck with your camera.

MR. MICHAEL KAWCZYNSKI: There she is. All right, Prabha, you ready?

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

DR. PRABHAKARA ATREYA: Yes, I am ready. Thank you so much, Dr. Monto. Good morning everyone. This is Dr. Prabha Atreya, and it is my great honor to serve as the designated federal officer. That is the DFO for today's 169th Vaccines and Related Biological Products Advisory Committee meeting.

On behalf of the FDA, the Center for Biologics Evaluations and Research, and the VRBPAC Committee, I would like to welcome everyone for today's virtual meeting. As Dr. Monto mentioned, the topic for today's meeting is to discuss in open session the emergency use authorization, EUA, of the Janssen Biotech, Incorporation's COVID vaccine for the administration of

a booster dose to individuals 18 years of age and older. Today's meeting and the topic were announced in the Federal Register Notice that was published on October 7, 2021.

I would like to introduce and acknowledge the excellent contributions of the staff in my division and the great teams we have in preparing for this meeting. Can we have the slide, please? So, Ms. Kathleen Hayes is my co-DFO providing excellent support in all aspects of preparing for and conducting this meeting. The other staff who contributed significantly are Ms. Monique Hill, Ms. Karen Thomas, and Ms. Christina Vert who also provided excellent administrative support. I would also like to express our sincere appreciation to Mr. Mike Kawczynski, who is facilitating the meeting today. Also, our kudos to many FDA staff working hard behind the scenes, trying to ensure that today's virtual meeting will also be a successful one, like all the previous VRBPAC meetings on the COVID topic.

Please direct any press or media questions to the FDA's Office of the Media Affairs at FDAOMA@fed.hss.gov.

The transcriptionist for today's meeting are Ms. Linda Giles and Ms. Erica Denham.

We will begin today's meeting by taking a formal roll call for the Committee members and temporary voting members. When it is your turn, please turn on your camera and unmute your phone and then state your first and last name. And, when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slide, which will begin with the chair. Dr. Monto? Can you start?

DR. ARNOLD MONTO: Yes, I can, and my webcam is working now. I'm Arnold Monto, I'm professor of epidemiology and public health and global public health at the University of Michigan School of Public Health. And I've worked for many, many years on vaccines, particularly flu and have been involved in pandemic response on several occasions. Back to you, Prabha.

DR. PRABHAKARA ATREYA: Great, thank you. Dr. Amanda Cohn.

DR. AMANDA COHN: Good morning, I'm Amanda Cohn, a pediatrician with experience in vaccine-

preventable diseases at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning, everyone, my name is Archana Chatterjee, I'm a pediatric infectious diseases specialist with expertise in vaccines. I'm also the Dean of Chicago Medical School at Rosalind Franklin University of Medicine and Science in North Chicago.

DR. PRABHAKARA ATREYA: Thank you, Dr. Chatterjee. Next is Dr. Meissner, Cody Meissner. We can't hear you, Dr. Meissner.

MR. MICHAEL KAWCZYNSKI: Give us a second, let me unmute Dr. Meissner. Sorry, there you go, Cody.

DR. CODY MEISSNER: Thank you. My name's Cody Meissner. I'm a professor of pediatric infectious disease at Tufts University School of Medicine at Tufts Medical Center in Boston. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Gans.

DR. HAYLEY GANS: Good morning and thank you. I'm a professor of pediatric infectious diseases at Stanford University (audio skip) director of our pediatric infection program for (audio skip) research focus is on (audio skip).

DR. PRABHAKARA ATREYA: Thank you, Dr. Gans, next, Dr. Michael Kurilla.

DR. MICHAEL KURILLA: Good morning. Mike Kurilla, I'm the director of the division of clinical innovation at the National Center for Advancing Translational Sciences within the National Institutes of Health. I'm a pathologist by training with a background in infectious diseases and vaccine development.

DR. PRABHAKARA ATREYA: Thank you, Dr. Kurilla. Next is Dr. Paula Annunziato.

DR. PAULA ANNUNZIATO: Good morning. I'm Paula Annunziato. I lead global clinical development for vaccines at Merck, and I'm here today serving as the non-voting industry representative.

DR. PRABHAKARA ATREYA: Thank you, Dr.

Annuziato. Next, Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Atreya, I'm Steve Pergam. I'm an adult infectious disease physician and an associate professor at Fred Hutchinson Cancer Research Center and University of Washington in Seattle.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Fuller.

DR. OVETA FULLER: Good morning, Dr. Atreya, I'm Dr. Oveta Fuller. I'm an associate professor of microbiology and immunology at the University of Michigan in the medical school and a member of the STEM initiative in the African Studies Center. I'm a virologist by training, and I work in community implementation.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Rubin.

DR. ERIC RUBIN: (Audio skip) editor in chief (audio skip).

MR. MICHAEL KAWCZYNSKI: Start again, Dr. Rubin.

DR. PRABHAKARA ATREYA: We can't hear you, Dr. Rubin.

MR. MICHAEL KAWCZYNSKI: You were muted.

DR. ERIC RUBIN: Oh, wow, okay. I'm Eric Rubin, again. I'm a microbiologist at the Harvard T.H. Chan School of Public Health, an infectious disease physician at the Brigham and Women's Hospital, and editor in chief with *The New England Journal of Medicine.*

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. James Hildreth.

DR. JAMES HILDRETH: Good morning. I'm James Hildreth, the president and CEO of Meharry Medical College and professor of medicine. And I'm a viral immunologist by training, thank you. Good morning.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Hawkins.

DR. RANDY HAWKINS: Hi, good morning, everyone, Dr. Randy Hawkins, physician in private practice internal and pulmonary medicine, Charles Drew University. I'm a temporary consumer representative.

DR. PRABHAKARA ATREYA: Thank you, Dr. Hawkins. Next, Dr. Jeannette Lee.

DR. JEANNETTE LEE: Yes, good morning. My name is Jeannette Lee. I'm a professor of biostatistics and a member of the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Lee. Next, Dr. Sawyer.

DR. MARK SAWYER: Good morning, this is Mark Sawyer. I'm a professor of pediatrics and pediatric infectious disease specialist at the University of California, San Diego, and Rady Children's Hospital, San Diego. My area of focus is in vaccine policy.

DR. PRABHAKARA ATREYA: Thank you, Dr. Sawyer. Dr. Melinda Wharton.

DR. MELINDA WHARTON: Good morning, I'm Melinda Wharton. I'm an adult infectious disease physician at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr.

Ofer Levy.

DR. OFER LEVY: Good morning, everyone. My name is Ofer Levy, and I'm a physician scientist and director of the Precision Vaccines Program at Boston Children's Hospital, where we use cutting-edge approaches to optimize vaccine safety and efficacy towards vulnerable populations. And I welcome everybody here today, good morning.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Moore.

DR. PATRICK MOORE: Good morning. I'm Pat Moore. I'm a professor in the department of microbiology and molecular genetics at the University of Pittsburgh Hillman Cancer Center, and my interest is in (audio skip) viruses.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Stanley Perlman.

DR. STANLEY PERLMAN: Good morning. I'm Dr. Stanley Perlman from the University of Iowa Department of Microbiology and Immunology and a pediatric infectious diseases specialist. And I have a long-term

interest in coronaviruses.

DR. PRABHAKARA ATREYA: Thank you. Last, but not least, we are joined by Dr. Paul Offit.

DR. PAUL OFFIT: Yes, good morning. I'm Paul Offit. I am a professor of pediatrics in the division of infectious diseases at Children's Hospital Philadelphia and the Perelman School of Medicine at the University of Pennsylvania. And my area of expertise is vaccines. Thank you.

DR. PRABHAKARA ATREYA: Thank you. We also will be joined by Dr. Michael Nelson soon, and then we'll introduce when he comes in. So, next, I will proceed with the reading of the conflicts of interest statement for the public record.

The Food and Drug Administration, FDA, is convening virtually today, October 15, 2021, the 169th Meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act of 1972. Dr. Arnold Monto is serving as the acting voting chair for today's meeting.

Today, on October 15, 2021, on the topic to the Committee will meet in open session to discuss the emergency use authorization, EUA, of the Janssen Biotech, Incorporation's COVID-19 vaccine for the administration of a booster dose to individuals 18 years of age and older.

The topic is determined to be a particular matter involving specific parties. With the exception of industry representative members, all standing and temporary voting members of the VRBPAC are appointed special government employees, or SGEs, or regular government employees, RGEs, from other agencies and are subjected to federal Conflicts of Interest laws and regulations.

The following information on the status of this Committee's compliance with Federal Ethics and Conflict of Interest laws including, but not limited to, 18 U.S. Code Section 208 is being provided to participants today and to the public. Related to the discussions at the meeting, all members, RGEs and SGEs consultants of this Committee have been screened for

their potential financial conflicts of their own; as well as those imputed to them including those of their spouse or minor children; and, for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements or CRADAs, teaching, speaking engagements, writing, patents, royalties, and their primary employment. These interests may include that are current interests or under negotiation.

FDA has determined that all members of this Advisory Committee, both regular and temporary members, are in compliance with the Federal Ethics and Conflicts of Interest laws.

Under 18 U.S. Code Section 208, Congress has authorized the FDA to grant waivers to special government employees and also to regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's services outweighs the potential

for the conflict of interest created by the financial interest involved or when the interest of the regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda, and all financial interests reported by the Committee members and consultants, there have been one Conflict of Interest waiver issued under 18 U.S. Code 208 in connection with this meeting.

We have been following consulting serving as temporary voting members, Dr. Fuller, Dr. Hawkins, Dr. Hildreth, Dr. Lee, Dr. Levy, Dr. Monto, Dr. Moore, Dr. Perlman, Dr. Rubin, Dr. Nelson, Dr. Sawyer, and Dr. Wharton. Among all these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure.

Dr. Paula Annunziato of Merck will serve as the industry representative for today's meeting.

Industry representatives are not appointed as special government employees and will serve as a non-voting member of the Committee. They act on the behalf of all regulated industry and bring general industry perspective to the Committee deliberations. The industry representative on this Committee is not screened and does not participate in any closed sessions we have and do not have voting privileges.

Dr. Randy Hawkins is serving as the temporary consumer representative for this Committee today. Consumer Representatives are appointed as special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

The guest speaker for today's meeting is Dr. Kirsten Lyke, a professor of medicine at the University of Maryland. Disclosure of conflicts of interest for speakers and guest speakers follows applicable federal laws, regulations, and FDA compliance.

FDA encourages all meeting participants, including open public hearing speakers, to advise the

Committee of any financial relationships that they may have with any affected firms, its products, and if known, its direct competitors. We would like to remind the standing and temporary members that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussions and that their exclusion will be noted for the record.

This concludes my reading of the Conflicts of Interest statement for the public record. At this time, I would like to hand the meeting back to Dr. Monto, our chair for the day. Thank you so much. Dr. Monto, take it away.

DR. ARNOLD MONTO: Thank you very much, Prabha. A few points of information before we go into the beginning of the meeting with Dr. Marks. The first is that, because we have a limited number of speakers who have requested to participate in the open public hearing, we will probably start the question and answer

sessions, in terms of the presentations, the sponsor and the FDA presentations, before lunch rather than after lunch. This is to inform you about something which we did yesterday as well.

And, speaking about yesterday, I just want to remind the Committee this is a two-day meeting, so we may be discussing things today which were also discussed yesterday. This is a continuing meeting. Having said that, I'd like to turn it over to Dr. Marks, who is the head of CBER and will be telling us what our instructions or action are today. He will introduce the topic, Dr. Marks.

INTRODUCTION OF THE TOPIC

DR. PETER MARKS: Thanks very much, Dr. Monto. Greetings to all. I want to thank all the members of the Committee for a very productive discussion yesterday. I also want to thank our staff, the sponsors, and our open public hearing speakers. I also want to recognize and thank those who submitted some

very thoughtful comments and even some data to the public docket. Now I'd like to take a few minutes to briefly review where we came to yesterday and preview our agenda for today.

Yesterday morning, we heard a presentation from our Israeli colleagues on the use of a third dose of the Pfizer BioNTech mRNA vaccine to try to address the Delta wave of COVID-19 that occurred in Israel over this past summer. Our colleagues presented data indicating the potential efficacy and the safety of this intervention, which appeared to reduce the incidence of severe COVID-19 in individuals down to the age of 40 years. Following that, we heard presentations by Moderna and FDA colleagues regarding the use of third doses of the Moderna COVID-19 mRNA vaccine. There was some discussion regarding concerns about the studies size there, but, ultimately, the Committee voted unanimously to recommend authorizing the Moderna COVID-19 mRNA vaccine for a similar population as the Pfizer BioNTech mRNA vaccine.

Following that, there was a discussion of

whether there should be an expansion of the population eligible for third doses of the mRNA vaccines. And, although some members noticed they might be comfortable with moving the age eligibility for mRNA vaccine boosters for the general population down to between 30 and 50 years of age, the consensus of the Committee appeared to be that there was no urgency to do so at this time.

So, for today, we'll continue the discussion of boosters, first with consideration of Janssen's request to authorize a second dose of their human adenoviral 26 vectored COVID-19 vaccine, and that will be a voting topic. And, following that, we'll hear a presentation of the heterologous booster, or "Mix and Match" Study that's being conducted by the National Institute of Allergy and Infectious Diseases. And that will then be open for discussion. We'll very much look forward to the Committee's deliberations, and I want to thank you once again for your engagement and contributions to this process. Thanks very much and I wish you a great meeting.

DR. ARNOLD MONTO: Thanks, Dr. Marks. First, we are going to have some background about the day's activities and to present this, including some added information I think, we are going to be hearing from Dr. Sudhakar, who is from the Division of Vaccines and Related Products Applications from CBER. Please, Dr. Sudhakar.

FDA INTRODUCTION - JANSSEN COVID-19 VACCINE APPLICATION FOR EMERGENCY USE AUTHORIZATION OF A BOOSTER DOSE

DR. SUDHAKAR AGNIHOTHRAM: Thanks, Dr. Monto. Good morning, everyone, and can you hear me okay? And, then, is my camera working well?

MR. MICHAEL KAWCZYNSKI: Yeah, you're good. Take it away, sir.

DR. SUDHAKAR AGNIHOTHRAM: Thanks, Mike. Good morning, everyone, and welcome to the second day of the Advisory Committee meeting discussing the boosters. And, again, I'm Sudhakar Agnihothram, Division of Vaccines and Related Product Applications, OVRR, CBER.

And I'm going to talk to you today about the Janssen COVID-19 application for emergency use authorization of the booster dose.

Here is the outline of my talk, I'll start with the description of the Janssen COVID-19 vaccine and their EUA request for the booster dose. And I'll do an overview of today's agenda following presentation of the voting and discussion questions for the Committee.

Janssen COVID-19 vaccine was authorized for use under emergency use on February 27, 2021. The indication and usage, Janssen COVID-19 vaccine is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Janssen COVID-19 vaccine is administered as a single dose of volume 0.5 mL and each dose of Janssen COVID-19 vaccine contains five times ten to the tenth viral particles for replication-incompetent recombinant adenovirus type 26, which is abbreviated as Ad26 vector expressing the SARS-CoV-2 spike protein from the isolate Wuhan-Hu-1 in a stabilized confirmation.

The amendment for booster dose for the emergency use authorization came in on October 4, 2021. And the proposed use of booster dose of five times ten to the tenth viral particles under the emergency use is as follows: "A booster dose is recommended at six months or later, based on the strength of the immune responses, although a booster dose may be administered as early as two months. The need for a booster dose and/or its timing will depend on the local and epidemiological situation and the needs of individuals/specific populations."

The clinical package in this amendment includes information from Phase 1/2 studies evaluating safety and immunogenicity of a second dose, or a booster dose, of five times ten to the tenth viral particles administered at various intervals starting from two to six months following primary vaccination.

There's also information from Phase 3 studies evaluating safety and efficacy of a single dose of five times ten to the tenth viral particles and a two-dose regimen of five times ten to the tenth of each dose

that is administered two months apart. Data has also been submitted from observational effectiveness studies of Janssen COVID-19 vaccine in the U.S.

Overview of today's agenda. FDA introduction will be followed by a brief question and answer session for five minutes. That'll be then followed by a sponsor presentation from Janssen titled "Efficacy, Safety and Immunogenicity Data for a Booster Dose of Janssen COVID-19 Vaccine." And there will be five speakers from Janssen: Dr. Heaton, Dr. Van Hoof, Dan Barouch from Harvard, Dr. Schneeweiss, and Dr. Macaya Douoguih.

This will be followed by an FDA presentation from Dr. Rachel Zhang and Dr. Timothy Brennan from OVRR CBER, and Dr. Artur Belov from OBE CBER, and Dr. Narayan Nair from Division of Epidemiology, CBER. There will be a question and answer session for ten minutes. There will be a break of ten minutes after that and there will be an open public hearing, and we just heard that because of a low number of public hearing speakers, that additional question and answer

sessions may be preponed prior to the lunch.

And, after that, there will be Committee discussion and voting. This will be followed by a break, and we will have a presentation from NIH on the Mix and Match Booster Study from Dr. Kirsten Lyke, Professor of Medicine University of Maryland. And there will be a Q&A session for ten minutes that is followed by Committee discussion, FDA questions for 45 minutes.

Here is the voting question for the Committee for today's meeting: "Do the available data support the safety and effectiveness of Janssen COVID-19 vaccine for use under EUA as a booster dose in individuals 18 years and older at least two months after a single dose primary vaccination? If yes to this number one, do available data support that an interval of at least six months between a single primary dose and a booster dose may result in a more robust booster response? If no to number one, then do available data support the safety and effectiveness of Janssen COVID-19 vaccine for use under EUA as a booster dose in individuals 18 years and

older at least six months after a single dose primary vaccination?"

There is also a non-voting discussion question that is related to the NIH presentation on the Mix and Match Booster Study. And that discussion question is as follows: "Taking into consideration the limitations of the study design and sample size, please discuss any general observations that can be made regarding the data on heterologous boosters presented by NIH from their Mix and Match Booster Study."

Again, I would like to thank the Advisory Committee members and my supervisors and management for the opportunity to present here. Thank you very much.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, and before we go on to a couple of questions for clarity, I'd like to review with you the two voting questions and the distinction between them because it's very subtle.

MR. MICHAEL KAWCZYNSKI: Did you want me to

pull them on screen for you so you can see them?

DR. ARNOLD MONTO: That would be helpful. Put them on screen. I think we need some clarity about this before we start deliberating.

MR. MICHAEL KAWCZYNSKI: Hold on one second.

DR. PETER MARKS: Dr. Monto, Committee members, the sponsor will be presenting data from studies looking at their vaccine where it was used at a six-month interval to boost individuals and other studies, looking at other intervals including two months or two or three months. And, because of those different intervals, there could be different outcomes of what the Committee feels is most supported.

If the Committee feels that the two-month interval is supported, it could be then you'll also feel that a six-month interval might be supported by those data. On the other hand, if you do not feel that a two-month interval is supported by the data, it's possible that you'll feel that a six-month interval is supported by the data. Alternatively, you might feel neither of that is the case, but the way this question

is worded is so that you could either choose a two month, a six month, or a two month and six month. And the two month and six months would be that it's a two-month interval with this idea that the six month could provide a more robust booster response. Does that make a little bit more sense here?

DR. ARNOLD MONTO: If we like the two months, then we vote yes to the A?

DR. PETER MARKS: Correct. Well, if you like the two months --

DR. ARNOLD MONTO: Because the two months (inaudible).

DR. PETER MARKS: -- if you like the two months (inaudible). I think, just to make it clear, first, we'll vote on the main question at the top. And then we'll have a vote on that, and, based on that, if the vote on that is yes, then we move to question 1A, if the vote on that is no, we move to 1B.

DR. ARNOLD MONTO: Okay, so there are three votes. So there are potentially three votes. Or it's A and B depending on the vote on the major question

that's up there.

DR. PETER MARKS: Correct, there should be two votes. It would be the main question and A, and the main question and B.

DR. ARNOLD MONTO: Okay then, A or B.

DR. PETER MARKS: Right.

DR. ARNOLD MONTO: Do I have that right?

DR. PETER MARKS: Yes, I think I have that right now, yes.

DR. ARNOLD MONTO: That helps. Okay. Thank you very much.

SPONSOR PRESENTATION - EMERGENCY USE AUTHORIZATION (EUA) AMENDMENT FOR A BOOSTER DOSE FOR THE JANSSEN COVID-19 VACCINE (AD26.COV2.S)

DR. ARNOLD MONTO: Okay, we're moving on to the sponsor presentations, which are being led by Dr. Penny Heaton, Global Therapeutic Area Head, Vaccines at Janssen. Dr. Heaton.

DR. PENNY HEATON: Thank you, Dr. Monto, and

good morning, everyone. My name is Penny Heaton and I'm the Global Therapeutics area head for vaccines at Janssen.

We want to thank the Committee today and the FDA for this opportunity to present the data from our recently submitted EUA amendment. And I also want to thank you for your enduring commitment and your hard work throughout the course of this pandemic.

Today, we are seeking authorization for use of Janssen's Ad26 COVID vaccine as a homologous booster in those individuals who were previously vaccinated with the single dose. More than 14 million individuals in the U.S. have received Janssen's vaccine, and, while the efficacy has been stable, it's been consistent, but we think that the data we're going to share today will highlight the opportunity that we have to further increase the efficacy and the protection with the booster dose.

So, before we share the data, I think it's worthwhile to note the differences in the Ad26 vaccine and our development strategy as compared with that of

other COVID vaccines. First, our initial Phase 3 study evaluated the safety and efficacy of a single-dose regimen for pandemic response globally.

Second is the durable efficacy. The single dose had 74 percent efficacy against severe disease and 70 percent efficacy against all symptomatic disease. And that efficacy has persisted for six months with no drop off, as you will see today in our data from the randomized clinical trials and the real-world evidence studies.

Third, is we have a unique immuno-profile as compared to the other vaccines. Antibody titers, they peak later, they're broadly reactive against multiple strains, the variants, that we tested. And they persist; we have data now out to eight to nine months post-vaccination.

Further, our cell-mediated immune responses are strong with robust CD8 and CD4 positive T cell responses that are likewise persistent. These findings, I think, really underscore the opportunity that we have with the Ad26 booster to further increase

protection against COVID.

Now, in total, over 9,000 participants have received a booster dose of Janssen's vaccine in our randomized clinical trials. Shortly after we initiated the single-dose study, we started a second Phase 3 study: the safety and efficacy of two doses of the vaccine, a booster that follows the first dose by two months. And that study showed that a booster is safe and efficacious against COVID. In terms of safety, when compared to the single-dose regimen, the reactogenicity profile of the booster was similar. There was no increase in unsolicited adverse events and no new trends in any AEs of special interest.

The vaccine was also efficacious against symptomatic disease. It was 94 percent; that was up from 70 percent, of course, in the single-dose study. And we have complete protection against severe disease caused by COVID-19 globally.

Now, in a separate study, we looked at a booster that was administered six months after the single dose, and what we saw there is the booster

induced an immune response, a 12-fold rise in titers as compared to the baseline. Further, regardless of the timing when you give the booster response, we see increased antibodies against all the variants that we have tested.

So, given all of these data, we are seeking emergency use authorization for a homologous booster for all individuals in the U.S. who receive the single-dose Janssen vaccine. We want to provide optimal protection against COVID, and we know that a booster dose will do that. It will increase efficacy against severe disease, it will increase efficacy against all symptomatic COVID, and it will increase the breadth of the immune response against variants. The booster may be given at least two months after the initial vaccination, but our data suggest that boosting at six months will induce an even stronger immune response.

So this is what we're going to present to you today. First, we'll share the final analysis of the Phase 3 study of the single dose showing durable protection against COVID-19. We're then going to

present data from the randomized control study showing that a homologous booster with the Janssen vaccine further increases protection against COVID-19. We will show additional immunogenicity data from other studies of boosters that were given at different intervals after the single dose, and then, finally, we will share a safety update.

We'll confirm the favorable benefit/risk profile of the Ad26 vaccine. We're also going to provide you with a short summary of our post-authorization safety experience as well, of course, as showing you the safety data and reactogenicity profile after the boost.

So let me now please pass the microphone to my colleague, Dr. Johan Van Hoof, my predecessor who'll be retiring next year and who has led the development of Janssen's COVID-19 vaccine. Johan?

DR. JOHAN VAN HOOF: Thank you, Dr. Heaton. Good morning, my name is Johan Van Hoof. Since we presented to you in February, we have accumulated additional data from the single-dose (audio skip)

trial. Following emergency use authorization, this study allowed post-COVID participants on placebo. This took place at different timepoints depending on the country resulting in regional differences in duration of the double-blind follow-up period.

The median follow-up was four months, while 23 percent of participants had a follow-up of six months or more in the double-blind period. The incidence of SARS-CoV-2 infection was highly variable in time in between regions.

Also, importantly, new lineages of virus emerged becoming dominant in most of the study countries. In this study, we saw persistent efficacy of 75 percent against severe COVID-19 after a single dose over the duration of the observation period.

The vaccine efficacy plotted over time on this slide shows no evidence of waning protection through at least six months. As the number of time participants decreased over time, the confidence intervals around the point has been widened, indicating a higher level of uncertainty. In addition, protection against severe

disease, also in context of the variants, remains strong.

When we look at vaccine efficacy against symptomatic disease, we see a trend that vaccine efficacy decreases over time. Although there are several common factors for any vaccine that could drive these trends, we believe a reduction in global vaccine efficacy for symptomatic COVID-19 is mostly driven by the emergence of particular variants rather than declining immune responses. Especially three variants with vaccine efficacy below 50 percent: Gamma, Lambda, and Mu became prevalent in regions, or countries, outside of the United States during the period of analysis. Important to note that protection against severe COVID caused by these variants was still strong.

The variant picture inside the U.S. is a bit different. In the United States, there is persistent vaccine efficacy of a single dose against symptomatic disease over time. This data set essentially removes Gamma, Lambda, and Mu as they were not prevalent strains in the U.S. As to the Delta variant, there

were a few cases observed not allowing a conclusion, and therefore, as Delta cases became dominant, the crossover occurred.

I would like to invite Dr. Schneeweiss to share some real-world evidence that includes analysis of the Ad26 vaccines that begins pre-Delta and goes through its peak in the U.S.

DR. SEBASTIAN SCHNEEWEISS: Thank you, Dr. Van Hoof. Good morning. My name is Sebastian Schneeweiss, and I am a Professor of Medicine and Epidemiology at Harvard Medical School and the Science Lead of Aetion.

Today I will share findings from multiple real-world evidence studies with a focus on the Janssen-Aetion cohort study with the single-dose Janssen vaccine in the United States.

Now several published real-world evidence studies independent of Janssen have reported the effectiveness of the Janssen vaccine, including studies reported by the CDC, where the estimate for vaccine effectiveness for COVID-19-related hospitalizations and ER visits range from 60 to 84 percent. While other

studies from multiple geographies, such as South Africa as well as a study from the Dutch Ministry of Health, reported vaccine effectiveness ranging from 67 to 91 percent for hospitalizations. Just this week, a cohort study from the New York Department of Public Health reported estimates for vaccine effectiveness ranging from 81 to 96 percent for hospitalizations across different age groups. A Janssen-Aetion real-world evidence study showed 81 percent vaccine effectiveness or hospitalization.

So the objective of this real-world evidence study was to access the vaccine effectiveness of the Janssen vaccine in the United States in a large cohort of Janssen vaccinated individuals, with a particular focus on the time period when the Delta variant was dominant in the United States. This longitudinal cohort study identified about 422,000 individuals vaccinated with a single dose of the Janssen vaccine and about 1.6 million classified as unvaccinated but otherwise similar individuals and followed them for the occurrence of COVID-19 infections as recorded by

physicians and COVID-19-related hospitalizations.

We used data from HealthVerity covering the entire United States that would de-identify patient-level longitudinal complaints and laboratory data, including commercial insurance, Medicare and Medicaid beneficiaries. To ensure balance between the Janssen vaccinated individuals and the unvaccinated comparator cohort, we matched groups exactly on dates and location, age, sex, and propensity score matched 17 COVID severity-related predictors to further minimize confounding.

The under-recording of vaccination status of those classified as unvaccinated in claims data could lead to an underestimation of our vaccine effectiveness estimates. We, therefore, corrected for 40 percent under-recording of vaccinations in our analysis, which is based on CDC national data and data from the Louisiana State Registry.

Now, on the left-hand side, you see month-over-month vaccine effectiveness for COVID-19 infections as recorded by physicians, as well as COVID-

19-related hospitalizations. The plot shows that the vaccine effectiveness was consistently stable month over month across the entire study period, including in the pre-Delta timeframe as well as the time period when the Delta variant emerged and became dominant in the United States, as is highlighted in the red box for the months of June, July, and August.

The same stability was found in younger and older adults. Note that the uncorrected estimates also show stable response month over month and are about ten percentage points lower.

On the right-hand side, the Kaplan-Meier curves for the time-to-event analysis for COVID-19 infections, along with the Schoenfeld residuals, demonstrate stable vaccine effectiveness during the six months after vaccination. The same was shown for COVID-19-related hospitalizations.

In summary, the results from this real-world evidence study complement the Phase 3 randomized control trial and show that the single dose of the Janssen vaccine is effective against the Delta variant

in clinical practice in the United States and is stable over time during the six months post-vaccination. Given current vaccine effectiveness levels against hospitalization and infection, we all note that there is an opportunity to improve the protection via a booster. Thank you, and I will now hand over to Dr. Barouch.

DR. DAN BAROUCH: Thank you, Dr. Schneeweiss, my name is Dan Barouch. Good morning. I'm a Professor of Medicine at Harvard Medical School and the Director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center.

The durability of immunity is one of the most important characteristics of COVID-19 vaccines to control the pandemic. Data from Janssen has shown excellent durability of antibody responses elicited by the Ad26.COV2.S vaccine in two cohorts. In individuals 18 to 55 years old, shown on the left, and in individuals over 65 years old, shown on the right, neutralizing antibody responses were stable for up to eight months. There was very good stability in the

younger age cohort and approximately a 2-fold decline of antibody titers in the older age cohort. We then studied the durability of humoral and cellular immune responses in greater immunologic detail in a smaller cohort of individuals.

In a study published this morning in *The New England Journal of Medicine*, we compared the kinetics and durability of humoral and cellular immune responses elicited by the two-shot Pfizer, the two-shot Moderna, and the one-shot J&J vaccines in 61 individuals. In these graphs, blue represents BNT162b2, green represents mRNA-1273, and black represents Ad26.COV2.S.

Live virus-neutralizing antibody titers were measured by Ralph Baric's lab at University of North Carolina. And we measured pseudovirus neutralizing antibody titers and RBD-specific binding antibody titers by ELISA. The BNT162b2 and the mRNA-1273 vaccines induced very high peak antibody responses by all three assays. But these titers declined sharply by month six and then declined even further by month eight. In fact, live virus-neutralizing antibody

titers following mRNA vaccination declined by 34- to 44-fold at month eight as compared with peak titers. These findings are similar to data reported by other investigators.

In contrast, the single-shot Ad26.COV2.S vaccine induced initial antibody titers that were substantially lower. However, these responses then remained durable over time with little evidence of decline for over eight months for all three assays.

Neutralizing antibody responses against SARS-CoV-2 variants of concern followed similar trends. Antibody titers to the Delta, Alpha, and Beta variants showed substantial decline over time for the mRNA vaccines, whereas, antibody titers to these variants were generally stable for the Ad26.COV2.S vaccine. And, as you focus on the upper right panel, neutralizing antibody titers against the Delta variant at month eight were comparable for all three vaccines in this study.

Cell-mediated immune responses are also likely important for vaccine protection against severe disease

and for immune memory. By intracellular cytokine staining assays, CD4 and CD8 T cell responses were relatively stable over eight months for all three vaccines. CD8 T cell responses, which are critical for antiviral defense, were higher for the Ad26.COV2.S vaccine than the mRNA vaccines in this cohort.

These data, together with other published data, demonstrate that Ad26.COV2.S induces a distinct and complex immunologic profile with robust durability. Ad26.COV2.S elicits a diversity of immune responses including neutralizing of Fc functional antibodies and CD4 and CD8 T cell responses.

Humoral and cellular immune responses are remarkably durable for at least eight months. Consistent with the observed durability of protective efficacy.

Immune correlates of protection are not yet known for this vaccine, but multiple immune responses, including both antibodies and CD8 T cells, likely contribute to protection with Ad26.COV2.S. The potential importance of CD8 T cells is supported by

several observations including there is robust protection against the Beta variant in South Africa despite minimal neutralizing antibody responses to the Beta variant. And, in studies in nonhuman primates, CD8 depletion partially abrogated protection of natural immunity against SARS-CoV-2 challenge. Thank you. I'll hand it back to Dr. Van Hoof.

DR. JOHAN VAN HOOF: Thank you. Let's now turn to the data from Study 3009 that supported the administration of a booster dose of the single-dose primary regimen of the Janssen vaccine. In this study, we will refer to a second dose of Ad26 as a booster dose in view of the robust immune response to the single-dose regimen in all vaccinees and the anamnestic responses observed in all vaccinees after the second dose similar to what was observed on other intervals studied.

Our Phase 3 Study, 3009, allowed us to evaluate the efficacy of Ad26 when a booster dose was given two months after the single-dose regimen. This large, global, randomized placebo-controlled trial was

conducted in nine different countries across three continents. Once our vaccine was authorized for emergency use, the study allowed unblinding and offered any participants on placebo to receive our vaccine.

Of the more than 31,000 participants who received the single dose, 53 percent received the booster dose before the placebo was completed and thus, are part of the double-blind analysis being presented today. Twenty-five percent of participants evaluated for efficacy were at least 60 years of age.

The median follow-up after the booster does in the double-blind phase was 36 days. Twenty-nine percent of participants had at least two months follow-up after receiving the booster dose.

The availability of 3001 and 3009 Study allows us to compare vaccine efficacy between the single-dose primary regimen and the booster dose administered at two months.

Let's first look at U.S. data. As you can see in Study 3001, vaccine efficacy against symptomatic infection was 70 percent after the single dose. In

3009, vaccine efficacy reached 94 percent after the booster.

Looking at the global data from the study, the vaccine efficacy against symptomatic infection was 53 percent after the single-dose regimen and 75 percent post-booster, thus meeting the primary objectives of the trial. The lower vaccine efficacy of the overall population compared to that observed in the United States can be attributed to the differences in vaccine efficacy for particular variants, Lambda, Gamma, and Mu, that emerged later in the study and became prevalent outside of the U.S. Let's now have a look at those variants.

Vaccine efficacy for the Alpha and Mu variants, which were the most prevalent variant strains across both trials, were substantially higher with the booster than with the single-dose regimen. These data support that the booster dose administered at least two months after the primary single dose increased protection against symptomatic infection across the variants.

In this study, we also observed complete protection against severe infection, hospitalization, and death as of two weeks after the booster. However, due to the limited follow-up time after the booster, the number of cases occurring during the observation period in the double-blind part of the study was irrelevant.

Next, let's look at the immunogenicity data following a booster dose at least two months after the primary regimen, and then we'll review data that suggests that boosting at six months provides an even stronger immunologic response.

The data package on immune responses after boosting includes several independent studies with consistent lines of evidence. Depending on the study, booster doses have been applied at two and three months both in younger and older adults and six months after initial vaccination in younger adults.

It is important to emphasize that humoral immune results from different assays are highly correlated for ELISA versus the live virus

neutralization assay shown on the left, and versus the pseudovirus neutralization assay on the right. Note that not all assays have been completed for all different samples, but these correlations emphasize that these assays, for a very large part, measure different features of the same antibodies. Hence, we are comfortable interpreting trends across the different sets.

The immunogenicity of the homologous booster dose of Janssen vaccine administered two months after the first dose was studied. For the younger cohort on the left, we see a 4.9-fold increase in titers two weeks after the booster compared to 28 days after the primary vaccination and a 3.5-fold boost as compared to the pre-boost levels at the day of boosting.

On the right, we see an even slightly higher increase after the boost in people of 65 and older. In this older cohort, all vaccinees showed an anamnestic response, including the subjects who no longer had the detectable neutralizing antibody levels at the time the booster dose was given. This indicates that the first

dose had installed a robust immune memory.

Although not predefined, the humoral immune responses after the booster dose at two months meet the non-inferiority criteria as described in FDA guidance on the immunological boost requirements. And this was also the case with the Beta variant, for which the highest neutralization resistance has been reported based on pseudovirus neutralization data.

Finally, the immune response after the booster dose was durable in both cohorts with antibody levels at six months still well above the antibody levels in people who had not received a booster.

In Study 1001, a substantial increase in immune response was evident following the booster dose given at six months. Notably, at 7 days and 28 days post-boost, the binding antibodies grows in all participants with a 4.2- and 5.4-fold increase respectively as compared to the immediate pre-boost levels. All participants had antibodies detectable before administration of the booster dose supporting the durability of humoral immunity after a single dose.

And, compared to 28 days following the primary single dose, binding antibody levels were 9- and 12-fold higher at 7 and 28 days respectively, following the booster dose. The booster-induced antibody levels -- it also meets and post hoc analyzes the criteria for non-inferiority as described in FDA's guidance. As already mentioned, it was also, in this case, the case has better strength.

Thus, administration six months after the primary dose in 18 to 55 years old results in substantially higher antibody levels than when given at two or three months. Similar increases were observed in those 65 years and older. In Study 1001, we saw similar increases for several variants.

Let's take a look at the immunogenicity of the booster against variants of concern. Importantly, using an internally developed fit-for-purpose pseudovirus neutralization assay specific to the original strain and four variants, a proportional increase in variant-specific neutralizing antibodies was observed after a booster at six months, including

for the Delta variant, as compared to immediate pre-boost titers.

Overall, other clinical studies demonstrate that a booster dose of Ad26 enhances the immune responses and individual-level protection against COVID-19. The benefit of a booster dose may be higher when given at six months or later. This finding, combined with the durability profile, is reassuring for the many people in the U.S. who received their Janssen vaccine more than two months ago and could benefit from a great immune response at this later time period.

The data also show increased levels of neutralizing antibodies against the variant strains. Importantly, enhanced immune responses with the booster dose are congruent with a higher level of vaccine efficacy observed in Study 3009.

Thank you. I'll turn now the presentation over to Dr. Douoguih.

DR. MACAYA DOUOGUIH: Thank you, Dr. Van Hoof. Good morning. My name is Macaya Douoguih. I'm the Head of Clinical Development and Medical Affairs for

Vaccines at Janssen.

Today I'll be presenting our safety experience with the Ad26 booster dose. First, I'll describe the cumulative exposure we have to date for the booster dose, followed by the reactogenicity profile administered at two- and six-month intervals. And then I'll cover the safety profile of the booster at two months from the same large, randomized, placebo-controlled trial. I'll also review adverse events of interest and special interest, and I'll close with a review of post-authorization safety.

This slide presents the cumulative exposure to a booster dose of Ad26 following a single-dose primary regimen. Our safety database includes 9,222 participants across five clinical studies. Our exposure data for the six-month and three-month intervals between the primary vaccination and booster dose come from safety and immunogenicity Studies 1001 and 2001. We'll also present preliminary information from Study 2008, which remains blinded to dose level, and where approximately 127 participants have received

a booster at the five times ten to the tenth dose level. I'll elaborate more on the design of Study 2008 later in the presentation. The preponderance of data comes from Study 3009, where the second dose was administered two months after the primary vaccination.

Approximately 15,500 participants were randomized to receive two doses of Ad26 or placebo and received at least the first injection. So this is the full analysis set which comprises this primary safety population. Solicited and unsolicited adverse events were collected in a planned subset of approximately 3,000 individuals per group, referred to as the safety subset.

Study 3009 was ongoing when the EUA was issued for the single-dose regimen. The study was unblinded at that point to allow placebo participants to cross over to Ad26 or to receive another vaccine outside of the study. So not all participants received their second injection during the double-blind period. More than 8,000 participants per group received the second injection. The number of participants within the

safety subset that received a second dose was correspondingly smaller.

So, now, I'll review the reactogenicity for the booster dose administered at two months in Study 3009. Since our briefing document includes the data showing local reactogenicity was quite similar between the primary and booster dose, I'm only going to review the systemic reactogenicity here.

On the next slide, systemic reactogenicity for individuals 18 to 59 years old is displayed on the left. And the data for those who are 60 years and older is on the right. So, within each column, the left bar shows the reactogenicity profile for the primary dose and the right bar shows the booster dose. The orange number above each bar is the percentage of Grade 3 events.

The data show that solicited systemic adverse events were less common and generally of lower severity with the booster dose as compared to the primary dose in both younger and older age cohorts. You'll note that the frequency of fever following the booster is

approximately half of what it was after the primary regimen in the younger cohort. The frequency of events was lower among the older cohort and Grade 3 events were low overall. And there were no Grade 3 fevers in the elderly after either the primary dose or booster dose.

Next, I'll cover the six-month reactogenicity profile from Study 1001, which was our first in human study, and preliminary blinded data from Study 2008, which is ongoing. In Study 1001, a subset of participants were boosted at six months following the primary dose. The frequency of solicited systemic adverse events was lower with the six-month booster than the primary dose, and although the numbers are limited, it appears that systemic events were milder in severity for the booster dose than for the primary dose, a trend similar to what we just saw in Study 3009.

Study 2008 is an ongoing randomized double-blind trial of participants originally enrolled in Study 3001, the single-dose pivotal trial, and this

study is evaluating three dose levels of an Ad26 booster at least six months after the primary vaccination.

One hundred twenty-seven participants are estimated to have received the dose level being considered as a booster today. Blinded safety data are available in 83 participants, 32 of whom are 60 years or older. And, while the dose level data remains blinded, we did observe that no systemic Grade 3 reactogenicity events were reported.

Overall, a booster, when given at both two or six months, did not result in any increase in solicited reactogenicity compared to the primary dose, and in some cases showed a trend towards decreased reactogenicity.

Next, I'll present the unsolicited adverse events from the safety subset of 3009. Overall, the frequency of unsolicited AEs was similar between groups and was similar to the frequencies observed in the single-dose Study 3001. The rate of unsolicited adverse events was 15 percent in the Ad26 group,

compared to 10.9 percent in the placebo group after the first dose. This imbalance was driven by vaccine-associated events such as fatigue, injection site reactions, and headache captured outside of the safety subset.

The rate of unsolicited AEs was also similar between the groups after the second dose. The rates were balanced as well in the full analysis set for medically attended adverse events, any SAE, any SAE not due to COVID, and death. The number of deaths was numerically higher in the placebo group, 13 versus 4. Among those participants who died, none in the Ad26 group tested positive for COVID and none were considered related to the vaccine. Six of the 13 deaths in the placebo group were attributable to COVID-19 or COVID-19 pneumonia.

I'll now review the 3009 data on adverse events of interest and adverse events of special interest, or AESI. Following the identification of the safety signal for very rare events of thrombosis with thrombocytopenia syndrome, or TTS, in post-

authorization data, TTS was considered an AESI in our clinical studies. The CDC Tier 1 definition requires thrombosis to be in an unusual location, such as the brain or splenic bed. CDCs Tier 2 is defined as the thrombosis being associated with low platelets, but occurring in a more common place, such as deep vein thrombosis, but then requires a positive anti-platelet factor 4 antibody result to be considered a case.

In Study 3009, one case of thrombosis with thrombocytopenia occurred in each group. One participant in the Ad26 group experienced thrombocytopenia 86 days following vaccination followed by cellulitis and DVT approximately 100 days post-vaccination and also was diagnosed with COVID-19 during the event. The anti-PF4 results were not reported. One participant in the placebo group had deep vein thrombosis on day 27 during a double-blind phase and subsequently a pulmonary embolism two days later in combination with thrombocytopenia. Neither case met CDC criteria for definitive TTS based on available information.

Because we didn't see any confirmed events in the Study 3009, and because these events were extremely rare, we looked into post-marketing data for another viral vector COVID-19 vaccine, the AstraZeneca two-dose regimen administered at an interval of one to three months. (Audio skip) considered a potential for TTS after a second dose. Although the vectors in spike antigen are not entirely the same, the data may provide some insight into potential risk.

The Medicines and Healthcare Products Regulatory Agency conducts post-marketing surveillance of COVID-19 vaccines in the United Kingdom using a system for recording adverse incidents with medicines, which is referred to as the Yellow Card scheme. The number of AstraZeneca COVID-19 vaccines administered as of September 29th was 24.9 million for dose 1 and 24 million for dose 2. The estimated rate of blood clots with concurrent low platelets was 15.1 cases per million following the first or unknown doses, and 1.9 cases per million with the second dose.

Overall, the case fatality rate was 17

percent, 66 deaths occurred after the dose and 6 occurred after the second dose. The MHRAs current interpretation of these data is that there's no indication of an increased risk of these events after a second dose in any age group.

So, moving back to Study 3009, this slide shows the adverse events of interest for Study 3009. The first three listed were selected due to imbalances observed in our single-dose pivotal study, specifically embolic and thrombotic events, convulsions or seizures, and tinnitus. In Study 3009, we saw no imbalances for thrombotic events or seizures, however, although the numbers are small, an imbalance of tinnitus was also observed in this study following the first vaccination.

Guillain-Barre Syndrome and facial paralysis are events of interest for COVID-19 vaccines in general, and, for these, we saw no imbalances in the study. A numerical imbalance between the Ad26 placebo group was observed for arthritis, which is not observed in our single-dose pivotal study of 40,000 participants. In Study 3009, the observed imbalance

was due to events occurring within 28 days of the primary dose. There was no clear pattern of differences on the level of preferred terms between Ad26 and placebo. And a large proportion of the cases were apparent exacerbations of existing conditions. The majority of events were non-serious, and no imbalance in the 28-day period following the booster dose were observed.

Finally, let me provide a summary of our post-authorization safety data. As of August 31st, the total number of Ad26 vaccines administered worldwide was just over 33.5 million. More than 14 million of these were in the U.S., 13.5 million in the European economic area, and 5.6 million in the rest of the world.

Since the EUA, the following events have been added as an important adverse drug reaction to the U.S. fact sheet and product information based on primarily post-authorization safety reports. Thrombosis with thrombocytopenia, Guillain-Barre Syndrome, and Capillary Leak Syndrome. Let me walk you through a

summary of the data that we have on each of these events. Where possible the background rate is included for context.

With more than 33.5 million vaccines administered to date, there have been 193 post-authorization reports of potential TTS worldwide for a rate of 5.7 cases per million doses. Following Janssen's review of the available information of these reported cases of thrombosis with concomitant thrombocytopenia, 73 met the Tier 1 or 2 criteria per the standardized CDC case definition for a reported rate of 2.1 cases per million doses.

The demographics are provided in the table. The mean and median age of individuals with cases was approximately 45 with a range of 18 to 87. Most cases have occurred among women aged 36 to 64. The median time to onset of events were 15 and 12 days from administration respectively. And, of the 73 cases meeting CDC Tier 1 or 2 criteria, 12 reported a fatal outcome.

There have been 252 post-authorization reports

of Guillain-Barre Syndrome for a reported rate of 7.5 cases per million doses. Most of the cases have occurred in males. The average age of individuals was 53 with a range from 22 to 87. Most of the reports have been among those aged 51 to 64 years. The mean time to onset was 36 days, and the median was about half that, 14 days.

There have been seven spontaneous post-authorization reports of Capillary Leak Syndrome, or CLS, two in the U.S., five in Europe, and some of these cases had a prior history of CLS. Four events occurred in females and three in males, and all cases occurred in people between the ages of 50 and 92. The mean time to onset was 1.3 days and the median was one day. The outcome was reported in six of these seven cases, four individuals died, one case was not resolved, and one was resolving.

Venous thromboembolism and immune thrombocytopenia have been added as an important potential risk to our Pharmacovigilance Plan. In addition, there are other events listed here that are

being evaluated by the sponsor as part of our ongoing pharmacovigilance activities. Summaries of the available data for these events are provided in the briefing document.

In summary, safety events that have been linked to our vaccine, while serious, do remain very rare. And the cumulative data continue to support a positive benefit/risk for the Ad26 vaccine, which has also been endorsed by several health authorities and recommending bodies.

In the context of greater vaccine efficacy with the booster dose, the studies showed that the reactogenicity and safety profile of the booster dose at two or six months was similar to the single-dose primary regimen. The incidence and severity of local events was also similar regardless of the timing of the booster and systemic AEs appeared to be of lower and milder severity at six months relative to two months.

Our large, randomized placebo-controlled Study 3009 did not identify any new safety signals for AEs, SAEs, or AEs of special interest with the booster dose.

In contrast, we currently have no data on the safety profile of boosting Ad26 with different COVID-19 vaccines.

Global post-marketing surveillance of the two-dose AstraZeneca COVID-19 vaccine suggests that rare TTS events are less frequent with a second dose than the first. No TTS cases following the booster dose have been observed for Ad26. And, finally, Janssen will revise our ongoing and planned post-approval studies to incorporate follow-up for the booster doses in addition to the primary doses.

Thank you. I'll turn it back to Dr. Van Hoof.

DR. JOHAN VAN HOOF: Thank you. I'll offer a brief conclusion before we take your questions and also, I'll spend a moment discussing heterologous boosting.

It is encouraging to see studies aligned to NAIAD booster study, which adds to the body of knowledge on COVID-19 vaccines, as we work together to fight the pandemic. At the same time, it is difficult to be conclusive about the benefits and risks of a

heterologous boost as important open questions remain on efficacy, durability, and safety of heterologous boosting. Also, this study reports short-term antibodies at present and there are still no reports on the T cell responses. These findings are important, but they're only a piece of the puzzle and they don't give the complete picture.

Janssen's randomized placebo-controlled trial offers data on homologous boost of Ad26 and demonstrates strong evidence of efficacy and safety. The Ad26 vaccine kinetics are distinct and differ from the messenger RNA vaccines. The initial homologous response of the Ad26 vaccine, although lower than after two doses of an mRNA vaccine, assisted and even increased after four weeks.

These immune responses were associated with efficacy and durability for at least eight months. This kinetics is in sharp contrast with the rapid decay of antibodies reports for mRNA vaccines. It is also very likely that cell-mediated immune responses, including CD8 cells and CD4 T cells, are important

contributors to protection.

The homologous Ad26 boost results in greater protection against COVID-19. Evidence from this Study 2009 demonstrated a high point estimate of efficacy of 94 percent post-boost in the United States, which is similar to the peak efficacy reported for the mRNA vaccines. The efficacy of a heterologous boost of an mRNA vaccine has not yet been determined.

More than 9,000 participants have received the homologous booster providing a large safety database, which is currently not available for heterologous boosting of an mRNA vaccine.

For these reasons, when considering a booster dose for the Janssen vaccinated individual, a homologous booster is preferred.

In closing, we have shown how the Janssen COVID-19 vaccine could help U.S. further protect individuals from COVD-19 by optimizing immune responses, increasing protection from symptomatic infection, preparing for any future variants of concern, and potentially helping to reduce

transmission.

Thus, we are proposing the following dosing schedule: a booster dose recommended at six months or later based on the strength of the immune responses, although, the boosters may be administered as early as two months. The need for a booster dose and for its timing will depend on the local immunological situation and the needs of individuals and specific populations.

And, finally, I want to take a moment to say a few special thanks. Certainly to our collaborators at U.S. Departments of Health and Human Services, particularly the FDA, CDC, and National Institute of Allergies and Infectious Diseases, and the team at BARDA. A special thanks also to all trial sites and to the many trial participants. Our work would not have been possible without their involvement. We are happy to take your questions.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Hoof. We

have a few minutes here before the FDA presentation for a couple, or three or four, questions on clarity, to clarify some of the issues that have been brought up. And, then, we'll go straight into the FDA presentation. Dr. Gans.

DR. HAYLEY GANS: Thank you very much. Thank you for those wonderful presentations, and I appreciate the very up-to-date information regarding THE immune responses for the different vaccines that we're considering.

I guess one of my questions for you is, we're getting two messages and I think the data's speaking two different messages, so the very, what is being considered, robust and then (audio skip) immune response is the idea of needing the booster. So I guess my real question is the sense that, because vaccine efficacy has sort of been very stable at around the 70 mark, whatever it is, with a slight decrease in some of the variants, is the idea that we really want to get the vaccine efficacy up in the 90 range?

And, if that is really the goal, then it would

seem that that would be most available by having a series that boost up into that range more quickly than the eight-month (audio skip) at the 70. I'm not seeing the rationale for waiting for boosting if our goal is to make this as efficacious as can be.

DR. ARNOLD MONTO: Dr. Hoof.

DR. JOHAN VAN HOOF: Thank you for the question. It certainly, as we have indicated, we do think it depends really on the local circumstances. Let us come back to the efficacy that we see with the single-dose regimen. Where, indeed, as you indicated, we do have the 75 percent protection that was consistent across all countries. And that indeed gives a high level of reassurance. At the same time, it indicated there was some room to eventually improve it. And I'm talking 75 percent around severe disease.

When we look to the variants that actually had lower protection against symptomatic infection, we still see robust protection against severe disease, but we do see that those point estimates tend to lower. The lowest one is 63 percent there for that particular

variant, always with a wide confidence interval.

Although the fact that we deflect from giving a booster dose is really related to stay ahead of the game, make sure we prepare for if those variants, like Mu and Delta, would move into the U.S., we certainly would have more symptomatic breakthrough infections. And from that perspective, we are really in favor of there's always headroom to improve it, to give that booster dose.

With regard to the timing for the booster, we also have to consider the population level and the individual level. But certainly, when you look to the increased antibody rise that you observe when the vaccine is given six months after the first dose, versus two months, your titers also really are potentially much higher than when you give that two dose.

So, even on individual level, it looks like at least immunologically, the return on investment for your second dose is higher because your post-boost responses are higher, so you will actually, post-boost,

it can be anticipated that you will be better protected. And that is actually somewhat the trade-off where we see that in general population, we would look into giving it all the six months to have optimal benefit immunologically from that booster.

If we see specific situations, like people in an environment where it's an extremely high transmission rate of new variants, healthcare workers, or where people, especially people like elderly with comorbidities, there we might think that it might be beneficial to also give that booster earlier.

One observation that we didn't share is that when you look to the protection against death was 82 percent. When you focus on who were those deaths, then we don't see anyone younger than 60 years in active group being protected, having a breakthrough infection. So it looks like there are perhaps some populations that might benefit more than others, which we would look more at those individuals to be considered for early boosting.

DR. ARNOLD MONTO: Okay, thank you. Only one

more question at this point but keep your questions ready for the later discussion. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah, I agree, with the time constraints, we'll have more time to talk about the specific data this afternoon.

The question I wanted to ask you though is, given the large Phase 3 two-dose regimen, do you intend at some point to actually submit that for approval for a primary vaccination scheme rather than a single-dose primary vaccination followed by some booster at a later time?

DR. JOHAN VAN HOOF: We actually are considering to file with BLA in its current form with the single-dose regimen being supplemented with a booster dose, with the flexibility that we are looking for today. That would be the thinking, but of course, it will also be subject to interactions with FDA what the final outcome is.

DR. MICHAEL KURILLA: All right. Thank you.

FDA PRESENTATION - FDA REVIEW OF EFFECTIVENESS AND SAFETY OF JANSSEN COVID-19 VACCINE (AD26.COV2.S) BOOSTER DOSE EMERGENCY USE AUTHORIZATION AMENDMENT

DR. ARNOLD MONTO: Thank you, and we are going to move on now to the FDA presentation, which is going to be in three parts. Rachel Zhang and Artur Belov and Narayan Nair are going to be talking to us. They're all from different parts of CBER. So I assume, Dr. Zhang, you're starting first.

DR. RACHEL ZHANG: Thank you, Dr. Monto, and good morning, everyone. I'll just make sure I have my screen correctly. All right. Just jumping right into the data.

MR. MICHAEL KAWCZYNSKI: And, Dr. Zhang, you should be able to see. Do you see them in the side now? Where you can see the notes and everything?

DR. RACHEL ZHANG: Oh, yeah, I do now. Thank you for that.

MR. MICHAEL KAWCZYNSKI: Okay.

DR. RACHEL ZHANG: All right. So this is an

outline of what will be presented today. I will first start with a quick overview of the background and the studies to be discussed. Then go over the available efficacy results from the single-dose and two-dose efficacy studies. Next, we will look at the immunogenicity followed by the safety data from studies evaluating an additional dose of the vaccine given at different dosing intervals, before concluding with an overall summary of the data presented.

Okay. All right, and just as a background, the Janssen COVID-19 vaccine is a recombinant, replication-incompetent adenovirus type 26 vectored vaccine, which encodes the SARS-CoV-2 spike protein. The vaccine is administered intramuscularly as a single-dose regimen at the dose of five times ten to the tenth viral particles.

On February 27, 2021, the Janssen COVID-19 vaccine was authorized under EUA for active immunizations to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. On October 4, 2021, Janssen submitted a request to amend their EUA

to include the use of a booster dose at five times ten to the tenth viral particles in individuals 18 years of age and older. Janssens proposed interval is a booster dose is recommended at six months or later based on the strength of the immune responses, although a booster dose may be administered as early as two months.

This slide summarizes the studies with relevant data on an additional dose given at varying intervals. Study 1001 is a Phase 1 study, which evaluated the safety and immunogenicity of two doses of the Janssen COVID-19 vaccine given at two-, three-, or six-month intervals. Studies 1002 and 2001 both evaluated the safety and immunogenicity of two doses of the vaccine given two to three months apart. Finally, Study 3009 was a Phase 3 study to evaluate the efficacy and safety of two doses of the vaccine given two months apart.

For comparative purposes, safety and efficacy data from the final analysis from 3001, the Phase 3 efficacy study, used to support the current emergency use authorization for the single-dose regimen, will

also be presented.

Please note that when we discuss results from these studies, except for immunogenicity assessments of the six-month booster dose interval in Study 1001, data sets for the studies were not submitted in sufficient time for FDA to conduct an independent review to verify the sponsor's analyses.

A graphical depiction of the studies mentioned, and their dosing intervals is shown in this slide. The numbers inside the circles represent the number of months after the first dose when a second or booster dose was administered. As you can see, the only study with currently available immunogenicity data on a booster dose at six months is Study 1001.

Next, we will look at the vaccine efficacy results from the two Phase 3 studies, starting first with Study 3001. COV3001 is an ongoing Phase 3 efficacy study of a single-dose regimen of the Janssen COVID-19 vaccine in participants 18 years of age and older with and without comorbidities. More than 44,000 subjects were randomized one to one to one dose of the

Janssen COVID-19 vaccine or placebo. The co-primary endpoints of the study were vaccine efficacy against protocol-defined moderate and severe critical COVID-19 with onset at least 14 or 28 days after vaccination.

Summarized here are the vaccine efficacy results for both the primary and final analysis. On the left-hand column are the results for the primary analysis with a data cutoff of January 22, 2021, and a median follow-up of two months, which was used to support the initial EUA in February.

On the right-hand column are results from the final analysis of efficacy for the double-blinded phase with the data cutoff of July 9, 2021, and a median follow-up of four months. Please note that for this and for subsequent slides with efficacy FDA has not independently verified the data from the July 9th data cutoff.

For ease of comparison, only the co-primary endpoint of onset of cases starting 14 days after vaccination is shown. The vaccine efficacy point estimate decreased from 66.9 percent based on the

January 22nd cutoff, to 56.3 percent at the July 9th cutoff. This decrease was also seen when assessing vaccine efficacy for each of the two protocol-specified age cohorts. However, it's important to note that the confidence intervals for the primary analysis and the final analysis estimates overlapped.

When looking at the more severe endpoints of efficacy against severe critical COVID-19 -- COVID-19 requiring medical intervention or COVID-19-related deaths -- the vaccine efficacy point estimate appears to be similar between the primary and final analyses.

Analysis of vaccine efficacy stratified by time since vaccination was conducted based on data from the final analysis. Results show a trend in decreasing efficacy against moderate and severe/critical COVID-19 with increasing time since vaccination, as shown in the left-hand column. However, this trend was not observed when only including severe/critical COVID-19 cases, as shown in the right-hand column.

In an exploratory analysis of vaccine efficacy against moderate and severe/critical COVID-19,

including only those cases which occurred in the U.S., vaccine efficacy appears to be similar between the primary and final analysis in contrast to the more notable decrease in vaccine efficacy point estimate observed in the overall study population. Due to differences in availability and approvals or authorizations of COVID-19 vaccines in the country's where this study took place, the progression of un-blinding varied among the study sites.

In the U.S., the last available primary endpoint that contributed to the final efficacy analysis occurred on April 16, 2021. The majority of cases from the U.S. were sequenced to be D614G with some cases due to the Alpha variant between February and April.

Multiple variants of SARS-CoV-2 were circulating during the conduct of this study. These variants differed by country and changed over time. Sequencing data at the time of the final analysis was available from 77 percent of subjects with molecularly confirmed COVID-19 cases. Of the sequenced cases, the

most prevalent variants were Gamma and Zeta.

As shown in the table on the slide, analysis of vaccine efficacy by variants suggest a decrease in efficacy against many of the variants of concern or interest as compared with a reference strain. However, for many variants, the case numbers were small with wide confidence intervals around the efficacy point estimates. Only about two percent of cases sequenced were attributable to the Delta variant. The number of Delta cases accrued in the study was insufficient to enable a precise determination of vaccine efficacy specifically against Delta.

Now I will present the results from Study 3009, which is the Phase 3 efficacy study evaluating a two-dose regimen of the vaccine given two months apart in individuals 18 years of age and older with and without comorbidities.

More than 31,000 participants were randomized one to one to receive two doses of the Janssen COVID-19 vaccine, or two doses of placebo. However, due to the EUA for the single-dose regimen, which occurred in

February, while this study was ongoing, only 54 percent of participants received two doses of the study vaccine or placebo prior to unblinding. This also resulted in a limited duration of follow-up for the double-blind placebo-controlled phase of the study, with a median follow-up of 36 days at the time of the data cutoff for the primary analysis.

The primary efficacy endpoint was vaccine efficacy against protocol defined moderate and severe/critical COVID-19 with onset at least 14 days after dose 2.

Results from the primary analysis are displayed in the table shown. Again, the analysis for the study have not been independently verified by the FDA.

Vaccine efficacy against moderate and severe/critical COVID-19 was estimated to be 75 percent overall across the entire study population, and 94 percent when only including cases which accrued in the U.S. There was a lower efficacy point estimate observed for participants 60 years of age and older,

but the confidence intervals are wide due to the small number of cases. There were very few cases accrued for the more severe disease endpoints and the confidence intervals are wide or unable to be calculated for these endpoints. The short follow-up time for this analysis also limits the interpretation of the results of this study.

Similar to Study 3001, multiple variants of SARS-CoV-2 were circulating during the conduct of Study 3009. Sequencing data was developed over approximately 68 percent of COVID-19 cases at the time of the primary analysis. Of the sequenced cases, the most prevalent variants were Alpha and Mu. And the efficacy analysis by variant was only able to be performed against these two strains. There was an insufficient number of cases from Delta to conclude on vaccine efficacy specifically against Delta.

This slide shows a side-by-side comparison of the key efficacy analysis presented from the two Phase 3 efficacy studies. The blue bars show results from the primary analysis of the two-dose efficacy Study

3009 with a data cutoff in June, and a median follow-up of 36 days.

And the red bars are results from the primary analysis of the single-dose efficacy Study 3001 with a data cutoff in January, and a median follow-up of two months.

Finally, in the green bars are the results from the final analysis of the single-dose study with a data cutoff in July, and a median follow-up of four months. You can see that, for the majority of these analyses, the efficacy point estimate was higher for the two-dose study compared to the primary analysis and final analysis for the one-dose study. However, note that for all these analyses there is substantial overlap in confidence intervals among all three analyses.

Due to the small number of cases accrued, there was much greater uncertainty around the point estimate for the two-dose study compared to those from the one-dose study, which is especially apparent when looking at the analysis for efficacy in participants

over 60 years of age and for the severe/critical only endpoint.

Next, we will look at the data available from the Phase 1 and 2 studies, examining the immune response after an additional dose of the vaccine given two to three months after the primary dose. As we look at data from each of these studies, please note the relatively small sample sizes which contributed to these analyses. For all of these studies with a two- to three-month interval, the immunogenicity data has not been independently verified by the FDA.

In Study 1001, Cohort 1a Group 1, immunogenicity data was available from 25 adults between the ages of 18 and 55 who are administered two doses of the Janssen COVID-19 vaccine two months apart. Immune response was measured by a qualified, wild-type virus neutralization assay against VICTORIA/1/2020 reference strain. The same assay was used for all the groups assessing two- to three-month intervals, which will be presented in a subsequent slide. There was an increase in immune response observed at 28 days post-

dose 2 with a geometric mean increase in titers of 2.9-fold compared to pre-dose 2 titers on day 57. By six-month post-dose 2, there is a suggested decrease in neutralizing antibody titers, but still 1.6-fold higher compared to the levels observed pre-dose 2.

In COV1002, Cohort 2 Group 1, immunogenicity data was available from 50 adults 65 years of age and older who were administered two doses of the vaccine two months apart. There was an increase in immune response observed at 28 days post-dose 2, with a 1.5-fold rise in GMT titers compared to pre-dose 2 titers on day 57.

In COV2001, Group 1, immunogenicity data was available from 38 participants 18 years of age and older who were administered two doses of the vaccine two months apart. There was an increase in immune response observed at 28 days post-dose 2 with a 1.8-fold rise in GMT titers compared to pre-dose 2 titers on day 57.

In COV1001, Cohort 3 Group 1, immunogenicity data was available from 25 adults 65 years of age and

older who received two doses of vaccine three months apart. The initial study protocol specified a dosing interval of two months, however, due to a study pause triggered by an SAE in the Phase 3 study, the actual timing of the dose 2 for participants in this cohort ranged from 86 to 107 days with a median of 87 days. There was an increase in the immune response observed at 28 days post-dose 2, with a 4.3-fold rise in GMT titers compared to pre-dose 2 titers on day 87.

In COV1002, Cohort 1 Group 1, immunogenicity data was available for 51 adults 20 through 55 years of age who received two doses of the vaccine three months apart. The initial study protocol specified a dosing interval of two months, however, due to the study pause as mentioned previously, the actual timing of dose 2 for participants in this cohort ranged from 73 to 88 days with a median of 78 days. There was an increase in immune response observed at 28 days post-dose 2, with a 2.3-fold rise in GMT titers compared to pre-dose 2 tiers on day 78.

In COV2001, Group 9, immunogenicity data was

available from 37 adults 18 years of age and older who received two doses of the vaccine three months apart. There was an increase in immune response observed at 28 days post-dose 2 with a 2.9-fold rise in GMT titers compared to pre-dose 2 titers on day 99.

Next, we will look at the immunogenicity data in participants who received a booster dose at six months after the primary dose. In Study 1001, Cohort 2a Group 2, participants 18 through 55 years of age were enrolled to receive a booster dose of the Janssen COVID-19 vaccine six months after primary vaccination at the same dose level. Immunogenicity data after a booster dose are available from 17 participants.

SARS-CoV-2 neutralizing titers were assessed using a non-validated, non-qualified, pseudovirus neutralization assay against WASHINGTON/1/2020 with D614G mutation. Note that this assay is different from the wild-type DNA used for the other study cohorts which we just looked at.

When looking at the results observed at 28 days post-primary dose, the GMT in this group of

healthy, non-elderly adult subjects was below the limit of detection, which is in contrast to the immunogenicity results observed at the same time point in the other study cohorts, and previously when using the wild-type DNA, indicating that the pseudovirus assay used for this study likely has low sensitivity.

Looking at the right-hand column, an increase in the neutralizing antibody response is observed after a booster dose at six months with a 4.5-fold rise in GMT at 28 days post-booster compared to pre-booster.

Study 1001 did not include pre (inaudible) a post hoc analysis was conducted by Janssen to evaluate the ratio of GMT of neutralizing antibodies against a reference strain at 7 days and 28 days post-booster compared to 28 days post-primary vaccination in this group of participants who received the booster dose at six months.

Although this analysis showed that the GMT ratios are above the conventional, non-inferiority criteria of a lower bound of 95 percent confidence interval greater than 0.67. This analysis only

included a small sample size of 17 participants. Furthermore, interpretation of GMT ratios may be confounded by the low sensitivity of the assay, resulting in titers below the limit of detection post-primary vaccination. No analysis of different zero response rates was provided.

A descriptive analysis on neutralizing antibody response against the Delta variant was conducted for the same 17 participants. For this analysis, a non-qualified, non-validated pseudovirus DNA against the Delta strain was used. Results from this analysis are shaded in green in the table shown next to the analysis at the same time point against a reference strain for comparison.

At 28 days post-booster there was a 3-fold rise in GMT against the Delta variant compared to pre-booster. At all time points evaluated, the GMT against the Delta variant and the fold rises were lower than those observed against the reference strain.

Next, I will turn it over to Dr. Brennan to take you through the safety data.

DR. TIMOTHY BRENNAN: Hi, good morning. My name is Dr. Timothy Brennan. I'm a medical officer in the Office of Vaccines, Research, and Review at the Center for Biologic Evaluation and Research.

I will be discussing the safety data summaries reviewed for this emergency use authorization amendment. First, I will discuss the safety data available after a second dose is administered within a two- to three-month interval.

I want to start off by going over the safety monitoring in Study COV3009, which represents the bulk of the safety data following a second dose of the Janssen COVID-19 vaccine. The primary safety objective of this study was to describe the safety in terms of serious adverse events and medically attended adverse events leaving the study discontinuation for the duration of study. Medically attended adverse events not leading to study discontinuation will be monitored through six months after the last double-blind vaccination.

Out of 15,708 participants who were randomized

and vaccinated in the full analysis set, 8,655 received a second dose of the Janssen COVID-19 vaccine during the double-blind phase. A safety subset was used to evaluate safety and reactogenicity in terms of solicited local and systemic adverse events during seven days after each vaccination and in terms of unsolicited adverse events during 28 days after each vaccination.

Out of 1,559 participants in this safety subset, 1,032 completed a one-month post-dose 2 follow-up. Here you can see a summary of the solicited local and systemic adverse events for both vaccinated and placebo groups, partitioned by age group and occurrence after the first or second dose.

Overall, the frequency of solicited adverse events was similar post-dose 1 versus post-dose 2. There was a trend towards decreasing frequencies of solicited systemic adverse events following dose 1 relative to dose 2. There were small numbers in Grade 3 local solicited adverse events, which were similar in frequency post-dose 1 relative to post-dose 2.

This slide presents a summary of the solicited local adverse events recorded in the safety subset. As you can see in this table, pain represents the majority of reported solicited local adverse events post-dose 1 and post-dose 2. Erythema is the next most common followed by swelling. Rates of pain are similar post-dose 1 relative to post-dose 2 for both the 18 to 59 years of age group as well as the greater than or equal to 60 years of age group. There were small numbers of Grade 3 local adverse events with similar frequencies between age groups and number of doses.

Overall, as has been seen in other studies, there appears to be a trend towards decreased reactogenicity in the greater than or equal to 60 years of age group. There are small numbers of Grade 3 local adverse reactions with similar frequencies between age groups and number of doses.

Overall, as has been seen in other studies, there appears to be a trend towards the increased reactogenicity in the greater than or equal to 60 years of age group.

Here you can see the most commonly reported solicited systemic adverse events in the safety subset. As you can see in the table, fatigue represents the majority of events followed by headache and myalgia. This pattern was similar across age groups and number of doses as well as the grade of severity. As with solicited local adverse events there is a pattern of decreased reactogenicity in the greater than or equal to 60 years of age group relative to the 18 to 59 years of age group. There is also a trend towards decreased reactogenicity post-dose 2 relative to post-dose 1.

This table represents an overview of the unsolicited adverse events reported in the safety subset within 28 days following dose 1 and dose 2 categorized by grade and age cohort. As you can see, there are small numbers of Grade 3 and Grade 4 unsolicited adverse events reported with similar frequency across age groups and between doses.

Overall, the rates of unsolicited adverse events were higher in the vaccinated group versus placebo group post-dose 1 as well as post-dose 2. And,

as we've seen previously with the solicited adverse events, there remained a trend towards decreased frequencies of unsolicited adverse events post-dose 2 relative to post-dose 1.

This table represents the unsolicited adverse events reported in the safety subset within 28 days following dose 1 and dose 2 by system organ class and preferred terms. The events that occurred in at least one percent of vaccine recipients are included. As you can see, the most common unsolicited adverse events post-dose 1 were fatigue at 3.5 percent and headache at 3.5 percent. These rates were similar to those in the placebo group, the fatigue at 3.1 percent and headache at 3.2 percent. This was also the case post-dose 2. The numbers of Grade 3 unsolicited adverse events are small and similar between groups.

MR. MICHAEL KAWCZYNSKI: Dr. Brennan? Yeah, is Dr. Brennan disconnected?

DR. ARNOLD MONTO: We see him, but we don't hear him.

DR. TIMOTHY BRENNAN: Can everyone hear me?

MR. MICHAEL KAWCZYNSKI: There we go, thank you, Dr. Brennan. Go ahead.

DR. TIMOTHY BRENNAN: Okay, thanks. Sorry about that; I don't know what happened. Okay. Here we're looking -- this table summarizes the serious adverse events reported in the blinded and open-label phases of Study COV3009 and were considered related by the investigator. Eight participants reported SAEs considered by the investigator to be related in the vaccinated group compared to three in the placebo group. Additionally, a total of four participants reported SAEs considered related by the investigator after unblinding in the open-label phase. All of which were thrombotic events or potential thrombotic events.

Overall, there were small numbers of serious adverse events reported and no significant imbalances identified between groups that received study vaccine compared with that received placebo. However, it is important to note that the FDA has not had the opportunity to verify safety datasets or review narrative summaries of reported serious adverse events.

Additionally, although no significant imbalances were identified in Janssen's summary of adverse events of special interest between vaccinated and placebo groups, the FDA likewise has not had the opportunity to independently conduct standard MedDRA queries to evaluate for constellations of unsolicited adverse events.

This slide presents some additional safety data in the form of adverse events of special interests from Studies COV1002 and COV2001. One SAE was reported as of the cutoff date of December 28, 2020, in Cohort 1 Group 1 of Study COV1002, which corresponded to a male participant 18 to 59 years of age, who experienced sudden hearing loss in one ear starting 34 days after dose 1. Two thrombotic events were reported in Study COV2001. One participant had thrombophlebitis one day after a single five times ten to the tenth dose of the Janssen COVID-19 vaccine, and one participant had a Grade 3 ischemic stroke eight days after the 1.25 times ten to the tenth dose on month six.

Now we'll focus on safety data we have

available after a second dose is administered with a six-month interval. This slide shows the solicited local and systemic adverse events for Study COV1001, Cohort 2a Group 2, which included 19 participants who received the five times ten to the tenth booster dose of the Janssen COVID-19 vaccine with a six-month interval following a five times ten to the tenth primary dose of the Janssen COVID-19 vaccine.

The tables show the frequencies of solicited local and systemic adverse reactions within seven days of a primary vaccination and within seven days of a booster dose of the Janssen COVID-19 vaccine. The most frequently reported solicited local reaction after a booster dose was injection site pain at 78.9 percent. The overall rate and severity of injection site pain was similar post-booster dose compared to post-primary vaccination. The most frequently reported solicited systemic adverse reactions after a booster dose were headache at 47.4 percent followed by fatigue at 26.3 percent and myalgia at 21.1 percent and nausea at 10.5.

As seen previously, there is a trend towards

lower rates of adverse reactions post-dose 2 relative to post-dose 1 though the small numbers preclude a reliable conclusion.

This table presents an overview of unsolicited adverse events within 28 days after each dose, and it has a data cutoff of July 21, 2021. There were no SAEs or AEs leading to discontinuation of Cohort 2a Group 2.

And, finally, I will summarize the data reviewed in consideration of this emergency use authorization amendment. This slide presents a summary of the Janssen efficacy data analyses considered in the evaluation of an additional dose of the Janssen COVID-19 vaccine.

In Study COV3001, the final placebo-controlled efficacy analyses for a single dose suggest a stable efficacy over time against severe and critical COVID-19. However, there is some evidence of decreasing efficacy over time against moderate cases, which may be due in part to vaccine-resistant strains in study regions outside of the U.S.

From Study COV3009, a placebo-controlled

efficacy analyses for two doses administered two months apart suggests higher efficacy estimates relative to a single-dose study in COV3001. However, any conclusions regarding improved efficacy are limited by small numbers of COVID-19 cases, particularly cases of the Delta variant, as well as wide confidence intervals around the efficacy point estimates, which overlap those from the one-dose study, COV3001. An additional limitation is the median follow-up of 36 days after the second dose.

Finally, this slide presents a summary of the Janssen immunogenicity and safety data analyses considered in the evaluation of an additional dose of the Janssen COVID-19 vaccine. A second dose of the Janssen COVID-19 vaccine administered at two to six months after the first dose elicits geometric mean titer increases in neutralizing antibodies of approximately 1.5- to 4.5-fold above a pre-booster baseline. However, the interpretation of this data is limited by the small sample sizes, including only 17 participants for the six-month interval, as well as the

exploratory non-validated pseudovirus neutralization assay used in the assessment of neutralizing antibody titers.

There were no new safety signals identified following a second dose of the Janssen COVID-19 vaccine. However, the interpretation of this data is also limited by low sample sizes. Particularly for the six-month interval, as well as the limited duration of safety follow-up after the second dose, including Study COV3009, which is the main source of safety data for participants exposed to two doses. Thank you very much.

DR. ARNOLD MONTO: Dr. Belov? You go ahead and review the real-world evidence.

FDA PRESENTATION - REVIEW OF RWE TO ASSESS THE EFFECTIVENESS OF A SINGLE DOSE OF JANSSEN COVID-19 VACCINE (AD26.COV2.S)

DR. ARTUR BELOV: Hi there, can people see and hear me?

MR. MICHAEL KAWCZYNSKI: We can hear you. We don't see you yet. There we go, now we see you. All right, Artur.

DR. ARTUR BELOV: Yeah, sorry, my computer had just crashed, and I was frantically restarting.

MR. MICHAEL KAWCZYNSKI: That's okay. It happens. It's a great example. All right, take it away.

DR. ARTUR BELOV: All right. Great. All right, good morning, everyone. My name is Artur Belov, and I work in the Office of Biostatistics and Epidemiology in the Center for Biologics Evaluations and Research.

Today I'll give a brief overview of the real-world evidence study that assessed the effectiveness of Janssen's COVID-19 vaccine. The purpose of this study was to gather supportive evidence for effectiveness of the Janssen single-dose COVID-19 vaccine and the real world using observational data. Here's the outline of my summary, and we'll start by discussing the data sources and study design.

Janssen used HealthVerity as its real-world data source, which is a collection of around 75 healthcare-related data sets. These data include medical and pharmacy insurance claims, laboratory data from select service providers, as well as hospital transaction records for inpatient and outpatient medical encounters.

Depending on which of these data sources are considered, the expected data lag is between two to six weeks. All data that was generated between March 1st and August 31, 2021, was eligible for inclusion in this study. While HealthVerity is by no means a comprehensive resource for capturing all health-related claims and populations in the United States, it generally shows good agreement with the U.S. Census populations as listed in the table to the right of the slide.

Individuals were included in the study as long as they had no documentation of any COVID-19 vaccine product administered prior to their start date, which would be their vaccination date or at least one medical

claim or record in the prior 12 months from their start date and, also, continual enrollment in the medical insurance in the prior 12 months. In order to calculate vaccine effectiveness, the identified vaccinated individuals are matched to those with a health encounter plus or minus four days of the vaccination date of their matched pair. And follow-ups started 14 days after cohort entry.

This matching was initially performed using exact approaches for age in four-year bins starting from age 18 and older, sex, a combined comorbidity index, and three-digit zip codes. Upon initial exact matching, pairs were refined to only include individuals that were within a specific propensity score caliper distance which was based on a number of other patient characteristics and comorbidities, such as diabetes, hypertension, heart disease, among others.

The endpoints of the study included any observed COVID-19, which was identified by an ICB10 code related to COVID-19 diagnosis or a laboratory-confirmed PCR result and COVID-19 related

hospitalizations assessed as an inpatient stay in the medical claims.

The final analytic cohort was constructed based on the exposure to Janssen's COVID-19 vaccine or no documentation of vaccination and matching to those who are vaccinated. The cohort included just under 397,000 vaccinated individuals which were an exact match to close to four million unvaccinated individuals. Upon the further refinement using propensity score, a final ratio of one vaccinated individual to up to four unvaccinated individuals was achieved. And it was for this cohort that vaccine effectiveness was estimated. Median follow-up time was 129 days.

As I mentioned briefly and the sponsor alluded to before, the HealthVerity claims, and hospital encounter data sets are not comprehensive and will not capture all of the potential exposures to vaccination. This is in large part due to vaccination at places of employment, vaccination clinics across the country, as well as general missingness to exposure to the vaccine.

This will result in an overall under-ascertainment of the total vaccinated population in the analytic cohort described a slide earlier. This is somewhat verified by the fact that CDC reported that just about 57 percent of individuals aged 12 years and older were vaccinated while HealthVerity only showed vaccination for 34 percent of eligible individuals in this collection of data sets, which is roughly about 60 percent of the CDC number.

To explore the effects of vaccination under-ascertainment, the sponsor proposed to perform a sensitivity analysis that would explore various levels of vaccine, vaccinations that may go undocumented in the referent cohort and compare the impact that vaccine effectiveness estimates to unadjusted effectiveness estimates.

For the remainder of the presentation, adjusted vaccine effectiveness numbers will be referring to adjusting for under-ascertainment based on the vaccination numbers seen in CDC versus HealthVerity, 40 percent was used as the primary

correction factor for adjusted vaccine effectiveness estimates.

Here is the overall and cohort subsets for corrected and uncorrected vaccine effectiveness estimates. In general, uncorrected vaccine effectiveness estimates were 10 to 13 percent lower than the corrected estimates for any observed COVID-19 endpoint, and 7 to 13 percent lower than the corrected estimates for COVID-19-related hospitalizations. That's in the national cohort.

Those aged less than 65 showed 7 percent and 14 percent improved vaccine effectiveness for both endpoints compared to those aged 65 or greater. Immunocompromised individuals were estimated to have 16 percent and 19 percent less vaccine effectiveness for documented COVID-19 and COVID-19-related hospitalizations respectively.

To examine the potential effects of waning immunity and the potential impact of variants of concern circulating in the U.S. when estimating vaccine effectiveness, the sponsor performed a month-over-month

analysis of vaccine effectiveness. In general, vaccine effectiveness remained stable over the study period of March to August, with corrected vaccine effectiveness ranging from 75 to 78 percent for any observed COVID-19 and between 78 to 82 percent for hospitalizations related to COVID-19.

Observational studies come with inherent difficulties and limitations. As mentioned throughout the discussion, the unknown vaccination status among the referent cohort remains difficult to fully account for with a sensitivity analysis. Linking the patient claims to state registry vaccination data may be helpful to explore as this would not require assumptions and adjustments to vaccine effectiveness estimates due to vaccination exposure.

Additionally, the sponsor was unable to perform matching for geography with more than three-digit zip codes, which did not fully adjust for factors that are known to vary by more granular, such as five-digit or more zip codes, such as socio-economic status, race, and other factors that are not otherwise

accounted for in this analysis.

Finally, there were only just under 400,000 individuals with a documented Janssen vaccine, which is well under the CDCs recording of just over 15 million in the United States. This leads to general realizability concerns as the available data and/or enrichment strategies via inclusion criteria or other study factors may have selected a cohort that is not a random sample of the Janssen vaccinated individuals in the U.S.

So, in summary, Study 4002 showed similar vaccine effectiveness to what was reported in 3001 using real-world data. Vaccine effectiveness remains stable between March and August 2021, showing supportive evidence for effectiveness during months when Delta variant was the dominant strain in the United States. The real-world effectiveness data provides supportive information but has important limitations. I'll now hand it off to Dr. Narayan.

FDA PRESENTATION - REVIEW OF POST AUTHORIZATION SAFETY DATA FOR JANSSEN COVID-19 VACCINE

DR. NARAYAN NAIR: Can people see and hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can, sir, take it away.

DR. NARAYAN NAIR: Great. Good morning. I'm Dr. Naryan Nair, the Division Director for the Division of Epidemiology in the Office of Biostatics and Epidemiology, and I'll be presenting a review of post-authorization safety data for the Janssen COVID-19 vaccine.

This is an overview of my talk. I'll be discussing the passive surveillance safety data from the Vaccine Adverse Event Reporting System, or VAERS. I'll be discussing existing safety concerns and potential emerging safety concerns. And I'll conclude with a summary of FDA active surveillance.

This slide illustrates the adverse event reporting under EUA. For vaccine recipients, there's voluntary reporting. For vaccine providers, there are

mandatory reporting requirements listed here. And for the vaccine EUA sponsor, there's mandatory reporting requirements as well as a requirement for a monthly periodic safety report.

The passive surveillance data is submitted to VAERS. CDC and FDA coordinate and share data. At FDA, we screen all incoming serious adverse event reports. We conduct literature reviews, data mining, and potential safety signals are further evaluated for possible regulator action.

I wanted to touch upon VAERS, as Vaccine Adverse Event Reporting System. This is our passive surveillance system for vaccines. It's the nation's early warning system for vaccine safety. VAERS accepts all reports regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event.

The strengths of VAERS are that it can rapidly detect potential safety problems. There's potential to detect rare adverse events, it's open-ended for hypothesis generation, it allows for geographic

diversity, and there's the capability to monitor production logs.

The limitations of VAERS are that there may be missing or inaccurate data, reported diagnoses are not verified, there could be under-reporting, there could be reporting bias or stimulated reporting, there's an absence of unvaccinated control group, and inability to assess causation. And it's not likely to detect long latency events.

This slide shows the reports to VAERS after the Janssen COVID-19 vaccine. As of October 7th, there were 14.6 million doses of vaccine administered. There were 12,699 serious non-fatal reports submitted to VAERS, and you can see the breakdown between U.S. and foreign reports here. For deaths, there were 1,367 reports submitted.

I would emphasize, as I said in the previous slide, there is a mandatory reporting requirement for deaths to be submitted to VAERS for vaccine providers and the manufacturer. So this number doesn't represent deaths attributed to the vaccine.

For non-serious reports, there was 48,778, and you can see the breakdown between U.S. and foreign. And the total number of reports submitted to VAERS was 62,844 as of October 7th for the Janssen COVID-19 vaccine.

This slide shows the most commonly reported adverse events to VAERS after the Janssen COVID-19 vaccine, again, the denominator is 14.6 million doses and this data as of October 7th. The most commonly reported adverse event was headache followed by pyrexia, chills, fatigue, pain, nausea, dizziness, pain in the extremity, myalgia, dyspnoea. And you can see the numbers as well as the percentages listed here in the right side of this table. And these terms are not mutually exclusive.

I'm now going to summarize some of the existing safety concerns. Starting with thrombosis with thrombocytopenia syndrome. Post-authorization surveillance in VAERS identified reports of cerebral venous sinus thrombosis, or CVST, with thrombosis with thrombocytopenia syndrome after the Janssen COVID-19

vaccine. On April 13th, use of the vaccine in the U.S. was paused because of concerns about a potential association with the vaccine.

On April 23rd, the fact sheets were updated to include a warning about TTS and the pause was lifted. As of October 5th, there are 47 U.S. cases of TTS that have been confirmed after the Janssen COVID-19 vaccine. An evaluation of this safety issue is ongoing. I provided here at the bottom of this slide a reference that describes some of the cases of CVST that occurred following the Janssen COVID-19 vaccine.

Now I wanted to summarize another existing safety concern, Guillain-Barre Syndrome, or GBS. Post-authorization surveillance of VAERS identified 130 reports of GBS after the Janssen vaccine as of July 24, 2021. The number of observed reports exceeded the number expected across multiple age groups without respect to the Brighton Collaboration criteria. The reporting rate for GBS was higher for Janssen than for the mRNA vaccines and the estimated observed-to-expected ratio was 4.18.

On July 12th, the EUA fact sheets were updated to include new information about GBS. And the bottom of this slide provides a reference to a published article that describes the cases of GBS that occurred after the Janssen vaccine.

I now wanted to discuss the summary of potential emerging safety concerns, starting with myocarditis and pericarditis. Our post-authorization surveillance of VAERS has identified this as a potential emerging safety concern. As of August 27th, there were 93 reports of myocarditis/pericarditis in VAERS following the Janssen COVID-19 vaccine. And these reports have not been adjudicated.

Based on a preliminary review, the number of observed to expected values were elevated for all adults 18 and older, with significant elevations in both sexes and various age strata with different risk windows and different background rates, with the reporting rate ratio of 4.14 with the confidence intervals listed here. There were five death reports, all in people 30 years or older, and three in women.

Evaluation of myocarditis is still ongoing.

Post-authorization surveillance of VAERS have identified a potential emerging safety issue concerning thromboembolic events, or TEE. As described in the fact sheets, section 6.1, Clinical Trials Experience, there was a numerical imbalance with more events in the vaccine than placebo recipients observed for TEE including deep vein thrombosis, pulmonary embolism, and transverse sinus thrombosis with thrombocytopenia.

As of October 4th, there were 2,792 reports of TEE in VAERS following the Janssen COVID-19 vaccine. These reports are non-adjudicated and may include the aforementioned TTS cases. At their meeting that was held September 27th, the European Medicines Agency Pharmacovigilance Risk Assessment Committee, PRAC, concluded that there is a reasonable possibility that rare cases of venous thromboembolism are associated with the Janssen COVID-19 vaccine. An evaluation of TEE is ongoing.

Post-authorization surveillance in VAERS has identified a potential emerging safety concern

regarding ITP, or immune thrombocytopenia. As of October 4th, we have 185 reports of ITP in VAERS following the Janssen COVID-19 vaccine. These cases have not been adjudicated. Our preliminary analysis found the number of observed exceeded the number expected with a reporting rate ratio of 1.37 with the confidence interval shown here.

At their meeting September 27th, the EMA PRAC assessed cases of ITP following the Janssen COVID-19 vaccine and AstraZeneca COVID-19 vaccine and recommended updating the product information for both vaccines to include ITP. Our evaluation of ITP reports is ongoing.

The FDA is currently monitoring the safety of the Janssen vaccine in three large health insurance reimbursement databases. This slide shows the active surveillance in the FDA BEST system with near real-time surveillance of the Janssen COVID-19 vaccine. As the vaccine data accrues in the databases, we test for statistically elevated rates compared to historical rates prior to vaccination on a biweekly or monthly

basis.

On the left-hand side of this table, you can see the adverse event of special interest listed. The next column shows the risk window, which is the interval in days, which the occurrence of AESI will be included in the analysis. And then you can see the number of AESI post-vaccination events, and in parenthesis, the number of Janssen vaccine doses for the three large health insurance reimbursement databases, including the Centers for Medicare Services, CMS; Optum; and Health Core, listed here as HCI. And, again, in parenthesis, is the number of Janssen vaccine doses.

And, as you can see, we did not detect any safety signals for any of these AESIs following the Janssen COVID-19 vaccine. However, the number of doses in events are relatively low and FDA is continuing to monitor the safety of these vaccines.

The applicant submitted a Pharmacovigilance Plan to monitor safety concerns associated with the Janssen vaccine, utilizing active and passive

surveillance. The safety specifications of the Pharmacovigilance Plan are shown here. The important identified risks are anaphylaxis, TTS, and GBS. And the important potential risks are vaccine-associated enhanced disease, venous thromboembolism, and immune thrombocytopenia. The important missing information is listed here.

So, to summarize, FDA and CDC continue to follow cases of GBS and TTS reported to VAERS following the Janssen COVID-19 vaccine. Information regarding these adverse events is currently communicated in the fact sheets. FDA and CDC continue to assess cases of myocarditis, pericarditis, ITP, TEE, that are reported to VAERS following the COVID-19 vaccination.

Preliminary analysis of unadjudicated cases in VAERS reveal an increased observed-to-expected ratio for myocarditis and pericarditis as well as ITP. And with regard to active surveillance, FDA near real-time surveillance of 16 potential outcomes does not reveal any safety signals for these adverse events at this time.

I'm presenting on behalf of a team that's been working tirelessly to monitor the safety of these vaccines. You can see my colleagues at CBER listed here, as well as leadership in OBE. And I wanted to acknowledge them for their contributions to this presentation, as well as our non-federal and our federal partners at CDC Immunization Safety Office. And that concludes my remarks. Thank you.

DR. ARNOLD MONTO: Thank you to the whole team at FDA for this comprehensive report.

We have just a few minutes before the open public hearing for a couple of questions related to, again, the detail that has been presented to us. Dr. Levy, do you have -- is your hand raised for this one or -- okay. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you very much. This is a question, I think, for our sponsor's slides, adverse events, and I thought that there was a label of arthritis with a spike in incidents, but --

DR. ARNOLD MONTO: If it's sponsor, let's go -- let's park that and we'll have another session later

on.

DR. RANDY HAWKINS: Okay. Okay. Thank you.

DR. ARNOLD MONTO: Dr. Marks? You're muted.

DR. PETER MARKS: Hi, Dr. Monto, just a reminder. We need to take a break before the open public hearing, I think, so that they can get the speakers ready. Unless Michael tells us otherwise.

DR. ARNOLD MONTO: Okay, we'll just -- taking that into advice, we will take a break. Let me give you some time for our return. We will resume after the open public hearing, which should give people time to get organized, for the question and answer session at 11:30 Eastern. That's a little more than half an hour from now.

We will have the question and answer session going through 12:15, and the lunch will be 12:15 to 12:45 with the Committee discussion and voting session beginning at 12:45. So the question and answer session, which can include questions for both the sponsor and the FDA, will resume at 11:30 after the open public hearing. And I'll let the technical staff

get ready for the open public hearing and the rest of the session will resume, again, at 11:30.

MR. MICHAEL KAWCZYNSKI: All right, thank you, Arnold. All right, we're going to go to break.

[BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: -- Vaccines and Related Biological Products Advisory Committee meeting. We will now be entering into our Open Public Hearing session. With that being said, I'd like to hand this off to our chair Dr. Arnold Monto. Dr. Monto, are you ready?

DR. ARNOLD MONTO: I am ready. I'd like to welcome everybody to the Open Public Hearing session. Please note that both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing

session of the advisory committee meeting. FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you the Open Public Hearing speaker at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsors' payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Over to Prabha.

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Before I begin calling on the registered speakers, I would like to add the following additional guidance. FDA encourages participation from all public

stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing session during which interested persons may present relevant information or view, and participants during the OPH are not FDA employees or members of the committee. FDA recognizes that the speakers may present a range of viewpoints.

The statements made during this open public hearing session reflect the viewpoint of the individual speakers of the organization are not meant to indicate the Agency's agreement with the statements made. With that guidance, I would like to state we have two registered speakers today with PowerPoint presentations, and I'll first call upon the first speaker Mr. Jared Krupnick. Mr. Krupnick.

MR. JARED KRUPNICK: (Audio skip) project.

MR. MICHAEL KAWCZYNSKI: Jared, can you hear us now?

MR. JARED KRUPNICK: Yes, yes, I can hear you now. (inaudible).

MR. MICHAEL KAWCZYNSKI: All right go ahead.

(inaudible). Yup, we hear you now. Go ahead and take it away.

MR. JARED KRUPNICK: Perfect, thank you. Yes, hi, I have no financial relationships to disclose. Hi, I'm Jared Krupnick. I'm the President of Uniting for Action and Founder of the Vaccine Considerations Project. We help people make informed decisions and take effective actions by providing science-based expert COVID-19 vaccine information.

Thank you very much for this opportunity. We were unable to put our slides together before the FDA submission deadline, so all of our articles and other reference materials used to create this presentation are available live on vaccineconsiderations.com right now.

If you have the ability, I encourage you to follow along on vaccineconsiderations.com right now. I want to begin by introducing one of our student interns doing her practicum with us this fall, Katie MacQueen (phonetic), and then I will be back to wrap up our presentation.

All of the assessments and recommendations that Katie and I will be sharing are our own personal viewpoints and may be different from the neutral stance of the Vaccine Considerations Project. Thank you and take it away Katie.

MS. KATIE MACQUEEN: I have no financial relationships to disclose. Hi, I'm Katie MacQueen. I'm a masters of Public Health candidate at the Colorado School of Public Health. Thank you very much for this opportunity, please turn your attention to Slide 2.

A major concern is the WHO's moratorium and their critique that booster doses would be better served going towards lower-income countries vaccinating their populations. This is especially vital as we have seen that unvaccinated populations have the potential to develop variants.

That is patient supply also further aggravates health inequities and disparities that these communities face. Please pay attention to Slide 3.

We must consider that not only the U.S.

responsibility to the worldwide community but also to our own communities. We continue to have significant portions of our population unvaccinated and at risk. Many experts have pointed out that the way to end the pandemic is to address hesitancy.

These expert opinions support the U.S. focusing our resources on the vaccine-hesitant population. The concerns discussed in the WHO moratorium are mirrored in low-income versus high-income areas in the U.S. with vaccinations in rural areas lagging behind their urban counterparts. Large (inaudible) in rural areas is, in fact, vaccine hesitancy. People in rural areas who already face health disparities require assistance and resources to address the hesitancy of their community members.

To quote Director-General Dr. Ghebreyesus, economically, epidemiologically, and morally, it is in all country's best interests to use the latest available data to make life-saving vaccines available to all. This includes the U.S. as well. Please pay attention to Slide 4.

The data that the CDC has collected on vaccinations reveal that the rate of people (inaudible) their booster vaccinations has already overtaken the rate of people getting their first dose or getting fully vaccinated.

This information is important for us to understand since the COVID-19 death toll took over a year to surpass 2.5 million globally. While with the new variant Delta, a 2.5 million death toll was recorded in under eight months. As mentioned previously, lower-income people are more susceptible to variants. Turn your attention to Slide 5.

Thus, the focus should be on improving vaccinations for people all around the world to protect the young and old as well as the rich and poor.

Thank you very much for this opportunity, over to you, Jared.

MR. JARED KRUPNICK: Thank you, Katie. Slide number 6. I'm quoting the *New York Times* from two days ago. "People who received the Johnson & Johnson coronavirus vaccine may be better off with a booster

shot from Moderna or Pfizer BioNTech according to preliminary data from a federal clinical trial published on Wednesday. That finding, along with a mixed review by the Food and Drug Administration of the case made by the Johnson & Johnson for an authorization of its booster could lead to a heated debate about how and when to offer additional shots to the 15 million Americans who have received the single-dose vaccine."

So, is this topic worthy of thoughtful consideration and discussion? Slide number 7.

So, the deadline to apply to present today was one week ago. And the notice of that deadline was one day before that. And the deadline for slides and written comments was just three days ago. And the public release of most of the data being considered today was two to three days ago. So, my question to the committee is, are any of you troubled by the fact that thousands of your colleagues across the country have been systematically and procedurally excluded from providing their meaningful input?

Not just for this meeting, but for meeting

after meeting for a year now by unnecessarily tight scheduling that consistently has feedback deadlines nearly simultaneous to, if not before data is released. So, trust is not just an external problem out there that needs to be overcome. It's a problem internally within the FDA and frankly within this committee, as long as you're all willing to go along for the ride without speaking out on behalf of your peers that are being excluded from this process, not because of their lack of interest, but by a process designed to provide no opportunity for meaningful public input.

So, quite frankly, if each one of you had the personal and professional integrity that Dr. Gruber and Dr. Krause have demonstrated, you would all refuse to participate in a process that looks more and more like a rubber stamp than a thoughtful scientific consideration.

I encourage each one of you to consider your own reputation amongst your colleagues before you agree to participate in one more meeting that makes a mockery of the idea of peer review. How long do you think your

colleagues' voices can be systematically excluded before they see you as part of the problem?

Please go to vaccineconsiderations.com to dig deeper. Thank you for the opportunity to present today.

DR. PRABHAKARA ATREYA: Thank you, Mr. Krupnick. The next speaker is Dr. Robert Edmonds.

DR. ROBERT EDMONDS: Hello, I do not have any financial conflicts of interest to disclose. So, I will now begin.

Dear Committee, my name is Robert Edmonds, I will now read from my pre-written remarks. Today I will speak about tinnitus in the Johnson & Johnson vaccine. COVID-19 vaccines including Johnson & Johnson's vaccine have saved many lives. Identification, though, of low-frequency adverse events connected to vaccination are important. Not to discourage vaccinations, but to encourage patient education to seek timely care and for provider education to apply the appropriate treatment should these low-frequency events occur.

Peer-reviewed case studies of tinnitus following vaccination potentially suggest a small window of time for treatment of tinnitus after onset utilizing corticosteroids. After this limited window though, minimal treatments exist which are primarily management in nature. On the following slide, I discuss the numerical imbalances observed within Johnson & Johnson's trial data. In February, John- -- (audio skip).

MR. MICHAEL KAWCZYNSKI: Like I said, we just had to momentarily reconnect your audio break, so we're going to restart with Dr. Robert Edmonds. Dr. Robert Edmonds, are you there?

DR. ROBERT EDMONDS: Yes, I am here.

MR. MICHAEL KAWCZYNSKI: All right, take it away.

DR. ROBERT EDMONDS: Okay, so I apologize if this is a slight repeated due to the connection issues. Again, I have no financial conflicts of interest to disclose. Okay, dear Committee, my name is Robert Edmonds, I will now read from my pre-written remarks.

Today I will speak about tinnitus in the Johnson & Johnson vaccine. COVID-19 vaccines, including Johnson & Johnson's vaccine have saved many lives. Identification, though, of low-frequency adverse events connected to vaccination are important.

Not to discourage vaccination, but to encourage patient education to seek timely care and for provider education to apply the appropriate treatment should these low-frequency events occur. Peer-reviewed case studies of tinnitus following vaccination potentially suggest a small window of time for treatment of tinnitus after onset utilizing corticosteroids. After this limited window, though, minimal treatments exist which are primarily management in nature.

On the following slide, I discuss the numerical imbalances observed within Johnson & Johnson's trial data. In February, Johnson & Johnson's preliminary review and subsequent peer-review publication described a numerical imbalance of six tinnitus cases in the vaccine group and zero in the

placebo group. While discussion of the preconditions in the six cases was discussed, follow-up discussion of the distribution of preconditions in the placebo group was not provided.

Without this information, we can only surmise the six versus zero imbalance results in this being a 1 in 64 chance of being a coincidental signal and their, perhaps, preconditions in combination with Johnson & Johnson vaccination could increase a risk for tinnitus. If real, still something that should be communicated for that subset of the population. Today, Johnson & Johnson has provided data that indicates a combined imbalance from all Phase 3 trials of 24 versus 9 for tinnitus.

The chances of a coincidental signal is approximately 1 in 143 for this scenario. That is the confidence in tinnitus as a real signal has increased. The 95 percent confidence lower bound to the signal already above zero, increased away from zero with this update as well. The predicted average rate a 95 percent upper confidence both increased as well. Note

the confidence intervals, nor the confidence estimates have not been provided for these adverse events in any documentation.

Note the confidence in the signal also increases, even more, when you consider the additional case of tinnitus in Phase 1. The resulting chance of a coincidental signal is approximately 1 in 156 when you consider all trial phases of Johnson & Johnson's vaccine development. I urge the committee to recognize tinnitus as being a related low-frequency adverse event to Johnson & Johnson vaccination so that individuals know to seek timely care and that providers know to provide appropriate treatment.

Should the committee not recognize tinnitus, unlike the European Medicines Agency, please conduct follow-up investigations beyond passive monitoring. Investigations of this nature would probably first indicate what tinnitus background to compare to. Like what comparisons should be conducted against what was include and assumed non-bothersome tinnitus background or a smaller more severe extremely bothersome tinnitus

background. Without investigation of this nature, it would be difficult to detect a tens of percent rise in an assumed large background without consideration of severity as suggested in the trial data here.

Additionally, more careful examination of cases may or may not identify an innate unique nature to the cases to include or exclude any potential causes, include identifying unique cases hard to explain without a causal relationship. I would be happy to expand upon these last three points with the committee members after these remarks since I cannot due to time limitations.

In my closing remarks, I would repeat combined trial data here presently indicates a 1 in 156 chance of there being a coincidental signal. If you agree these events are unlikely to be coincidental as the trial data statistics suggest, I urge meaningful patient-provider education to occur. Thank you for your time.

DR. PRABHAKARA ATREYA: Thank you, Dr. Edmonds. This concludes the Open Public Hearing

session for today. I will hand over the meeting to the chair, Dr. Monto. Dr. Monto, please take it away from here. Are we going to have a Q&A session now or are we going to take a lunch?

DR. ARNOLD MONTO: We are going to have a short break until 11:30 when the Q&A will begin. That's what we announced before we went to the Open Public Hearing, so a short break until 11:30.

MR. MICHAEL KAWCZYNSKI: All right, so just an eight-minute break. All right, so no problem, I'll put up our break slide.

BREAK

MR. MICHAEL KAWCZYNSKI: All right, hi, again I'm Mike Kawczynski, and welcome back from that short little break. We're now going to go into our Q&A session. Dr. Monto, it looks like you're ready, take us away.

ADDITIONAL Q&A REGARDING SPONSOR AND FDA PRESENTATIONS

DR. ARNOLD MONTO: Okay, well Dr. Hawkins has been waiting patiently since before the open public hearing to ask a question of the sponsor. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you, Dr. Monto and sponsors. So, this is a question on the adverse events slide. I may have misread it. The error was entitled "arthritis" and the FDA does not mention it, so I'm not sure if there's an error in how it's titled. So were there truly arthritis flares in Study 3009? And, if so tell us about the duration, severity, and whether you (audio skip) affect the quality of life, and, if the survey was done is in fact is truly arthritis, thank you.

MR. MICHAEL KAWCZYNSKI: I want to make sure we have his (inaudible). Go ahead (inaudible).

DR. MACAYA DOUOGUIH: Thank you for the question. Well, so it's difficult to know if these are true arthritis cases in some of these events because the majority of these -- all but four -- were non-

serious, so sometimes you just get the code and there's not a lot of detail. What we did see was in terms of arthritis is the reports of arthritis. There were six in the active groups, six in the placebo. In terms of osteoarthritis, it was also balanced two versus two. We had four SAEs, two were in active and two in placebo.

One was in subacromial clavicular -- the arthritis -- which was deemed to be due to poor injection site technique. And then worsening of osteoarthritis and, again, there were two in the placebo. So, the only real imbalance where we could say it's probably a flare was with respect to gout. So, there were 8 cases Ad26 group and 1 in the placebo. I don't have at hand the duration of those events, but they were reported as flares of existing gout in all but one case.

DR. ARNOLD MONTO: Thank you. Dr. Pergam.

DR. STEVEN PERGAM: This is a question for the FDA speakers about the cases -- the breakthrough cases that occurred after the Janssen/Johnson & Johnson

vaccine. Could they discuss a little bit about the age ranges of these if they have that data? I wasn't clear in their discussion whether that was discussed.

I'm curious about the vaccine efficacy waning specifically in the older adults and was curious if, in that sort of large epidemiologic data, they looked at that they could clarify specifically age range differences. (Inaudible). This is for the FDA specifically.

DR. ARNOLD MONTO: FDA on breakthrough cases' ages.

MR. MICHAEL KAWCZYNSKI: Dr. Van, do you want to try to respond to that? Or is it Dr. Fink? There you go.

DR. DORAN FINK: I'm sorry I think the FDA might need some clarification to understand. Is this question with regard to the real-world evidence study that was presented by Dr. Belov?

DR. STEVEN PERGAM: Yes, Dr. Fink, that's correct. The real-world evidence data would probably be the most relevant.

DR. DORAN FINK: Okay.

DR. ARTUR BELOV: Hi there, the breakthrough cases this was for the real-world evidence following a single dose of the Janssen vaccine. So those were coded with specific IPV-10 (phonetic) codes, the user 7.1 (phonetic) in any position or a positive PCR test that was provided by a laboratory. Was there anything more detailed there? I don't have the exact age ranges of those outcomes as we don't have access to the data and we're not able to look at it independently. So, Janssen might be able to provide additional information for the age ranges.

DR. ARNOLD MONTO: Dr. Van Hoof.

DR. JOHAN VAN HOOF: Yeah, thank you. I would ask Dr. Schneeweiss to comment on this one because we have, indeed, analyzed more in detail some of these by ages and perhaps we can give more insight from that perspective. Dr. Schneeweiss.

DR. SEBASTIAN SCHNEEWEISS: Yeah, happy to comment. We actually stratified our analysis by age group, and we demonstrate the vaccine effectiveness for

those younger than 65 and older than 65. And we see the same stability during the six months after vaccination and the same durability across the time period where Delta was highly prevalent in those younger as well as older adults. Does that answer the question?

DR. STEVEN PERGAM: Yes. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thanks, Dr. Monto. My question actually is for the FDA folks. I've been bothered by this by reading the briefing documents and wanted to get some clarification from them about how the FDA verifies data. What puzzled me was, in the briefing documents and in their presentations today, they spoke repeatedly about data not being verified by the FDA. And the question I had around that is the reason for bringing this before VRBPAC without being able to verify the data. So, if they could address those two questions, please.

DR. ARNOLD MONTO: And, in doing so I think a more general discussion of the complications and the

challenges that the timing provided.

DR. DORAN FINK: Thank you, so I'll try to address that question. The FDA recognized that there was intense public interest and a sense of urgency in providing options for a second dose should the data support those options amongst individuals who had received a single dose Janssen vaccination was made available previously under eWay (phonetic).

An advisory committee meeting was scheduled to discuss the data that are available and Janssen was asked to submit available data to the FDA for review. It was a very large package of information. The datasets were not submitted to FDA until just recently. Specifically, when FDA reviews a sponsor's submission, we review the analyses that the sponsor has conducted themselves. We also do our own independent analyses of the dataset in order to both verify the sponsor's analyses and to conduct our own analyses as well to address questions that come up during the review.

As a consequence of the review time, at specific VRBPAC meetings, we were not able to conduct

an independent verification of the sponsor's analyses or to conduct our own analyses on the data sets. Instead, we noted those limitations (audio skip) briefing document and our presentation.

DR. ARNOLD MONTO: Thank you. Dr. Marks, would you like to continue?

DR. PETER MARKS: Yeah, I'd just like to add -- I think Dr. Fink got most of this -- but just so we understand that, when we have these booster submissions, we would generally be expecting data on an immunogenicity study of a few hundred subjects. And instead, we have studies here which involve thousands of patients which would've taken the review team literally probably months to go through our normal process for.

As it is, they did a rather remarkable job and are to be incredibly commended for going through a tremendous amount of data and making sense of it in a way that is more acceptable.

But it's for you to decide here based on the key issues presented, and I think we're just trying to

be transparent here about what we were able to do in the time that we had. Thank you.

DR. ARCHANA CHATTERJEE: Just a quick point of clarification. If I could ask, Dr. Monto.

DR. ARNOLD MONTO: Go ahead, Dr. Chatterjee. Go ahead.

DR. ARCHANA CHATTERJEE: I'm just trying to understand the process. Was it -- from Dr. Fink's comments -- was this review requested by the FDA of the sponsor to submit these data or did the sponsor do so spontaneously on their own?

DR. PETER MARKS: So, this was a case where there was a discussion with Janssen. Janssen ultimately submitted a request. We did not undertake this on our own. I think there was a thought that there was some solution needed potentially for boosting people with Janssen because some data was provided today in this regard but there are other data out there that also suggest waning efficacy or effectiveness of the vaccine. Particularly in certain populations such as diabetics and other subsets of patients in the trial

who may not have had the best responses to begin with.

DR. ARCHANA CHATTERJEE: Okay, thank you.

DR. ARNOLD MONTO: And, Dr. Marks, does this relate to the whole issue of two months and six months and what's a booster?

DR. PETER MARKS: That is correct. I think we would say -- I mean, this is the issue of whether we're dealing with two doses as part of a primary series versus a booster. I think what we're considering today is the use of a booster. I think we are not on the table today talking about changing a primary series to a two-dose primary series.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla. Excuse me, Dr. Meissner, you're next.

DR. CODY MEISSNER: Thank you, Dr. Monto. Can you hear me?

DR. ARNOLD MONTO: I can.

DR. CODY MEISSNER: Yes, and I also have a question for Dr. Fink and Dr. Marks, and it's really a follow-up to Dr. Chatterjee's question. So, is the only option that we have today a binary decision? Yes

or no? Because, one, looking at the data, some of it sounds promising but also the numbers are pretty small on which to base a recommendation.

And is there an option of saying it's a little early? There are a number of issues that are still outstanding such as the issues that you just discussed. Or, for example, I'm a little confused about the neutralization titers using a pseudovirus assay. I wish somehow we could get a better feeling of really what is a neutralizing. I mean, can the FDA ask for a plaque production assay, for example? I realize that's more dangerous than doing a pseudovirus, but it seems like there are a lot of uncertainties at this point making it hard to vote for or against this.

Do we have any maneuvering room?

DR. ARNOLD MONTO: Well, and I'm going to add another comment and that is there is a public health imperative here because what we're seeing is that this is a group with overall lower efficacy than we have seen with the mRNA vaccines. So there is some urgency here to do something. Does FDA want to comment?

DR. PETER MARKS: Hi, so thanks, Dr. Monto and Dr. Meissner. So, I think, I would suggest we work our way through the process, go through the questions, and, if at the end of the day, the feeling of the committee is that this is not ready, then I think we can have some comments after that would go along the lines of what could be done to make this acceptable in the future.

So, I hear you and I think let's just work through the process, and then, at the end, we can certainly formulate recommendations if it does not make it on the merits right now.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thank you all. Dr. Kurilla, finally.

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah, I have a question for the sponsor, for Janssen. This is not an easy discussion topic as we've seen. The reality is that your vaccine does seem to be holding up actually quite well in terms of durability. So, the immediate need for a booster is not apparent

other than the fact that it's been sort of placed in front of the public that neutralizing titer is the only thing that matters, and the higher it is, the better it is for everything.

But that being said, the two aspects where I think a booster may have some benefit which your vaccines -- the work you've done does seem to indicate something in this direction. And that is because of the international focus -- which actually makes your vaccine look a little worse relative to the U.S. data -- is that you're seeing less efficacy against some of the variants that are considered more in the vein of vaccine escape mutants. However, even there, you're seeing relatively good efficacy holding up in terms of protection against serious disease.

And so, one aspect there is that might actually indicate that disconnect between the lower efficacy against symptomatic disease versus better efficacy against serious disease would suggest the population that might actually indicate some better correlative protection at least of the serious disease

which I think we should be concerned with.

And, for the U.S. at least, what variants may come down the road, the question I would have for boosters is, does that actually enhance the broadening of the overall immune response that might be better informed in terms of protection against variants either what we've seen right now or what may be coming down the road? Any comments?

DR. JOHAN VAN HOOF: Yeah, this is Janssen, Johan. I apologize, my camera isn't working. But so certainly the data that we have suggested by boosting the immune responses you do get (inaudible) of the breadth of protection, and we do see that we have these increasing neutralizing titers against the different variants which would indeed help us to allow us to predict that protection against dose variants would also be better.

Actually, I think we are in a rather unique situation where we have been able to do an efficacy study -- a real efficacy study -- to observe the benefit of the effect of that booster dose and to see

how an increase in immunogenicity turns (inaudible) or no in protection. And there we do see that these point estimates for (audio skip) vary to the variants do rise substantially. So, I think that that observation is in line with what you just have been mentioning.

I also would like to take the opportunity, if that's okay, to comment on the questions that have been raised around the assays and which ones have been neutralized or not because it's not that none of the assay work that was presented was validated.

Several of them have been validated, and I would like to give the floor if the chair allows that. I would like our person in charge of that to give you an overview of how the validations of different assays are such that you have a better view on what are the liabilities of the data that you're looking at.

DR. ARNOLD MONTO: That's okay, if you can keep it relatively brief.

DR. JOHAN VAN HOOF: Dr. Schuitemaker, can you comment?

DR. HANNEKE SCHUITEMAKER: Yes, thank you Dr.

Van Hoof. Indeed, we are using multiple assays to measure the immune responses against our vaccine. The assay ELISA that we are using is fully validated and the wild-type DNA that we are using is qualified. And we have a pseudovirus DNA that, as Dr. Van Hoof mentioned in the presentation, is fit for purpose, but, for this assay, we have expansively tested the optimal conditions. And we have done specificity, sensitivity, and LOD analysis and all other features, and we are moving to additional qualification of the assay. And more importantly, we do also have now access to pseudovirus DNA that is undergoing validation. So that is, of course, for near future.

But the correlation that we see between the assay ELISA and also the what we call fit-for-purpose pseudovirus DNA and the ELISA and the wild-type DNA that bridging should give, I hope, also the Committee some confidence in the value of the pseudovirus DNA data. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Perlman, please.

DR. STANLEY PERLMAN: Yeah, I just had a general question about some of the results. So, there were lots of little trials presented, and I think that's been commented on. But the question I have is it seems like there's almost a disconnect between how good the vaccine is and how the vaccine efficacy is all over the mRNA vaccines. It seems like the numbers -- other than the initial antibodies titers -- it seems like the numbers are at least as good as the other vaccines. So, is there an obvious explanation?

I'm sure people at Janssen have thought about this question. And also I don't know if Dan has run any assays yet, but what do we know anything about T-cell responses after boosting?

DR. JOHAN VAN HOOF: Thank you for that question. We certainly do consider the some (inaudible) immune responses from our platform as an important attribute and we strongly believe that it does contribute to the protection. There are also some recent articles that suggest that the disease or the features of low respiratory (inaudible) severe

infection might be a clinical picture where some suggest immunity to all of that is even more important than of neutralizing antibodies. But I would like to ask Dr. Schuitemaker also to comment on some of the key characteristics that we have now identified of (inaudible) immunities particularly with regards to the CD4 and CD8 and the effect on cells. Hanneke?

DR. HANNEKE SCHUITEMAKER: Yes. Hi. So, specifically to your question on the booster dose we have very limited data because also the cellular responses were very stable, and, in the younger population, the booster did not have inferred increases. But, in the elderly population, we do see that both the CD4 and CD8 compartment response to a second dose after a two-months interval.

And I think the characteristics of the cellular immunity really point to a very strong cellular effect and central memory build so that in addition to remediate effective cell functions that there's also strong memory not only in the cellular effective compartment but also in support of the

humoral immune responses.

DR. ARNOLD MONTO: Thank you, doctor. Would FDA like to give us a comment about the disconnect that Dr. Perlman referred to?

DR. PETER MARKS: So, this is Peter Marks. I think one of the issues here that we have to deal with is that there is more data that is out there than what we're seeing, and I think I might ask our CDC colleague perhaps, Dr. Cohn, to mention this. But there are data that suggest the effectiveness of this vaccine is actually less robust than the company's presentation here. And that is a finding of concern, particularly because that's been seen in minority communities potentially and others.

So, I think there is some concern that -- and I think Dr. Belov's presentation hinted to this -- that the idea of the Janssen vaccine as one dose is it was used as an outreach vaccine. Many of the people who got that may not have been a part of the health maintenance organization or an organized healthcare system, so tracking that may have been challenging.

So, there are some real challenges here, and all of the data do not fully align with this being a vaccine that retains excellent activity over time against all forms of disease or even against severe forms of disease.

And there was an MNWR that was published in this regard so might I ask, Dr. Cohn, do you mind saying a few words?

DR. ARNOLD MONTO: Please, Dr. Cohn. You're muted.

CAPT. AMANDA COHN: Hi. I can talk a little bit about the data that has been published both in the MNWR and some of this data was presented at the September 22nd ACIP meeting. Dr. Ruth Link-Gelles presented this. But, in our hospitalization networks -- so, in our active surveillance that looks at vaccine effectiveness in hospitalized individuals, we demonstrated that the Janssen vaccine was only 68 percent effective against hospitalization, and this was in adults greater than 18 years of age without immunocompromising conditions, which is both lower than what we saw from that real-world effectiveness

presentation.

And it's also substantially lower than the mRNA vaccines' effectiveness against hospitalization even with the waning. Additionally, there was some other data to suggest that real-world effectiveness is hovering more in the 50 to 60 percent, and this is from some data from a different surveillance system.

But I think that the overall perspective is that regardless of whether or not there's been waning or if this was the true effectiveness after a single dose, the effectiveness or protection with a single dose of the J&J vaccine is not equivalent to protection at this time with either two doses of an mRNA vaccine and certainly not in those groups who have now been authorized to receive a booster dose of an mRNA vaccine.

DR. ARNOLD MONTO: Thank you. Dr. Perlman, have we answered some of the questions?

DR. STANLEY PERLMAN: Yeah. The answers have been very good. I've just been curious though since the immune parameters seem to be good. Does Dr. Cohn

or anyone else have any idea why there is this disconnect? Is there anything that people are thinking about?

DR. ARNOLD MONTO: Well Dr. Heaton is going to reply from the company.

DR. PENNY HEATON: Yes, and so thank you and thanks for the question and thanks, Dr. Cohn, for this summary.

I think when you look at the efficacy across the different effectiveness study -- or the effectiveness, I should say, across the different studies, there is a wide range as Dr. Cohn discussed. And there's been several done ranging from 50 percent (audio skip) commented on all the way up to 90 percent. But what we're seeing is whether or not the magnitude of the efficacy, wherever that falls, it is consistent and it is durable.

However, because the magnitude is lower than I think what would be desired, the estimates that have been seen with the RNA vaccines there is headroom to improve the efficacy. If we have seen in our

randomized controlled trials, efficacy against severe disease is 74 percent, efficacy against any disease is 70 percent. There's clearly room to improve that.

Now we have not done a head-to-head study looking at the differences in the efficacy of one versus two doses, but that means we do have a very large placebo-controlled randomized trial looking at the efficacy of two doses.

And the point estimates from that study, so numbers very similar to the RNA, the 94 percent efficacy against symptomatic disease and then the 100 percent efficacy against severe disease. So, I think that actually there isn't a disconnect between all of these pieces of data.

DR. ARNOLD MONTO: Is that with boosters or without boosters?

DR. PENNY HEATON: Yeah, with boosters. The two-dose study showed the 94 percent efficacy against symptomatic disease -- any symptomatic disease -- 100 percent against severe disease with that second dose.

So, the bottom line is, single-dose you get a

lower efficacy, but it is durable, it is aligned with the immune responses, the consistency of the neutralizing antibodies, the consistency of that cell-mediated immune responses.

When you give that second dose, you get higher efficacy, and, based on the limited immunogenicity data we have, again, we see a boost in those neutralizing antibody titers. We see increased CD4 and CD8 responses as well and, again, on to the time points that we have, it's very durable. So, what we're trying to do --

DR. ARNOLD MONTO: Okay, I think we're going to have to move on because we've got a number of hands raised. Dr. Gans, next.

DR. HALEY GANS: No, that's perfect timing because I think I would like to follow up on Dr. Perlman. I think one of the struggles we're all having is of course because this is a new virus and also (audio skip) because respiratory and GI passages (audio skip) are dealt for us to determine in general.

I do think that it is important. There is a

lot of data so very clearly the only efficacy data we have between doses is 3001 versus (audio skip)3009 which is a two month, what we're calling a booster dose, but I think we're all seeing that it gets us in a primary series up to the other two dose regimens.

And there's clear differences between severity of disease it looks like in all (audio skip) so I think that's very important. I'm just wondering why we don't have efficacy data, and it might be a timing thing on the several other cohort studies that were presented where we have immunogenicity data. Even (audio skip) out today 239 so we must actually have some efficacy data along the lines of all the other COV1. I mean, there are several studies that I think would be relevant to the discussion today, and we have not been provided efficacy data except for that one evaluation. And there's six other studies that were presented.

There are parts of, I mean, there are parts of 001, 002, 2001. Three months of 001 --

DR. ARNOLD MONTO: Dr. Van Hoof would like to reply.

DR. HALEY GANS: That would be awesome.

MR. MICHAEL KAWCZYNSKI: Dr. Van Hoof, let me unmute you, but also, Dr. Van Hoof, if you want to fix your camera after you answer this question just log out, and we'll bring you back in and that will fix your camera.

DR. ARNOLD MONTO: But just let us hear your reply, please, Dr. Van Hoof.

DR. JOHAN VAN HOOF: Yeah, thank you for that question. So actually indeed the study numbers that you were mentioning, all are studies who have as an objective to evaluate the safety and the immunogenicity initially and over time. While the studies that are actually focusing on efficacy which are large-scale studies are Study 3001 where we have used the single-dose and Study 3009 where we have boosters after two months.

When we look at the data package, we really look at it holistically because we really do feel that the immunogenicity data should be very supportive and informative of what we observe in the efficacy studies.

And so, they often (audio skip) perspective indeed in line with our findings, and that is why when we reflect on the data package that we present today, when you look through all the pieces of the puzzle, you really clearly see that all makes sense. That we have the PNMU (phonetic) profile after the single-dose injection. That actually correlates with solid or burst and sustained protection against severe infection, but there is room for improvement as Dr. Heaton has said.

However, we see for that single dose that there was lower efficacy against symptomatic infection linked to certain strains was not observed in the U.S. While we do see that when you give a second dose and a second dose being given at two months, three months, or six months, every time we do see that it does induce anamnestic response, so we had to have that single-dose primed and inducive (inaudible) memory. But we have do see that with increasing that interval similar to with the other vaccines, the post-boost results do increase. And that (inaudible) combination of facts of link

immunology with the observations that make us come to the conclusion.

There are limitations to the Study 3009. Limitations are actually there beyond our will. It is led to the uniqueness of the pandemic situation where once emergency use approval was there, we actively could not justify to continue to expose the subjects/participants to placebo. We have to cross them over, and that is why the follow-up period in these double-blind appeared as limited, and, as a result, the number of cases is limited.

What we should not forget is that these subjects do not leave the study. These subjects are still in the study; they are crossed over now. And so it means that, over the weeks to come, we can still and do plan to do analyzers that allows us to evaluate the efficacy of late vaccination versus an early vaccination or in 3009 of a single dose against two doses. This being said, we do feel that -- sorry.

DR. ARNOLD MONTO: Yes, let's move on. I think we've got the basic gist of the question that was

asked. Dr. Rubin.

DR. ERIC RUBIN: So, I'm going to echo a lot of my colleagues, and I think that Dr. Marks's comment does kind of change the tenor of the conversation. But it does seem as if what you're asking for should be a two-month booster. If the vaccine isn't adequate, then it should be boosted in everybody. I can't (audio skip). I'm not sure who doesn't get a second dose.

And then in six-month data, which is very thin, it's only been 17 patients in the immunology study is really asking the question: what about all those people who already got vaccines?

Should we be boosting them this far out, and will that help? But it becomes a very secondary question here. But I will say, and I'd love to hear from the sponsor. I'm not sure why you're asking for an indication that would apply to millions of patients with a dataset that includes 17 patients.

DR. ARNOLD MONTO: Dr. Van Hoof.

MR. MICHAEL KAWCZYNSKI: You're muted, sir. Go ahead and unmute yourself, Dr. Van Hoof.

DR. JOHAN VAN HOOF: So, I would like to address this question in two stages, or actually in three stages. And the first one is linked to that low number of subjects, what could be concerns? Concern could be related to immunogenicity, and the concern could be related to safety and efficacy.

Let's look at the immunogenicity. We have, even if it's only with 17 subjects, with those subjects we actually in a post hoc analysis have demonstrated that these immune responses are so robust that they do meet the non-inferiority criteria both for the ELISA and the functional antibodies.

What's also in your briefing book is that we have another 70 people -- 7-0 people -- who have received the booster dose six months after vaccination, but in that case with a quarter of a dose. That was done to evaluate the robustness of the immune memory that is installed similar to what is done to other vaccines whereby exposure to a low dose of antigen, we want to check that immune memory is solid and responses are induced. It is actually a figure that's in the

briefing book, and there you see that was even a quarter dose, still very solid immune responses, and also those responses do meet non-inferiority criteria.

When you look at that curve, you do see that anamnestic response was equally robust in all the population, and is actually, after the booster, all subjects in young or old in all the cohort had responded. That combined with the increase in antibody titers, we see after two months and after three months, from our perspective, it really addresses the question around if immunologically that booster doing what we expect it to do. We feel that indeed we recognize the limitations.

We do feel that this data are quite compelling, and it is very difficult to anticipate that in the study that is ongoing where we will see this in a few hundred people that the immunogenicity result would change. Next question I would like to say --

DR. ARNOLD MONTO: Okay, we're going to have to move on. We have two more -- we have time for two more questions before we break for lunch. Dr.

Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, my question is for the sponsor with regard to the adverse events, specifically with the tinnitus adverse events that were reported, is how long did those last? And also for the TTS, which was more prominent in women, was there an attempt to determine if these women were at risk for this because of other risk factors such as the use of oral contraceptives?

DR. MACAYA DOUOGUIH: Hi. This is Macaya Douguih, give me one second, trying to find my camera. Yep. So, in terms of the duration, we don't have information on all of them. Some of the cases are still ongoing and some have resolved, so it's difficult to comment on an exact timeframe in terms of the events. But the majority --

DR. ARCHANA CHATTERJEE: But, excuse me, I'm sorry to interrupt you but, when you say they're ongoing, how long is it since these folks were vaccinated?

DR. MACAYA DOUOGUIH: Yeah, we would have to

go back and look at the individual reports. I think the ones that are ongoing are from the more recent, from the 3009 study.

DR. ARCHANA CHATTERJEE: So, are we talking weeks, months? How long are we talking?

DR. MACAYA DOUOGUIH: Well, yeah, so and, of course, the updates on information -- particularly when the cases are non-serious -- are not always forthcoming. So, we don't have specific updates today that we can report.

DR. ARCHANA CHATTERJEE: Okay.

DR. MACAYA DOUOGUIH: And with respect -- oh, sorry, go ahead.

DR. ARCHANA CHATTERJEE: Yeah, go ahead.

DR. MACAYA DOUOGUIH: Oh sorry, it covers TTS, so I'll ask Dr. Maree to comment because, as you know, we have one -- two confirmed cases in our 3001 study of TTS, and that occurred in a male subject. And so the majority of cases are coming from the post-authorization reports. So, Dr. Maree, would you like to comment further?

DR. ARAN MAREE: Thank you, Dr. Douoguih. Aran Maree, Chief Medical Officer of Janssen. So, we have been tracking the TTS cases and have a total case break with CDC tier 1 and tier 2 in the U.S. up to 3.6 per million doses administered which is consistent through time. We do see that we have a slightly higher preponderance of those cases in women, but over time as we've accumulated the data, the age and gender balance has become more balanced, more spread. So, we do see a slightly higher preponderance in women between the ages of 20 and 49, but that's no longer the primary focus for those very rare events.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. You know the discussion, I think, this afternoon is probably going to focus on the two-month versus six-month and the rationale for the difference. One other aspect, while the antibody responses seem to be fairly durable, that seems to be a real distinction with the mRNA vaccines which have a relatively rapid decay rate,

half-life on the order of two months. So, the J&J vaccine does look like it offers better durability in that regard. What I'm curious about is, do you know if the boost studies are two, three, or six months?

Does that -- you probably don't know for the six month -- but does that impact the antibody decay rate? Does it actually improve durability of the antibodies?

DR. JOHAN VAN HOOF: The experience we have is preliminary. We don't have it for the six months, but we have it for the two months. And there we do see there's a slight decay, but that slope is certainly not very steep on the contrary. And so after six months, perhaps we can put up the slide that we had in the presentation.

DR. ARNOLD MONTO: Why don't we skip the slide. We really don't have time (inaudible).

DR. JOHAN VAN HOOF: Okay. Basically, we do see that the titers are pretty well persistent all throughout for the booster. (Inaudible).

DR. MICHAEL KURILLA: Does the booster

actually improve the durability -- does the booster lower the decay rate, reduce the decay rate?

DR. JOHAN VAN HOOF: That's difficult to judge because there was almost no decay between -- after the first dose, but so you just bring it up and it stays (inaudible).

DR. ARNOLD MONTO: It's lower but stable.

DR. JOHAN VAN HOOF: It was low, but unstable; you bring it up it remains stable.

DR. MICHAEL KURILLA: All right, thank you.

DR. ARNOLD MONTO: Final question from Dr. Moore before lunch. I think you're muted.

DR. PATRICK MOORE: Thank you, sorry. My apologies. My question is a follow up to Dr. Meissner's question, and if Dr. Barouch is still online perhaps you could address this very quickly before we go to lunch, and it has to do with immunogenicity and how we're thinking about it and it's quite important for us to be able to think about it this way.

So just to frame the argument for people who are not directly involved with measurements in virology

and immunology is that the pseudovirus assays and artificial virus that we can make that we can safely deal with. For instance, we can do those tests in our laboratory here whereas live virus assay has to be done under VSL3 and, of course, has inherent dangers with it.

It looked like the data comparing the different vaccines and particularly the durability over time for the neutralization titers were qualitatively different between the live virus and the pseudo-virus, particularly from the mRNA vaccines to me.

I'm just wondering if that's true or, am I misinterpreting your slides? It has to do with, do we have to -- is the pseudovirus a good measure for us of what we think the neutralizing titer should be, or do we have to worry that the live virus is better? Finally, is this telling us something about an immune escape, particularly the longer the duration after vaccination?

DR. DAN BAROUCH: Hi, yes, thank you Dr. Moore for that question. In the data that we presented, the

full decline was greater for the live virus neutralization assay compared to the pseudovirus neutralization assay. However, those two assays -- it's actually in our manuscript that's published today. -- I didn't present it today. But those assays are highly correlated similar to the data that Janssen showed that those assays are highly correlated.

There is a little bit of discordance at the lower end of the spectrum, and so I think some of those differences really are the individuals that have very low responses that might score in one assay but not another.

So, there might be a sensitivity difference but overall, those assays are highly correlated, both the research-grade assays in our lab as well as the developed assays and the validated assays in the Janssen lab.

DR. PATRICK MOORE: So just to finish following up (inaudible) --

DR. ARNOLD MONTO: Why don't you take this discussion offline? We're going to have to move to

lunch. We've got a tight schedule.

DR. PATRICK MOORE: Arnold, (inaudible).

DR. ARNOLD MONTO: Go ahead, Dr. Moore, since you want -- get your clarification.

DR. PATRICK MOORE: So in your professional -- your best guess is that the two assays are essentially telling us the same thing?

DR. DAN BAROUCH: Yes, in our paper -- I can send it to you by email. In our paper, we actually have a correlation plot that shows a very strong R-value of the correlation.

DR. PATRICK MOORE: Thank you.

DR. ARNOLD MONTO: Okay, lunch until 12:45 Eastern.

MR. MICHAEL KAWCZYNSKI: 12:45. So, everybody give me a second here. Everybody, stay muted, let me put the time up, and then studio you can put us on clear. So, you said 12:45 Eastern so that would be 25 minutes from now, correct?

[LUNCH BREAK]

COMMITTEE DISCUSSION AND VOTING

MR. MICHAEL KAWCZYNSKI: All right. Welcome back from that lunch. I'm Mike Kawczynski, and we'll get started here with our 169th VRBPAC meeting. We're now going to be entering into the Committee discussion. So, Dr. Monto, if you're there, please turn on your camera. How are you doing, sir?

DR. ARNOLD MONTO: Doing well.

MR. MICHAEL KAWCZYNSKI: All right. You're ready?

DR. ARNOLD MONTO: I didn't have time for the luxurious lunch. I think we need a little more clarification about the FDA conclusions about the submission. We've had a brief presentation and question and answer session. Dr. Marks, would you like to continue to present FDA views?

MR. MICHAEL KAWCZYNSKI: Make sure Dr. Marks is there.

DR. ARNOLD MONTO: And there's the voting

question. Good timing.

MR. MICHAEL KAWCZYNSKI: All right. You're unmuted now, Dr. Marks. And you can turn your camera on when you're ready. There we go take. It away.

DR. ARNOLD MONTO: I mentioned, Dr. Marks, that you were going to give us some more of the FDA views of this submission.

DR. PETER MARKS: Yeah, so I thank everyone. I think it's obvious that the Committee is carefully considering here and trying to do their best here to work through what is a complicated submission. I think one of the things that may be helpful perhaps is trying to put in perspective exactly why there is enough concern with this vaccine that one might need a booster given that there does seem to have been some conflicting push/pull shown.

I provided Kathleen with a slide. I'd like to try to bring that up right now. And I'm going to ask I'm going to beg indulgence from Dr. Rubin because this does come from the *New England Journal* from the past week or so. But just to give people an idea, in the

real world, there is a difference in effectiveness of the one-dose regimen versus the two-dose regimen of the mRNA vaccines that appears present.

Now, this is a study in adults greater than 50 years of age or at least 50 years of age, and it's only one of a number of representative studies that does seem to show that there is a difference in effectiveness including against hospitalization. So let's just leave aside the moderate COVID-19 where we can have a discussion about whether it's important to prevent that some other time later on. But right now in terms of hospitalization, you can see at least here that it's roughly 20, 25 percent difference there in rate for hospitalization. And so that I think is one of the things in that change over time that is leading this question.

I agree with Dr. Rubin that it is perfectly reasonable for the Committee to discuss whether a second dose after two months for those who haven't received a vaccine previously or a second dose whenever possible for those who have received the vaccine more

than two to three months ago is appropriate.

So I hope that provides some clarification of this. In retrospect, probably we should have presented a broader review of the real-world evidence. But I hope that this at least provides kind of a start of where the FDA's thoughts are coming from.

DR. ARNOLD MONTO: Yes, and I just wanted to add to what Dr. Cohn has said because we're one of the sites in the study that she referred to in terms of prevention of hospitalization. You're seeing differences in prevention of hospitalization of the Janssen vaccine compared to the mRNA Vaccine. So that's another real-world bit of information that we really need to consider.

Dr. Levy had a question he wanted to direct to you, Dr. Marks.

DR. OFER LEVY: Good afternoon and thank you, Dr. Marks, for that important clarification.

Before the lunch break, you took us through the reasons that the briefing document did not include FDA review of all the pertinent data, and it really was

framed as a public health urgency and the timeline it takes to review very large data sets, and we certainly understand that.

Just to drill down a little bit more on that. Do you have a rough estimate of how long it would take your team to do the independent analysis of the data? And if so, could it be something that's done between today's vote -- not prejudging the vote -- and any potential ultimate authorization by FDA? I mean, what kind of timeline are we looking at?

DR. PETER MARKS: So thanks for that question, and I'll ask Dr. Fink to also join me perhaps to answer this. But I think part of the issue here is that, for the 30,000 patient study, that is incredibly complex because of one dose versus two dose. Having done some review myself in the past, that could take a team of reviewers a month to get through. Now some of the smaller studies, that is something that could be on the order of weeks. But, Dr. Fink, do you want to make any comments on that?

DR. DORAN FINK: No, I really don't know what

to add to that.

DR. OFER LEVY: Yeah, and the question is not meant to pressure anyone, but I think it's educational to the public. So it's not just the matter, had you had another day or two, you would've had this done. This is really something that takes weeks, and therefore, in the context of the urgency and the kind of real-world data you're showing us here, the decision was made, let's move forward with this Committee meeting.

DR. PETER MARKS: Yes, Dr. Levy, we were expecting -- if one goes back to the type of data submitted, for instance for the submission yesterday, that was a different magnitude of review than having -- reviewing an immunogenicity study on a few hundred patients is still a very large undertaking. But it's not the same order of magnitude as 30,000 patients, especially in one where there's complicated crossover safety events over a period of time, et cetera.

DR. OFER LEVY: Right. I had a safety question. Is it okay, Dr. Monto, to ask the safety

question?

DR. ARNOLD MONTO: Yeah, go ahead.

DR. OFER LEVY: It's okay?

DR. ARNOLD MONTO: You've got the floor. I won't bring you back for a while. Go ahead.

DR. OFER LEVY: Okay, thank you, Dr. Monto. My safety question was, there was a presentation I believe from FDA that indicated that by VAERS certain adverse events may be increased in frequency relative to expected with the J&J vaccine. But, by other measures, there was not a signal. And I'm wondering if the individual who gave that presentation can take us through that distinction a little bit because obviously safety is an important dimension here. Thank you.

DR. PETER MARKS: That was Dr. Nair, I believe.

DR. OFER LEVY: Yep, that's right.

DR. NARAYAN NAIR: Yeah, can people hear me and see me?

DR. ARNOLD MONTO: Yes.

DR. OFER LEVY: Yes.

DR. NARAYAN NAIR: Yeah, so the two sources of data -- the path of surveillance from VAERS, we did find for the adverse events that the potential emerging safety concerns that I mentioned, we did find in our preliminary analysis the number of observed exceeded the number of expected when we used the kind of background rates from the literature. The active surveillance that I showed was the three large healthcare insurance databases. So that's the active surveillance where they look at the -- they do sequential statistical testing and look at the historical background rates.

In that for 16 adverse events of special interest, they did not find a statistical signal. So you know that is sort of -- the limitation each of those, the VAERS has the limitations I mentioned. The active surveillance, the limitation would be that, in the vaccine uptake, the numbers were relatively small, I think, on the order of 400,000 for some of the healthcare databases. So each of those systems have limitations, but that sort of summarizes the findings.

DR. OFER LEVY: And what does FDA conclude looking at the overall picture? Do you make any conclusions?

DR. NARAYAN NAIR: Our analysis is ongoing so we don't have any firm conclusions. For the existing safety concerns TTS and TBF that is in the label for thromboembolic events, there are a number of those events that occurred, and we're continuing to evaluate those. And our plan is -- those cases have not been adjudicated. Our plan is to go through those cases and assess them and then do another analysis to see whether the observed is greater than the expected.

Similarly for ITP in myocarditis and pericarditis, right now in VAERS are a number of cases that we've observed is greater than expected. And we want to do further adjudication of those cases, and then we'll have discussions and discuss our findings with OVRR and then any kind of decision on potential regulatory action will be made by them.

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Offit.

DR. PAUL OFFIT: Yeah, thank you, Dr. Monto. So here's how this strikes me. I'll be curious to hear what others think. In the end of February when we met to discuss J&J's one-dose vaccine, at that time, they had already published data showing that in preclinical studies in nonhuman primates with a second dose given two months later at a two-and-a-half- to 3-fold increase in neutralizing antibodies. They'd also found the same thing in their Phase 1 studies for people.

So I think we're in the midst of doing a two-dose trial, a trial that they would finish a few months later. So I think this frankly was always a two-dose vaccine. I think it's better as a two-dose vaccine. It'll be hard to recommend this as a single-dose vaccine at this point given those two months' data.

The issue for me -- and this is what Dr. Rubin brought up -- that I think is hard is that is regarding giving this at six months after the first dose, you have 17 participants. I mean, with the Pfizer, you had 306. With Moderna, you had about 171. And although I think it's likely to be fine, it's really hard to make

a decision for thousands and tens of thousands of millions of people based on 17 people.

However practically, if you say, okay, we're fine with two months but not beyond that because we don't have data beyond that, most people who have gotten a dose of J&J's vaccine got it more than two months ago. So we're not recommending a booster dose with them, just for those who got it recently which practically is really difficult. So it just seems to be the most logical thing to do at this point would be to say that a second dose is recommended for at least two months later. But again that's just the way I see it. I'll be curious to hear what my colleagues think.

DR. ARNOLD MONTO: I think you've summarized very succinctly, Dr. Offit. Dr. Rubin.

DR. ERIC RUBIN: I'm kind of upset with Dr. Offit for saying exactly what I was going to say.

DR. ARNOLD MONTO: Yeah.

DR. ERIC RUBIN: The only thing I'd add, which is totally consistent with what he said, is that, if they had presented us that two-dose data and the one-

dose and two-dose data together back several months ago, we would have said two doses. It seemed safe. It could likely be more effective despite the large confidence intervals. But that part's actually not that difficult. It's clearly the six-month data that add only a minimal amount to this.

DR. ARNOLD MONTO: Okay. Dr. Hildreth.

DR. JAMES HILDRETH: Thank you, Dr. Monto. When we first reviewed the Janssen vaccine back in February, I expressed the viewpoint that prior to November or December of 2019, the human species was all immunologically naive to this virus. So that any single shot Vaccine was likely to induce a primary response and a second shot would be necessary.

I even suggested that a single shot to those who've recovered from COVID-19 might be a great use for their vaccine. So, as far as I'm concerned, it was always going to be necessary for J&J recipients to get a second shot.

And, as for the voting question, with all due respect to the folks at FDA, it is way too convoluted.

I think we should vote on Question Number 1 and leave 1A and 1B to the ACIP at CDC. That would be my recommendation. Thank you, Dr. Monto.

DR. ARNOLD MONTO: Thank you, Dr. Hildreth. I'll park that question and ask Dr. Marks a little later in the discussion. Let's see. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah, I'm in agreement with many of my colleagues here that this more than likely is a two-dose vaccine and should be done. I think there was likely some degree of interest in the possibility of pursuing a single dose for a lot of obvious downstream reasons in terms of implementation, distribution, needs of administration, those sorts of things. So there's clearly advantages in the single dose. The single-dose data -- hello, can people hear me?

DR. ARNOLD MONTO: Yeah, we're getting some feedback.

DR. MICHAEL KURILLA: Okay.

DR. ARNOLD MONTO: We can hear you.

DR. MICHAEL KURILLA: My camera seems to be

frozen. So I think that, if there had not been the two-month data for EUA in terms of the mRNA vaccines which looked exceedingly so good with the caveat that we've never looked two months post-vaccination before for efficacy data, I think we'd be sitting here really struggling to think, why does this vaccine need to be boosted?

But I think that what they've demonstrated so far in terms of -- I think there's more than adequate safety for a two-month boost. I'm less concerned about a six-month boost having additional problems relative to the two-month boost. And what we've seen so far with their data which suggest some very good activity against variants and good durability even with a single dose, I'm inclined to just consider this a two-dose vaccine and that's how it should probably go forward.

DR. ARNOLD MONTO: Thank you, Dr. Kurilla. Dr. Gans.

DR. HAYLEY GANS: I love when my colleagues say what I was gonna say that we're kind of (audio skip). So I do think along the lines of everyone else

that we had thought about the idea (audio skip) had on the (audio skip) glad and encourage to see that the (audio skip) actually support that. And so my only two point (audio skip) not sure that there's (audio skip) booster all talking about this having been (audio skip) regimen or strategy that we should have had. (Audio skip) I agree that we should only (audio skip) I don't think we should a (audio skip) because it (audio skip)

But the only other piece of it is I'd talk about is the idea of homologous booster versus heterolo- (audio skip) having a different -- offering of a different vaccine especially if some- (audio skip) warnings that now come. (Audio skip) think considering that is an additional discussion point that it is some- (audio skip) thought about in a (audio skip) and I would be in favor of doing (audio skip) expect people who did get this as (audio skip) how we could expect them (audio skip) chose not to (audio skip).

DR. ARNOLD MONTO: Thank you, Dr. Gans. Just to point out what we already know and that is we are going to have a presentation of the Mix and Match

strategy after the voting. There's already been a pre-print of some of the data from that. So it may have direct relevance back to some of the issues that you just brought to us. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I think it's hard to think of a precedent when there are more adverse events that might occur after a six-month interval for the boost rather than two months for the boost. I'm not sure if it's biologically plausible although maybe someone else can help me with that.

So I think, Dr. Monto, your comments about the public health urgency are quite appropriate especially when we think about the number of people who've gotten the single dose and may now be experiencing waning immunity as was demonstrated earlier.

And then the third point is that this vaccine does have an advantage in terms of not requiring ultra-cold storage that the mRNA vaccines -- that refrigeration. So I don't think we certainly wouldn't want to be in a position of discouraging use of J&J by saying it's not as good as the mRNA vaccine. So I

agree with what has been said, and it probably makes the most sense to recommend a booster dose at least two months after the first dose.

DR. ARNOLD MONTO: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, thank you, Dr. Monto. When the voting question was posed and I read it in the briefing documents this morning and this afternoon as well, my initial response to the first question was, no. Based on some of the discussion that we've already had with the very limited number of participants who were in the studies that were presented, that was my initial reaction.

However, having listened to the conversation and seeing the data in its totality as well as placing it in the context of these 15 million people who have been vaccinated with a single dose and whose immunity may be waning, there could be as many as close to five million people who are at risk of hospitalization based on the CDC study. Again, this is still a public health imperative.

And so, taking all of those things into

consideration even though I remain concerned about a very limited number of participants on whom we've seen safety and effectiveness data, I would say that I'm in agreement with most of my colleagues who have suggested that the second-dose booster -- or whatever you want to call it -- is necessary in these individuals for them to boost up that immunity back into the 90 plus percent range.

DR. ARNOLD MONTO: Thank you, Dr. Chatterjee. Dr. Perlman.

DR. STANLEY PERLMAN: I have a question that's related more to what Dr. Gans was saying before because I agree with most of what's been said about the question at hand. But, at the end of all this, if we hear the next presentation and it turns out that the heterologous boosting is more impressive than the homologous boosting and we voted a certain way on this question, is there a way -- at the end, will we be able to make the appropriate caveats so that, if we approve this one and then the heterologous boosting is better that we don't end up saying that the homologous

boosting is approved and the other one's better but we're not going to approve it?

Is there a way to get around that so that the possibilities are more consistent? Maybe Dr. Marks can address that.

DR. ARNOLD MONTO: Yes, Dr. Marks, are you happy to answer that right now?

DR. PETER MARKS: Thanks. So I think we should take this on the merits of this particular case. But your point is very well taken that, as part of the discussion question of the next -- we won't be taking a vote. But I think we would like to hear the Committee's thoughts, and we'll obviously take those into consideration as we think about what we would do further in terms of labeling moving forward.

DR. ARNOLD MONTO: Dr. Marks, is it possible that there might be an EUA down the road not necessarily right away about the whole Mix and Match strategy?

DR. PETER MARKS: I would say it's possible.

DR. ARNOLD MONTO: That's all I wanted to

hear. Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Monto. I'm in agreement with a lot of the comments that colleagues have made.

I think the other piece that we haven't really talked about and maybe this isn't fair because it's a different vaccine, but we do have a similar vaccine and an adenovirus-vectored vaccine with the AstraZeneca vaccine, which has been shown to be better as a second dose. And there is data from England showing that the single dose is not quite as effective as that second dose. So I think we have at least in precedent with a similar platform that is helpful to think about. It's not necessarily obviously the same, but I think we can't discard some of that information.

The other question I had is, for the heterologous, we are not voting on that today. We are just discussing that today, is that correct? I didn't see a voting question specifically around that. So we're only voting on the Johnson & Johnson.

And then just really quickly before you answer

that question, Dr. Monto, is the question I have about the voting question, if we're calling this a booster, I'm sort of wondering is, is that term we want to use for this additional dose that we're giving or is this a second dose of the vaccine? Just as a question for Dr. Marks and the FDA.

DR. ARNOLD MONTO: Dr. Marks, you're up again.

DR. PETER MARKS: So the reason why there's not a voting question on the Mix and Match study is because, there, we did not feel like we were comfortable. We're not presenting that from the FDA perspective because we have not reviewed those data in detail. So we wouldn't want you to vote on something at this point. We thought it would be best for you to discuss that and then move from there afterwards.

As far as the wording here, I think this is -- what you're saying here is the wording here of -- if the sense of the Committee that they would prefer as an addition dose rather than as a booster dose, we can take that under advisement.

DR. ARNOLD MONTO: And, while I've got you,

some people didn't like, if yes and if no. Would there be a problem if we just vote on 1 and not 1A and 1B?

DR. PETER MARKS: I think at this point, I would just find it absolutely acceptable given the Committee's discussion to just vote on 1, and, as I say, I think we can leave others to deal with 1A and 1B as we contemplate further.

DR. ARNOLD MONTO: Thank you. That's very helpful.

DR. PETER MARKS: And I believe they'll take apart this question so that we'll just see one on a voting question.

DR. ARNOLD MONTO: Good. We need a little simplicity today. Dr. Fuller.

DR. OVETA FULLER: Thank you, Dr. Monto. This is very complex, and I just want to say thanks to the FDA for showing us the data that they brought in after lunch.

And I just want to remind us, as I think has been said, we are in a world global pandemic. We, as the Committee, enthusiastically approved or recommended

the J&J back in February because of where it could go and what it could do. Remembering that this pandemic will not be managed until we manage it globally -- and, yes, I know we are only concerned directly with the U.S.A. -- but it is important to remember that there are many people who cannot get vaccines at all, and this one can go places and do things and is highly effective as we approved or recommended in February.

And I think whatever we can do now to enhance its availability as well as its effectiveness in spite of the fact that I'd like to see some more data, I think the bigger cause is greater than my concern for the smaller number as a scientist. So I think, if we put it in the big picture, we've already approved or recommended it. And this is already available to be used. How can we make it better?

So I guess I think I'm agreeing with my colleagues here. And thank you for the discussion and the change in the question.

DR. ARNOLD MONTO: Thank you, Dr. Fuller. Dr. Pergam.

DR. STEVEN PERGAM: Apologies, Arnold. Can you hear me?

DR. ARNOLD MONTO: Oh, okay. Trying to confuse me when I'm already confused. Dr. Sawyer.

DR. MARK SAWYER: Thank you, Dr. Monto. I was gonna join the chorus of people asking for the simplified question, but Dr. Marks has just authorized that.

I think the data is insufficient to say anything about a six-month interval, and I would avoid doing that.

I think overall the benefit clearly outweighs the risk even though we have a paucity of data on some aspects of it.

I will point out this is going to be a complicated communication issue because we have subsets of the population for whom the mRNA vaccine boosters are recommended and here, where there's no qualification other than age, for who should get a second dose dash booster. So that probably falls mostly under the purview of ATIP to communicate

effectively about the difference.

DR. ARNOLD MONTO: Yes, and, Dr. Sawyer, we might have, since we seem to be moving quite expeditiously on this, we might have some time during our subsequent discussion after the voting question to revisit some of these messaging issues, which I agree could be a real problem going forward. Dr. Hildreth.

DR. JAMES HILDRETH: Dr. Monto, my hand was up from prior.

DR. ARNOLD MONTO: Oh, okay.

DR. JAMES HILDRETH: Sorry. Thank you.

DR. ARNOLD MONTO: Dr. Nelson.

DR. MICHAEL NELSON: Good afternoon. I just want to say I very much appreciate the conversation initiated by Dr. Chatterjee earlier this morning and the clarification and the context from Dr. Marks and the FDA team afterwards.

To me, I certainly agree with my colleagues that this does look more like a two-dose vaccine. And I believe that what we are looking at is not data that actually supports a recommended use for all across the

board at this point because we've already acknowledged the fact that the data is a little bit immature and somewhat scant in multiple areas.

For me, it comes down to a risk-benefit equation as to whether to enable those individuals who need or desire the vaccine to have access to it under these circumstances. And, with that in mind, I do believe the data supports the safety and efficacy and the risk-benefit equation does enable use under an EUA. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes. Thank you, Dr. Monto. I just wanted to follow up on Dr. Sawyer's comment with regard to the difference in the recommendation for the various age groups and risk categories for the mRNA-based vaccines versus this one.

I did actually think a fair bit on this after reading the briefing documents and pondering how I might vote on the voting question. I believe that we have, at least with the mRNA-based vaccines, acted based on the data that were presented then, limited as

though data were, and it's the same situation here. The big difference here is that the single dose does not seem to afford as much protection as the mRNA-based vaccines did.

And so this is really, with the second dose, bringing it I think on par with those other vaccines in terms of effectiveness. So I do understand the complexity of messaging and actually implementing these recommendations. That is a very difficult task. But nonetheless, I think again I go back to we work with the data that we are provided, and, in this instance, I think we've been provided the data to support the second dose based on the increased effectiveness.

DR. ARNOLD MONTO: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you very much, Dr. Monto. As I stated earlier, I'm a clinician on the frontline of patient care. I want to improve citizen trust in what we do and our process, and I believe we're doing this now. I appreciate the discussion.

DR. ARNOLD MONTO: Thank you. Dr. Heaton, you're not a Committee member. Do you want to add

something to the discussion now?

DR. PENNY HEATON: Yes. Thank you, Dr. Monto. I just wanted to reiterate a couple of the points and that is that we do have, of course, a large safety database on 9,000 patients who were in the two-dose efficacy study. Then we also have 14 million individuals in the U.S. who have received the single-dose Janssen vaccine longer than two months ago.

We have accumulating immunogenicity data and safety data for longer-interval boosters, longer than two months, at the three months and six months we presented to you today. And we've seen it with other vaccines that, having a booster at a later time point at six months, we can get better responses.

My last concern is really thinking about those who have had a vaccine longer than two months. They got their vaccine six months ago or so, yet they need an opportunity to have the same increased protection as those who are being newly vaccinated. There aren't data on that.

The data you will see from the NIAIV today,

while it's great it adds to the body of evidence, they don't have efficacy data. They don't have CMI data. They didn't draw the neutralizing antibody titers at a timeframe that reflects the kinetics of our vaccine.

So I think giving some flexibility for the vaccine to be administered at two months or greater and up to those longer time points -- three months, six months post-vaccination -- is really important for where these individuals in the U.S. are today and for where the state of the pandemic is today. So thank you, Dr. Monto, for allowing me to state that.

DR. ARNOLD MONTO: Thank you and, Dr. Heaton, we're just voting on this question and we're not going to be considering Mix and Match until afterwards.

DR. PENNY HEATON: Yes.

DR. ARNOLD MONTO: So I don't think that there's really a concern about that, but we can't predict what's going to happen going forward.

Well, this is very unusual that we are done with the discussion early. Usually, we have lots of hands raised when the time closes for the voting

question. So, Kathleen, can we vote now? Are you ready with pods for Question 1, which is the only one we are voting on? And then we will have time for explanation of votes then. And then we can see if our later presenters are ready early.

MS. KATHLEEN HAYES: That sounds great. Yes, so I will just go over the guidelines for voting. So thank you, Dr. Monto.

We have 19 voting members and one non-voting industry representative attending the meeting today. So only these 19 voting members, excluding the industry representative as seen on this slide and also including Dr. Offit and Dr. Nelson, should be voting in today's meeting. So, if you're not an official voting member, please refrain from voting as your vote will not be counted.

In regard to the process, Dr. Monto will read the final question for the record, and afterward, all members and temporary voting members will cast their vote by selecting yes, no, or abstain. You'll have two minutes to cast your vote after the question is read,

and, once the votes have been placed, we will then broadcast the results and read the votes aloud for the record.

Please note that, once you've cast your vote, you may change your vote within the two-minute time frame. However, once the poll has closed, all votes will be considered final. And unless anybody has any questions relating to the voting process, we can have Dr. Monto read the vote for the record.

MR. MICHAEL KAWCZYNSKI: I just want to make sure, Dr. Hildreth, is your hand up for the vote question?

DR. JAMES HILDRETH: Uh, I just wanted to clarify that we're only voting on Question 1, not 1B?

DR. ARNOLD MONTO: That is correct.

DR. JAMES HILDRETH: Thank you.

MR. MICHAEL KAWCZYNSKI: All right, so here is the original, and I did modify. This is now the question that we are voting on, correct?

DR. ARNOLD MONTO: So I will read for the record the question: "Do available data support the

safety and effectiveness of Janssen's COVID-19 vaccine for use under EUA as a booster dose in individuals 18 years of age and older at least two months after a single dose primary vaccination?" Dr. Marks?

DR. PETER MARKS: Yeah, I will say that I will stipulate that we'll take it under advisement that a number of Committee members have said that they would prefer "additional" rather than booster.

DR. ARNOLD MONTO: Right, and we'll have some discussions about boosters if we have the time later anyway.

DR. PRABHAKARA ATREYA: This is Prabha Atreya. Is Dr. Marks saying that this voting question needs to be revised to say --

DR. ARNOLD MONTO: No, not at the moment.

DR. PRABHAKARA ATREYA: Okay. Thank you.

MS. KATHLEEN HAYES: Okay, so, if we can pull up the voting pod for this question. Thank you, Dr. Monto, for reading it aloud.

And, at this time, you should see the options for yes, no, or abstain, so, if you can cast your vote,

please.

Great, it looks like all the votes are in, and I will read them aloud for the record. So Dr. Lee voted yes, Dr. Chatterjee voted yes, Dr. Nelson voted yes, Dr. Rubin voted yes, Dr. Sawyer voted yes, Dr. Hawkins voted yes, Dr. Gans voted yes, Dr. Pergam voted yes, Dr. Offit voted yes, Dr. Meissner voted yes, Dr. Hildreth voted yes, Dr. Cohn voted yes, Dr. Wharton voted yes, Dr. Levy voted yes, Dr. Moore voted yes, Dr. Fuller voted yes, Dr. Monto voted yes, Dr. Perlman voted yes, Dr. Kurilla voted yes.

So we do have 19 out of 19 unanimous yes votes for this question. Thank you. Dr. Monto, back to you.

DR. ARNOLD MONTO: Thank you, and, Dr. Rubin, did you want to explain your vote before we take a break until the next presentation? Anybody who wants to explain their votes can do so now.

DR. ERIC RUBIN: Thanks, Dr. Monto. I just want to kind of reiterate from the discussion before. Getting to what Dr. Heaton just told us and Dr. Pergam said before, I think we expect that getting a dose

later than two months is going to be fine, that there is little evidence. Although there aren't a lot of data, there isn't much to suspect that it's a lie. And, since that will apply to a large number of people, I think that I would say I certainly am supportive of those individuals by getting another dose.

DR. ARNOLD MONTO: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. I actually have already given the explanation for my vote, so that is not my comment here. But it's a follow-up to Dr. Mark's most recent remark about an additional dose versus a booster dose. That part also did occur to me, but, you know, there's so much confusion around these vaccines anyway that I thought introducing another term might be even more confusing. So, of course, the FDA will do whatever they will do, and we voted on the question that was posed to us. But I just thought that I would express that opinion here.

DR. ARNOLD MONTO: Thank you. No other hands are raised, so I think we should be having a break now. I'll leave it up to the organizers who know what

people's schedules are to tell us when we should resume to hear Dr. Lyke on the Mix and Match boosters.

MS. KATHLEEN HAYES: Dr. Lyke is online and in the meeting. Dr. Atreya, do you think we should take 15 minutes and --

DR. ARNOLD MONTO: Why don't we take 15 minutes and then reconvene at 1:45 Eastern?

UNIDENTIFIED FEMALES: All right, thank you.

DR. PETER MARKS: Sounds great.

MR. MICHAEL KAWCZYNSKI: All right, a 15-minute break it is. Studio, can you please put us on break?

[BREAK]

DMID 21-0012 – HETEROLOGOUS PLATFORM BOOST STUDY MIX AND MATCH

MR. MICHAEL KAWCZYNSKI: All right, good afternoon and welcome back all of you who are joining us at our 169th VRBPAC meeting. We are into the home

stretch. Just concluded our vote, and we now have a presentation and some discussion. So, Dr. Monto, are you ready to kick off the final stretch?

DR. ARNOLD MONTO: I am, and I'd like to introduce Dr. Kirsten Lyke, Professor of Medicine, University of Maryland, who is going to tell us about the NIH's Mix and Match Booster Study. Dr. Lyke.

DR. KIRSTEN LYKE: Thank you. I'm Kirsten Lyke. I'm from the University of Maryland, School of Medicine at the Center for Vaccine Development. And I'm pleased to be here today to present the Mix and Match Study results. And I'd like to thank the organizers for extending us an offer to come and speak to our preliminary results.

In terms of full disclosure, I have received funding as a co-principal investigator for the Phase I studies involving the Pfizer COVID-19 vaccine. I'm an investigator on the Moderna and Novavax Phase 3 studies. And I receive NIH funding as Chair and site PI for the Mix and Match Study.

So some key decisions need to be made in

regard to decisions for the late boost. And a variety of data is going to contribute to this decision. So our role in this process is to understand how to use current vaccines to be used as boosts. And the questions are, can one vaccine be used as a boost to a different vaccine? Is it safe to mix vaccines? And what happens to the immune response after booster vaccination. So our trial is primarily safety and immunogenicity; we do not have data on vaccine efficacy.

And before I start, I'd like to recognize the mix and match study team. My co-chair is Dr. Robert Atmar at the Baylor College of Medicine. And, we have ten sites who are part of the IDCRC network, funded by NIH. We have data and statistical support through SCHARP in Seattle. And our regulatory support is FHI360.

And we're fortunate to have a number of laboratories helping us with this project. So we have David Montefiori at Duke University, who's contributing with the neutralizing antibody results. We have Adrian

McDermott at the VRC, who's contributing binding antibody results. And we have ongoing cellular and B cell responses as well as live viral neutralization assays that are pending at this time.

Okay, so the study design and our population are volunteers who received EUA COVID-19 vaccine at least 12 weeks since the last vaccine dose. And this timing was driven by the urgency to have data available in the autumn. So, we realize that longer intervals generally result in better immunogenicity, and we felt that this was the minimum interval in which we could have good immunogenicity results and be able to look at things in a systematic and an unbiased fashion.

So each group has 50 participants. And our group is defined as the primary vaccine series followed by the booster. And they're equally stratified between a younger age cohort of age 18 to 55, and an older cohort who are greater than or equal to 56 years of age. And that number gives us a high probability of observing at least one adverse event with a true event rate between two and ten percent; however, it will not

capture uncommon or rare adverse events.

We've designed this trial to inform public health decisions, but it's not powered or designed to compare between groups.

This is an adaptive design. And I'm only reporting the first nine groups, but we have additional arms that are ongoing at this point. And it's divided, for these first nine groups, which I'm going to present today, into three stages. And each stage is comprised of 50 individuals who had previously been dosed with the Janssen primary series, 50 individuals who were dosed with the Moderna regimen, and 50 who received Pfizer/BioNTech.

And then, these groups of three were then boosted with a single vaccine. So Groups 1 through 3 received the Moderna at the full dose 100 microgram dose. We do have additional arms that received the 50 microgram dose, and we don't have those results currently but will down the line. Groups 4 through 6 received the Janssen at full dose boost. And Groups 7 through 9 received the Pfizer product.

All volunteers had been dosed from their final dose at least 12 weeks. The study visits occurred on Day 1, Day 15, and Day 29, and those are the results that I'm going to present today. But we will be following them Months 3, 6, and 12.

In terms of volunteer characteristics, we had an N of 458 over the nine groups. And it broke down between 49 and 53 individuals per group. All of these individuals self-professed to having not had COVID-19 infection and denied having monoclonal antibody infusion. We were fairly equally distributed between males and females. The age ranged from 19 to 85 years of age. We had a predominant Caucasian population, with about seven percent being Asian and roughly seven percent Hispanic.

We did note that two participants, one in Group 4 and one in Group 6, had high N-protein antibody levels at Day 1, suggestive of a prior infection presumably asymptomatic. And we had one participant in Group 5 who had a symptomatic COVID-19 event at Day 27. This was uncovered after the immunogenicity results had

been calculated, although we did look at their Day 29 N-protein, which did not appear to be elevated at that time.

I'm highlighting here the interval, the interval changed throughout the stages as this was a sequential staged recruitment. So, in the early Stage 1, we had a bit of a difference between the Janssen volunteers of approximately two weeks shorter in interval as compared to the two mRNA. Probably owing to the fact that Janssen received EUA in late February.

And here we have the time from vaccination to boost in the Stage 1, 2, and 3. And you can see that for Stage 1 the volunteers had just under four months as the interval between their last dose and boost, all the way to Stage 3 where the interval had increased to approximately six months or just under six months, so increasing interval with the sequential stage recruitment.

In terms of immunogenicity, so we have available data through Day 15 and in some cases Day 29, which I'll present here today. In green are the

results that I'm going to present. I've mentioned that we have the Montefiori Lab processing our neutralization assays. And we'll be reporting those in ID50s, ID80s, and then we bridge them to the international standard and report this as international units or IU50, IU80. I would also state that this is a pseudotype lentivirus presenting the protein spike of a variant of interest and has a luciferase expression system.

So this is a validated assay for D614G. And we performed analysis in all 450 plus volunteers. We also have subset analysis for variants of concern, which are in process, but not available to be discussed today. Similarly, the Vaccine Research Center in the McDermott Lab provided analysis for the IgG antibody, using a validated 4-plex assay assessing the WA-1, or Washington-1, circulating a wild-type strain in all volunteers reporting this is as arbitrary units. But we also did bridge this to the international standard known as Binding Antibody Units.

We also did a 10-plex Fit-for-Purpose research

assay. And we analyzed the control circulating wild-type as well as the Alpha and the Delta, which I'll present today.

Okay, our first sets of results are going to be the full dose Moderna booster. And, let me take a little time to sort of outline this. I know it's a busy slide, but they'll all be sort of similar in terms of the next few slides. And so what I'm presenting here are serum antibody responses. Here are the Ns. At the top panels, you'll see the entire age group collapsed together. And in the bottom, we have subgroup analysis. So in blue, we see the age 18- to 55-year-old subgroup. And in red, we see the 56 years and older subgroup.

Also, we have the timepoints across the X-axis, so days 1, 15, and 29. And this is a logarithmic scale. Across the top, we have their primary series, Janssen, Moderna, and Pfizer/BioNTech. In blue, we're reporting the geometric mean titer, as well as the binding antibody that bridged to the international standard. And then in red, we're reporting the

geometric mean fold rise.

And so what I would first say in regard to the mRNA-1273 booster product is that, at baseline, all volunteers had detectable binding antibodies. It was highest in the Moderna group, followed by the Pfizer, followed by the Janssen. But following boost, we had a robust response across all three primary vaccine series, ranging from approximately seven all the way up to 56 geometric mean fold rises. And peaking at Day 15 and then remaining stable at Day 29.

Okay, the next sets of results are neutralization and antibody titers to the Spike D614G. This is a validated assay, and again to the Moderna boost. And, again, at baseline, we have the Janssen individuals about 15.8 percent of which had no detectable neutralizing antibody at baseline. All Moderna individuals had baseline detectable neutralizing antibodies. And, the Pfizer then was in the middle of these two. Following boost, however, all three primary series had significant booster responses across the board, peaking at Day 15 and stabilizing at

Day 29. With the geometric mean fold rise being 76-fold in the Janssen group, owing to their lower starting point, and relative to the post-dose 2 Modern results following the early-stage results. This represents about two-and-a-half-fold increase over the post-dose 2 results.

The post-dose 2 peak IU50, so bridge to international standards was 247. So we see an extremely robust homologous response after the third dose of Moderna in the Moderna group.

I would also back up and just say that we saw very little difference between the age groups. And, so, we're not reporting the numbers here to keep it less busy, but essentially nothing that appeared significantly different between the older and the younger age group.

Okay, our next set of results are going to be the Janssen booster vaccine with the full dose five times ten to the tenth viral particle. This is binding antibody results once again to the WA-1 antigen, the wild-type strain. And, again, subgroup analysis at the

bottom, and the entire age group collapsed together at the top.

What I would first say is once again the Moderna group had the highest baseline binding antibody, followed by Pfizer, followed by the Janssen group. All individuals but one Janssen member had detectable antibodies. There was one individual that had no detectable antibody in the Janssen dose group. Following the boost at Day 15, we see evidence of a rise in binding antibodies across the board. However, there is about a 10-fold decrease in the response in the Janssen group as compared to the Moderna and the Pfizer group. And again, very little difference noted amongst the age subpopulations.

And here we have the neutralizing antibody results to Spike D614G, following the Janssen boost, reported in ID50s. Again, we're reporting this as IU50 in the green. At baseline, 22 percent of the Janssen individuals had no detectable neutralizing antibody at Day 1. All Moderna individuals had detectable antibody at Day 1. And about 95 to 97 percent of the Pfizer

individuals had detectable antibody at Day 1. And following the Janssen boost, we do see evidence of increase in neutralizing antibodies across the board, but again there appears to be a 7 to 10-fold increase in the mRNAs as compared to the Janssen homologous prime boost.

Lastly, the Pfizer/BioNTech booster vaccination at 30 micrograms, here's the binding antibody data. Once again, all volunteers had detectable antibody at baseline. And following the boost, and we're reporting here binding antibody to the WA-1 wild-type strain, we see results that essentially mirror that of Moderna, with a quite robust response across the board. And a 33 geometric mean fold rise in the Janssen volunteers owing to the lower start point. No particular difference in the sub-age groups.

Here we have the neutralizing antibody titers to the Spike D614G following the Pfizer boost. Again, we see about 22.6 percent of the Janssen individuals having no detectable neutralizing antibody as compared to about three percent of the Pfizer, and then all

Moderna individuals had detectable baseline neutralizing antibody. Following the boost, it's a very similar response as compared to the Moderna product, with anywhere from 11 to 35 geometric mean fold rise in titers.

And then putting this all together and trying to have a few take-home points. So, at the top, we have the Moderna boost, in the middle the Janssen, and, at the bottom, we have the Pfizer/BioNTech. And first what I would note is that the neutralizing antibodies did increase in response to any boost regardless of the primary vaccination series and ranged from 4.2 all the way to 76 geometric mean fold rise.

The second point I would make is that the homologous regimen, and that would be Janssen prime boost, Moderna prime boost, and Pfizer prime boost, had geometric mean fold rises ranging from 4.2 to 20. Whereas, the heterologous populations and groups ranged from 6.2 to 76, meaning that the heterologous had as good or higher neutralizing antibodies following the boost at Day 15.

A third point that I would make is that all groups, save for the homologous Janssen prime boost group, achieved post IU50 doses of greater than 100 in terms of IU50s, which has been associated with a 90.7 percent vaccine efficacy against symptomatic disease when analyzing Moderna results. And this was replicated in Oxford data published by Boise, where they had a cut point of approximately 140 in international units, representing a 90 percent vaccine efficacy against symptomatic disease, although our data may not reflect measures of protection against severe disease or death.

Okay, here are all the results I've just reported, and a few comments I'll make. On the top, you'll see Panels A through C, representing the binding antibody. And on the bottom, Panels D through E [sic], you'll see the neutralizing antibody. In general, the Day 15 titers, two were highest in those individuals who had the mRNA-1273 Moderna prime. So these individuals, they were in general higher following their boost, followed by Pfizer/BioNTech, and then

Janssen, irrespective of the booster vaccination.

Another observation that we would make is that the boost resulted in what appeared to be the highest serologic response at Day 15, in the mRNA boost, so the Moderna product and the Pfizer/BioNTech product. However, following the Janssen boost, we do see evidence of incremental rise at Day 29, which would be reflective of the Ensemble 2 data where there was incremental rise over time and then stabilization over a full eight-month period. And we're waiting for Day 29 neutralizing antibody results.

And one other point that I would make on this figure is that these dots, these red dots here, here and here, this is Group 4, and this is Group 6, these are the individuals with high background N-protein that we discovered in our post hoc analysis. And we've charted them here just so that you can get an idea where they landed within the immune response.

A bit of immunogenicity with our variants of concern, okay, so this is IgG serum binding antibody response to the WA-1, Washington-1, wild-type control,

in yellow, the Alpha strain in blue, and the Delta in pink. So at baseline, we see roughly 35 to 45 percent decrease in antibodies against the Delta as compared to the wild-type control.

Following the Moderna boost, we see a robust response across the board regardless of your primary vaccine series. And the degradation in antibodies as regards to the amount of antibodies detected against Delta, then decreased to between 15 and 35 percent as compared to the wild-type control, indicating a robust boost response and possible breadth cross coverage with the variants of concern.

Here we see the similar results with Janssen following the Janssen boost and the primary vaccine series. You can see at Day 1 there's quite a bit of dispersion in the Janssen primary dose volunteers. Following boost, all participants experienced an increase in their binding antibodies. And by Day 29, all of the individuals had detectable antibody against the variants of concern.

And here are the results following the

Pfizer/BioNTech, again, to the wild-type control, the Alpha and the Delta. And this mirrors our Moderna results, so that there's a robust response by Day 15, and we don't have Day 29 results as yet.

And here's the compilation figure with all of the results, demonstrating that all volunteers mount an antibody response, the mRNAs peeking at Day 15, and the Janssen continuing to rise till Day 29.

Safety results, we had two serious adverse events, one an acute renal failure due to rhabdomyolysis following a fall. This was deemed unrelated to study vaccination and occurred 30 days after a Moderna boost. The second was acute cholecystitis that was termed unrelated and occurred 24 days after the Janssen booster vaccination.

We had no pre-specified study-halting rules met, no new onset chronic medical conditions through Day 29, and had one related adverse event of special interest, which was a case of severe vomiting that led to a medically attended event the day after a Janssen booster vaccination.

In terms of unsolicited AEs deemed related to the boost of any severity, we see a fairly even distribution across all three booster dosages. Most were Grade 1 or 2 in severity. There were four related Grade 3 adverse events: two vomiting, one I've described following the Janssen that was an adverse event of special interest and vomiting in one participant who received the Moderna boost. There was also a reported Grade 3 fatigue, and one of insomnia in two individual participants following the Janssen booster.

And here we have our booster solicited adverse event, and I collapsed the age groups because we didn't see a particular trend between the younger and the older age group with the low numbers that we have. You'll see this is local and systemic reactogenicity through Day 8. And it really mirrors that reported in the primary series, so that 75 to 85 percent of individuals had experienced pain and tenderness. As well as a good amount of headache, malaise, fatigue, and myalgia, particularly in those that had received

the Moderna primary vaccine series.

In terms of limitations for the study, as we've mentioned, this is not randomized; it was an open-label design. The study was not designed to compare between boosts. We did not control for intervals, and we did not control for patient characteristics between the primary vaccine and the boosts.

The correlates of protection are not completely elucidated, and the correlates for severe disease and death are even less well understood. This is only antibody data and early immunogenicity data. We do have cellular and B cell immune responses that are still being analyzed. These data represent only early time points from the trial. And the vaccines may differ in time to reach peak responses, and they may have different durability of responses. So we will be following these participants for a full year.

Our conclusions are that the use of the Moderna, the Janssen, and the Pfizer/BioNTech as booster vaccines led to recall serologic responses in

all three EUA-dose vaccine groups. For a primary EUA COVID-19 vaccine, heterologous boosts elicited similar or higher serologic responses as compared to their respective homologous booster responses. The mRNA vaccines resulted in higher antibody titers in the first 28 days after the boost. And there were no significant safety concerns identified within this short time period.

Again, I'd like to recognize the Mix and Match study team, along with the contributions of the companies who allowed us to use some of their paperwork in cross reference, although all vaccine product was procured through government procurement offices. And with that, I'm available to take questions.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Lyke. That was a very clear presentation of very complicated data. I just want to ask a point of information before we open the presentation for general questions. Primary

series for Moderna and Pfizer/BioNTech was two doses, and for Janssen was one dose, correct?

DR. KIRSTEN LYKE: It was two doses, the Moderna interval being the 28-day recommended dose, and the Pfizer interval being 21 days.

DR. ARNOLD MONTO: Making this a real-world study.

DR. KIRSTEN LYKE: This is a real-world study. They were not dosed with us. They had already been dosed and came in for the booster portion.

DR. ARNOLD MONTO: Okay, thank you. Questions? Dr. Pergam.

DR. STEVEN PERGAM: Thanks a lot. This is a really great study you guys have put together.

I had a couple of questions just to remind us of the exclusion criteria for people who enrolled in the study. Can you remind us if you tried to enrich for specific high-risk populations within the study design?

DR. KIRSTEN LYKE: So that was not the point of this study. We wanted to have a real-world,

medically stable individuals. So while we didn't rule them out, they did have to be medically stable. We did not take individuals who were on immunosuppression. We did take them at their word that they had not had COVID-19 or received monoclonal antibodies.

DR. ARNOLD MONTO: Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. Thank you, Dr. Lyke, for that excellent presentation.

My question is about the other groups that you alluded to. You presented the data on these nine groups. Could enlighten us a little bit about what those other groups are, and when the data from those groups will possibly become available?

DR. KIRSTEN LYKE: Yes, so we always built this as an adaptive design. And, in fact, we're sort of building it as we were conducting it. So we started with Stage 1, and then looped in companies as we went along, so every two and a half to three weeks we added a new stage.

We've also completed a dose arm of individuals who received the 50-microgram Moderna product, so the

half dose that was just approved. And, we also have a series of individuals who have received -- we call it the 0.211 product -- so that the Moderna product that's 50 micrograms of the beta 0.351, as well as 50 micrograms of the 1273.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Pretty clear that the early focus has been on antibody responses and neutralizing titers. It's fairly easy to do, but we heard yesterday from Moderna that, even in the absence of neutralizing titers, they're still manifesting considerable protection. And we actually saw today from the J&J that with some of the newer -- or whatever you want to call it -- variants that we haven't seen yet in the United States where they're more on the lines of vaccine escape means that there's a real disconnect between preventing symptomatic infection versus protection from serious disease. So that suggested cellular immunity is very important.

There have been several reports that the

cellular responses induced by the mRNA vaccines do wane over time. So it would seem that exactly when you did these in time, you may get different responses measuring someone with an mRNA vaccine three months out versus six months out.

And, so, for the question, when are we likely to begin to see some of these cellular responses, which is probably going to be very critical going forward to understand the new landscape of what we're going to see in the future from COVID?

DR. KIRSTEN LYKE: I can't give you an exact date, but we've already shipped the samples to the laboratories and they're underway. Hopefully, by the sort mid-November I would estimate -- maybe late November, we'll start to see the earliest results. But it's literally a colossal amount of samples. We're collecting anywhere between 10,000 vials of product every week and then shipping them to the appropriate labs, so it's a logistical effort.

DR. MICHAEL KURILLA: And what about longer follow-up in terms of antibody responses the past 29

days?

DR. KIRSTEN LYKE: Yeah, we're following them all the way to 12 months, so we have time points at 3, 6, and 12 months. And we'll be following all the volunteers through that period.

DR. MICHAEL KURILLA: Thank you.

DR. ARNOLD MONTO: And it's interesting that you're seeing a little bit of waning already in the mRNA products, right?

DR. KIRSTEN LYKE: For stabilization, it wasn't a great deal, so we know that the mRNAs peak early. And it will be interesting to see what they do over time.

DR. ARNOLD MONTO: Right. Dr. Rubin.

DR. ERIC RUBIN: Thanks for sharing your interesting data. I wonder, what happened to the individuals who had no measurable neutralizing antibody? And, whether there was a correlation between antibody levels before the additional dose and after?

DR. KIRSTEN LYKE: Correlation meaning -- I'm not sure I follow with the correlation.

DR. ERIC RUBIN: In other words, did those who had very low titers end up on the lower end of the elevated titers after booster.

DR. KIRSTEN LYKE: Yeah, that's a good question. We'll have to pull out that data. What I can say is that everyone who was negative then became positive. Although a bit slower in the Janssen group, they all went positive by Day 29. So, it was a little bit more of a delayed response. And you might infer that that will continue to go up over time. That's something that we'll be looking at carefully.

DR. ERIC RUBIN: Thank you.

DR. ARNOLD MONTO: To my surprise, there are no additional questions. So you must have been crystal clear --

DR. KIRSTEN LYKE: Clear I hope.

DR. ARNOLD MONTO: -- in your presentation of very complicated data. Ah, we have another hand. Dr. Pergam.

DR. STEVEN PERGAM: I apologize. So, just a question since this has just been voted on for the

second dose of the Johnson and Johnson. The flexibility in your study, does that allow you to add another subgroup to do additional boosters from the study design you have? You've added additional questions related to these other vaccines. Does that sort of study allow you to sort of ask that? Because I think that's going to be a question down the road as people that have completed a two-dose series and whatever we want to call the J&J. Is there an option to do an additional boost beyond?

DR. KIRSTEN LYKE: That's not something we discussed. We do have a separate cohort of individuals who were dosed with a primary series so that we could have early immunogenicity. And we're reserving those on hand to boost with a product that we have yet to decide or to look at interval results. So, the flexibility of this study is pretty open-ended. And it allows us to adapt and move towards really any direction.

We anticipated that there may be more vaccines that were targeting variants of concern as new variants

rose in the population. And, so, we envisioned being able to rapidly implement new arms to this study. So, it's open-ended to last out to four years if needed, so that we can continue to answer new questions and add arms to help us make decisions.

DR. ARNOLD MONTO: Kathleen, I do not see any additional raised hands, do you?

MS. KATHLEEN HAYES: Dr. Nelson had his hand up earlier and went down, so I just want to see if he had a question.

DR. MICHAEL NELSON: Dr. Monto, I do have a question if that's okay.

DR. ARNOLD MONTO: Okay, Dr. Nelson.

DR. MICHAEL NELSON: Thank you, Dr. Lyke, for an outstanding presentation. I think we're all suitably impressed by the initiative and the design of this study, and the data it will yield over the next several years.

Two quick questions, I thought I heard that the solicited adverse events were similar to the primary series. We've seen data today and yesterday

that second or subsequent doses may have a lower frequency. Does your data bear that out?

DR. KIRSTEN LYKE: Yeah, from what we saw, it looked pretty similar to me. I mean, 75 to 85 percent reporting pain. And then a good percentage reporting headache, malaise, fatigue, and body aches, so at least, from the data that we have at hand, it did look pretty similar. There aren't enough numbers to really parse that out statistically perhaps, but it did seem that maybe there was a bit of drop-off in the older population. But, again, when we collapsed all the data together, it looked very similar to the primary series.

DR. MICHAEL NELSON: Yeah, we all had theoretical concerns that there might be increased rates when we crossed platforms with respect to the booster.

Similar question, is anybody looking at affinity or epitope mapping for across a platform dosing? With the advantage being that maybe the quality of the antibodies produced with that boost, in addition to the actual quantity, will provide some

added protection. Thank you.

DR. KIRSTEN LYKE: Yeah, so, with all the blood collections we devote half to preplanned assays and the other half is for future use. So we have the flexibility to add a whole host of additional assays. We are doing B cell assays, and whether we move to epitope mapping, et cetera, that's an open-ended question but obviously would be of great interest.

DR. ARNOLD MONTO: Dr. Kurilla, again.

DR. MICHAEL KURILLA: One other thought. Would you consider boosting with a strain change variant? Do you anticipate doing that when they become available?

DR. KIRSTEN LYKE: Yeah, that's exactly what we had anticipated. That's why we left this as an adaptive design. We started with 3 groups, and we're up to 14, with a projected possible 17. We wanted to add a protein vaccine to this as well just out of interest, but we're waiting to see in which direction that goes.

DR. MICHAEL KURILLA: Thank you.

DR. ARNOLD MONTO: Dr. Levy.

DR. OFER LEVY: Hello. Great study and thank you for that. I wanted to ask whether there was any thought given to measuring innate immune responses after the heterologous boost in your design? Because, as you know, that could shape adaptive immune responses, it may also potentially correlate with some types of reactogenicity. So what are the plans regarding that and what do you know about that?

DR. KIRSTEN LYKE: Yeah, so, it wasn't part of our original protocol design, but that doesn't preclude or exclude really anything that comes to the table. And, if that is a direction that we want to go, we certainly have plenty of samples that we can dip into to look at those questions.

DR. OFER LEVY: Yeah, you may be aware that Dr. Mihai Netea in the Netherlands, for example, has published the receipt of mRNA vaccine in some sense shifts the innate set point. And it would be interesting to see how that plays out in the context of a design like this.

DR. KIRSTEN LYKE: Yeah, agreed.

DR. ARNOLD MONTO: Dr. Perlman.

DR. STANLEY PERLMAN: Yeah, these data are great. Is there any thought about extending them to a vaccine efficacy study, obviously not all in a zillion (phonetic) lens, but a pertinent lens?

DR. KIRSTEN LYKE: Not as part of this study. I don't know if NIH has additional thoughts about that, but it wasn't part of the design for this study. This was purely for public health purposes and to really get to the bottom of a whole host of questions that just kept arising.

You know, there was a lot of debate whether we should even have a Moderna followed by a Pfizer, or Pfizer followed by Moderna. A lot of people felt that that wasn't going to be useful data. But I think it real-world practical questions that people want to know, is it safe to do that? So, I think there's value in looking at it in every which way.

DR. ARNOLD MONTO: Well, thank you very much. That seems to have exhausted the questions. Dr. Marks,

are you going to give us the discussion topic for our broader discussion now?

COMMITTEE DISCUSSION OF FDA QUESTIONS

MS. KATHLEEN HAYES: I believe we have the discussion questions pulled up.

DR. PETER MARKS: Sorry about that. Dr. Monto, what would you -- we had a discussion question here. It may be the focus was apparent.

DR. ARNOLD MONTO: Okay.

DR. PETER MARKS: There we go.

DR. ARNOLD MONTO: Okay, how do you want us to approach this? This is pretty open-ended.

DR. PETER MARKS: Could I make a suggestion, Dr. Monto --

DR. ARNOLD MONTO: Please do.

DR. PETER MARKS: -- that perhaps maybe we can just go down the Committee and just see if anyone wants to add anything in this regard. I don't think this has to be any kind of systematic -- we would just like to

hear the Committee's impressions here.

I also want to, again, just take the opportunity to thank Dr. Lyke. It was very nice to have this presented. It's clearly very important work, and I'm glad to be able to have the Committee hear this. But I think we'd just be interested if there are any comments that the Committee would like to make. And if you just want to go down the Committee members and just see if they wish to make anything.

DR. ARNOLD MONTO: What I would suggest rather than calling on the large number of people we have on the Committee, is to ask you how specifically we can help in making some recommendations about how we can be putting this into effect in terms of the scenario that we heard yesterday. That, for example, ACIP cannot do anything without an emergency use authorization from FDA.

So, for example, if somebody who has received the Janssen vaccine would like to get, based on some of these data, an mRNA booster, how is that going to be done not right away but down the line? What kind of

discussion would help you in trying to formulate the kind of EUA that would make that possible?

DR. PETER MARKS: I think we would want to know what the Committee would -- so, we have data now and, if you think about it, we have data, for instance, with Janssen boosted with an mRNI vaccine, and an mRNA vaccine boosted with Janssen vaccine. The question is, how much more data would the Committee like to see for the purposes of an emergency use authorization in this type of scenario for kind of mix and match of the vaccines? That might be helpful.

DR. ARNOLD MONTO: Okay, that is a very much more focused question, and let's start going around and seeing who all would like to comment about what kind of data they would like to see to justify an emergency use authorization. Dr. Rubin.

DR. ERIC RUBIN: Thanks, Dr. Monto. I was going to ask Dr. Marks what we would need, but, in fact, he's asking us, which is nice.

We just authorized additional doses of vaccines based on, in the case of Moderna at least, a

very small amount of safety data.

Here we have vaccines that are safe. We have modalities that we understand for delivering those vaccines. I'm pretty comfortable that with a relatively small sample size that we can be certain of safety. Given we don't need much more efficacy than the immunobridging that we have from Dr. Lyke's study, I think, because it's very similar to the kind of things that we've seen before and that we've approved on before.

So, I guess, a somewhat larger sample size for -- I wish I could name a number -- but a somewhat larger sample size for safety. Certainly, no less than 150ish that we had from Moderna I think. I'm making that up, but I think that those are all the data that I feel like we really needed.

DR. ARNOLD MONTO: And, Dr. Marks, if you would like to respond at any point, feel free. Because we'll go down the list of those who have their hands raised.

DR. PETER MARKS: Thank you, Dr. Rubin, that's

exactly the type of feedback I think we wanted here.

DR. ARNOLD MONTO: Dr. Gans.

DR. HAYLEY GANS: Thank you. I think it's very compelling and as some of us alluded (audio skip) Janssen (audio skip) extension of the primary series that this indication is actually something I would be interested in (audio skip) about and helping (audio skip) higher risk indica- (audio skip).

So, I think that we have all already voted on the safety of these vaccines. And I would be in favor -- I mean, we already have at least with this other study another 450, whatever it's mixed up, and for each one of them. So I think we already actually made a point (audio skip) people (audio skip) out in this. I would actually urge the FDA to (audio skip) this (audio skip)of those (audio skip) benefit of this actually have (audio skip).

DR. ARNOLD MONTO: Dr. Kurilla.

DR. MICHAEL KURILLA: Yeah, I'll take a slightly different perspective here. I don't actually see this as a EUA consideration. I think that the

safety data is great. And I think it does present potential options down the road for public health officials and our overall response to the evolving pandemic. But my concern is that -- a few things, one is that I know people are very highly swayed by high neutralizing titers, but we do not have a correlate of protection. And we clearly see evidence of protection from these vaccines in the absence of neutralizing titers, so there's a lot of other things going on.

And the reality is that, when this would be considered to be implemented in the future because, right now, everybody's probably just in the process of getting boosted with whatever their primary vaccination is, we're going to be in a slightly different environment with a whole new set of variants. And so I think we may end up in a situation not too dissimilar to influenza. No one talks about what influenza vaccine did you get last year, that's because we don't have a EUA or an approval for a particular booster for you if you got a certain vaccine.

So, I think this is very informative data. I

think largely in terms of safety and largely in terms of helping to better assess the overall components of the immune response that are really contributing to the critical aspects of protection, both from infection and symptomatic disease, as well as serious disease. So I would not go down the EUA route. I think we'll be struggling forever with every single combination, and it's just not going to be worth the effort.

DR. ARNOLD MONTO: Dr. Kurilla, the only problem is that we heard yesterday from Dr. Cohn that ACIP is constrained by the fact that these are not licensed products.

DR. MICHAEL KURILLA: But eventually these are --

DR. ARNOLD MONTO: So, we're going to have to figure that one out. But the flu, we've got licensed products.

DR. MICHAEL KURILLA: Right, but these products will be licensed. I mean, I don't think we expect to be in an emergency situation forever. And I don't think we expect these to stay under EUA forever.

The FDA itself does not regard EUA as an end state. So I think the focus should be on getting these products approved and doing adequate studies to demonstrate that there's a safety and there is evidence of clinical benefit from this. But I think trying to parse it out with each particular combination, we're going to be having VRBPAC meetings nonstop for the next several months if we try to do this.

DR. ARNOLD MONTO: I'd like to call on Dr. Cohn to give us the ACIP view about this.

CAPT. AMANDA COHN: Thanks, Dr. Monto. I think that there's a little bit of confusion here about whether or not FDA's talking about this as being an indication versus having some language somewhere in the EUA or factsheet that allows for heterologous boost. And I think from a public health perspective, we --

DR. ARNOLD MONTO: In other words, it doesn't have to be specific.

CAPT. AMANDA COHN: Yeah, so I don't think that it needs to be that you can -- I think that if there was some general language that would -- I don't

think there's any sort of need from a public health perspective to have a preference for mixing or matching, but I think that, from a public health perspective, there's a clear need in some situations for individuals to receive a different vaccine.

For example, J&J doses, while for those 14 million people who have been vaccinated, many of those individuals may not have access to a second dose of J&J. So, if there's not any allowable language in the FDA factsheets or EUA authorization, then those individuals are left behind. Additionally, the same goes for if an individual is a female who's 30 years of age, who may feel like she's at risk now for a reaction after she received her first dose of J&J before the TTS was recognized. So that would allow, for example, for that woman to get a different type of vaccine.

And, to the contrary, it allows, for example, in nursing homes, where most residents received mRNA vaccines, it would allow a pharmacy to go into a nursing home and only have a single vaccine product to boost individuals who receive either Moderna or Pfizer,

either of the mRNA vaccines or the J&J vaccine.

So, I think from a public health implementation perspective, given the setting of this pandemic, it would be really important to have some allowable language. And I think the safety data that has been presented today is very supportive, especially in light of the culmination of the millions of doses of these products that we've seen given and the safety evidence from all of those vaccines.

DR. ARNOLD MONTO: Thank you, very helpful. Dr. Lee.

DR. JEANNETTE LEE: So, I want to make sure that we don't confuse the public even more than we are already. So, we have approved both the boosters for the two mRNA products, for ages 65 and up, and then other categories of individuals, who are below that, either at high risk either through on health issues or through occupational exposure. Now, in the J&J vaccine, we have approved it for all of those who got it 18 and above, so that's a much broader group.

Now we're going to throw in another piece, and

that will be that you could get a different vaccine. And I do know, whether rightly or wrongly, I think there is a perception in the general public that the J&J one dose is perhaps not as effective as the mRNA. And, so, now you've sort of set up a possibility of sort of mixing, matching, and then different groups being eligible.

And I guess my question is about, when that might be implemented, some people may want to wait until they can get an mRNA. But what we're saying though, if you're between 18 and 65 and not in those categories, if you got J&J, yes, you can get an mRNA booster. But, if you got the mRNA to begin with, and you don't fall in those special categories, no, you can't get that, or you're not approved for that. So, I just want to point out that this is going to be very, very messy in terms of the messaging. And I don't offer suggestions, but I'm just making an observation. Thank you.

DR. ARNOLD MONTO: Dr. Lee, I agree with you completely about the age issue. I'm really concerned

about the fact that we can only vaccinate with boosters down to 65 years of age when we know that others, especially with a Pfizer/BioNTech, are waning according to data we have. And, if we have any time at the end of this, we might try to revisit that in terms of enabling language. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. I just wanted to make a few remarks with the discussion that's happening right now. I think the data that were presented by Dr. Lyke help us to get what I call a proof of concept, which is that heterologous boost does work, and, in some cases, works better than boosting with the homologous vaccine. So that's the first thing.

You know, the dogma has always been, for other vaccines, you always try to boost with what you've primed with. But, in this instance, that seems to be different.

Dr. Cohn comment about people with allergies, I think that that is a very important one that if someone is allergic to one of these vaccines, they have

the opportunity then to get a booster dose with a different vaccine, to which hopefully they would not be allergic.

With regards to Dr. Marks's comments about what else would we like to see? I have a few ideas. The first is, these are data primarily in adults and certainly, I'd like to see what happens in children with regard to heterologous boosting.

The second thing is the longevity of this boosted antibody response. I'm sure that these folks are going to be followed longer term to see how long these antibodies last.

A third area that I think deserves attention is underrepresented minorities. There are very few people who are actually included. As a percentage maybe, but, if you look at the absolute numbers, those are very, very small in each of the different groups. And I'd encouraged the folks who are conducting these studies to actually expand that if possible.

And then the last point I would like to make is about cellular immunity. The point been made before

that we are only looking at antibodies' responses, which is easy to measure and easy to look at, but it would be I think critically important to see what happens to the cellular immunity as well as we try to do this heterologous boosting. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Sawyer.

DR. MARK SAWYER: Thanks, Dr. Monto. So, to Dr. Mark's question what else do we need? I'm sold already, and that's because I agree completely with Dr. Cohn's comment that we need flexibility and improved access for everybody, which the flexibility of being able to mix and match will allow. I think all of these extra data points that can be collected going forward are going to be important, but I think the sooner we let this happen in the most straightforward way the better off we are.

Obviously, it's already happening. We just are tracking it indirectly through the VAERS reporting and/or the VSD, but this way I think it's going to improve overall access. So I'm in favor of getting this -- whatever is required from the FDA perspective

to allow broader use of the mixing and matching strategy.

DR. ARNOLD MONTO: Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Arnold. It's really interesting. I think we're in a situation where we just approved a booster for J&J, and we have data that suggest that the mRNA vaccine boost -- at least according to antibody responses and to Mike Kurilla's point -- we don't understand the T cell immunity piece which is coming. It looks better.

So, I think this is a challenge for people out in public to sort of sort this out and to make decisions about what they're going to do. And I know we're hearing this from our perspective that we have to be thoughtful about it.

I think, to Dr. Cohn's issue that a little bit of flexibility would be helpful, but I think the FDA is going to have to be more specific about which particular groups would be eligible to do mix and match. That maybe it needs to be people with a known or abnormal response to a primary vaccine dose, or

something more specific, but there needs to be some flexibility.

I think the way that they've worded it with the immunosuppressed population was helpful in the sense that, if you couldn't get the primary dose series that you had, if you had Pfizer as an example, you were allowed to get Moderna as a second dose. Are there ways to sort of couch that language to get a little bit of flexibility around that? Because I think right now state health departments and others are being very to the letter of the law not allowing a booster dose with any other version.

So, I'm leaning towards being more permissive to some of these, but I think we really have to think about not making it so that they regard that everyone who gets Johnson and Johnson is going to go get an mRNA vaccine without all of the data in place.

DR. ARNOLD MONTO: Dr. Marks, would you like to reply to that, or shall we park this and go with questions later for you?

DR. PETER MARKS: I appreciate the perspective

here, and there are clearly challenges here and I think we'll have to take these back and think about them. But if I could just summarize at least a little of what I heard here is it does seem like there's, again, some consensus that this is an important option for people to have. Some would like a little more data. Some feel like this is enough data. And certainly, whatever we did we would be looking to collect more data in the real world.

But there are some challenges associated with it. I think Dr. Kurilla really made clear, and I think rightly so, that we don't know from these short-term studies what's the longer-term effect of mix and match will be, and we just don't have those data. But I think to the extent that I think the Committee here has provided us with some food for thought. I think we got what we needed from this discussion.

DR. ARNOLD MONTO: And we have a number of other people who want to tell you more.

DR. PETER MARKS: Happy if they'd like to.

DR. ARNOLD MONTO: All right. Dr. Gans.

DR. HAYLEY GANS: Thank you. I just want to make sure, I mean, I know pieces have been said, and it's always so wonderful to hear the thoughtful conversation that comes out of this. And I think one thing that I would say the reason why we're often getting a lot of feedback from the public about confusion and this was said, that was said, is that we like to have a very robust debate so that we make sure that pieces of this are picked up for future study as Dr. Marks has said. This is a real-life event that we're learning as we go.

What I really would like to iterate is that previously many of us had concerns about the word "boost" for the previous vote. And, if we got rid of that that would actually solve a lot of the confusion that Dr. Lee was talking about. Because we did have a boost for certain populations, and people already had what we thought was a primary series. And now we argued earlier that the primary series for the Janssen vaccination should be two doses. And so, that's really not considered a boost, so it's more allowable. And

people who had gotten that of all ages can get that. So I think if we clean a lot of that language up, it actually won't be confusing.

I also just really need to iterate that, because of the way that the EUA is and it's so restrictive and other bodies can't make necessarily the recommendations, I think it's really important for us to think about how we allow people who have gotten what they've gotten to take advantage of the data in real time. We keep asking for real-time data. We get real-time data then we say we need more. So, I would urge the FDA to really allow us, or whomever, the language in more rapid fashion than waiting. I (audio skip) been a definite (audio skip) all challenging, but I think we can (audio skip).

DR. ARNOLD MONTO: Thank you Dr. Gans. The problem is we're not going to get away from the fact that the primary series for two of the vaccines that were approved is two doses, and the primary series for the other is one dose. And that's what you get in trouble with just looking at the results from the Mix

and Match Study. Dr. Annunziato.

DR. PAULA ANNUNZIATO: Thank you, Dr. Monto. So, this has been a really interesting discussion, and I really appreciate the data that was shown.

I just want to share from an industry perspective, following up on what Dr. Cohn had said, that it's quite typical in vaccine programs to provide interchangeability data from studies to allow for flexibility that's often required for a successful vaccination program.

And, so, from my view, I think that understanding that these heterologous boosts are not detrimental or do not appear to be detrimental to safety or immunogenicity can be used to allow that type of flexible language that the FDA could work with sponsors to incorporate into either labels or EUAs. And, this would be useful, I think, from a real-world perspective. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Annunziato. Dr. Moore.

DR. PATRICK MOORE: Thanks, Dr. Monto. So one

thing that hasn't been raised, and I think is important, is an advantage to the J&J vaccine what we don't have for the other vaccines is that the data that we have now is based on a very large global RCT that has been followed out over time, shows really clear durability of vaccine effectiveness, although it's clearly not peaking at the same level as the mRNA vaccines

So, the shorter-term studies in mixing antigens aren't going to catch that unless you follow people out for a longer period of time. In which case, it may be that mixing with the J&J vaccine actually gives you a very clear benefit of a long-duration vaccine efficacy. That's just something to consider in all of this.

DR. ARNOLD MONTO: Thank you. And I think long-term follow-up is going to be key here in terms of a number of elements, including those who get boosted and those who don't get boosted, in terms of the value of revaccination. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I

just want to make a few points. First of all, in terms of the heterologous boosting, as we've said, we don't know what the correlate of immunity is. We're placing a lot of emphasis on in vitro data in terms of neutralizing antibodies.

And so I guess that one question I have is, do we need some efficacy studies or some effectiveness studies to really come to a conclusion on how beneficial a heterologous boost would be? And secondly, remember there are many COVID vaccines, and so, if we're talking about a heterologous boost, I mean, it would have to be very clear that we're talking about the three vaccines that are authorized or licensed here in the United States. And I just worry that that could become a very confusing message for people.

And I assume, and I guess this is for the FDA, it certainly wouldn't be a preference for heterologous boosting in contrast to homologous boosting because that would make it so complicated for people who have already completed the primary series and received a

boost. And I just wonder -- I think the wording as it's been said will be so important because it could be quite confusing for the general public.

DR. ARNOLD MONTO: Dr. Fuller.

DR. OVETA FULLER: Thank you, Dr. Monto. I just want to remind all of us, and from my perspective as a virologist who studied entry, that all three of these approved at the moment vaccines are to the spike protein of coronavirus. And there's certainly a colleague here who studies coronavirus. But they may not be as different as we might think. The platform is different, but the antigen itself is the spike protein, which is so key to the entry of coronavirus.

So for coronavirus (SARS-CoV-2), for the public, that messaging coming from the FDA and CDC and others may be useful to say that regardless of how you get it, you're still getting immunity to a key molecule or key protein that this virus uses. And, so, that may be less confusing and allow the flexibility and access that is so important to do the things that Dr. Cohn mentioned at first.

So just a comment about that it's all the spike protein, and that there may be subtle differences, but because we've seen the studies on all of them, and all of them have passed the safety and efficacy, that they may not be that really different in what they do to the immune system specifically. Just a point on entry and virology.

DR. ARNOLD MONTO: Thank you. Dr. Wharton. You're muted, Dr. Wharton.

MR. MICHAEL KAWCZYNSKI: All right, let's come back to her.

DR. ARNOLD MONTO: Okay. Dr. Marks, you have your hands raised. Oh, everybody's clearing themselves. Dr. Levy.

DR. OFER LEVY: I wanted to add another wrinkle to the conversation. We've heard from several people, several Committee members, that it will be confusing to the public if we now start to consider authorizations for mixed or heterologous vaccines. And on the other hand, you know, we have to follow the science. We're still in a pandemic here, and, if

there's opportunity to offer benefit, that's our job.

And besides, many Americans are taking matters into their own hands, and I'm reading in the media that people are getting boosters or mixing different products through their primary care providers or by not revealing what they got before. And so, in the real world, all these kinds of combinations or extra boosters are already happening.

So, I think it's a matter of some urgency for FDA to help sort out what is admittedly a complicated and challenging scenario. But we can't hide from it, and I do think we need to give guidance to the public. So, that's my perspective. Thank you.

DR. ARNOLD MONTO: Right. And I couldn't agree more. And I think that is one of the issues about the age group for the boosters. Because people are reading that there's waning of protection, and they are getting boosters. Dr. Hildreth.

DR. JAMES HILDRETH: Thank you, Dr. Monto. I have a comment to make that goes back to earlier in the day, and I wish I'd said it earlier. But Dr. Marks has

gone on record to say that the FDA team has not fully evaluated the data presented to them. And we voted to approve this without them having done so.

So I think it's really, really important that it be clarified in public on the record that they're going to do so. And that if there are some challenges that arise in that analysis that appropriate actions will be taken. Because we have up to this point, as my colleague just said, followed the science. I think it's really important for the public to know that that's going to happen in this case just like it's happened in all the other cases.

There are numerous times when the FDA presenters said that we've not validated this data. That was confirmed by Dr. Marks, so I think it's important for the public to know that that is going to be done. And, if there are things that are challenging that come up in that analysis, appropriate steps will be taken. I just want to make that point. I think it's really important.

DR. PETER MARKS: That point's well taken.

Just by way of full transparency, I think the one place that may be challenging for us is to move timely on that. I think point's very well taken about the immunogenicity data we have for Janssen. The challenge will be on their larger 30,000 patient trial where it's very -- that could be quite slow going. And I hazard to guess how long it could take us to get through that.

But you have our commitment that for the trials that we're relying on for immunogenicity, the data that we're using from Trial 3001, those are the kinds of data that we can ensure with our usual rigor.

DR. ARNOLD MONTO: Dr. Nelson.

DR. MICHAEL NELSON: Thank you, Dr. Monto. I appreciate it. I go to the FDA zone description for emergency use authorization. "An emergency use authorization is a mechanism to facilitate the availability and use of medical countermeasures including vaccines." The words "facilitate the availability and use" I think is where I've centered my discussions and votes over the last two days.

Is the data supportive enough for safety and

efficacy to allow and enable options for the care of the patients in the U.S.? As of exactly six months ago today, 76.7 million have been classified as fully vaccinated. That's the number that's facing decisions with respect to boosters as the data recommendations emerge from both the FDA and the CDC.

In light of the discussions, I fully agree that the data isn't fully mature or exactly a mandate that we can get to the level of recommending these boosters in a heterologous fashion, but I do believe that we should be enablers in this respect and help those in need by providing access to these vaccines through the agent of an EUA. The bar for full approval is certainly higher and I agree that either correlative protection or actual clinical evidence and protection is needed to get there, but I believe we have enough on the table today to at least include some enabling language in a EUA. Thank you.

DR. ARNOLD MONTO: Thank you very much Dr. Nelson. Dr. Wharton.

DR. MELINDA WHARTON: Thank you. I'd like to

reiterate how important it is from a programmatic perspective to have a little bit of flexibility to deal with these circumstances that do happen, like the pharmacy coming into long-term care not having to bring two mRNA vaccines -- two vaccines -- to population. Or the people who don't really know what vaccine they got or don't have their record.

So, I think we all understand why the EUA process is as constrained as it is, but it's also important if a little bit of flexibility can be provided to address these programmatic circumstances that happen, as well as individuals who may have specific preferences for safety or other reasons to receive a different vaccine then they received initially, I think that will just be enormously helpful.

DR. ARNOLD MONTO: Thank you very much. Dr. Nelson, I'm going to ask you a question, since you brought up the wording of the EUA. And that is in terms of the cutoff at age 65 for the general population except for those in special risk groups.

Because my concern is, again, that ACIP is restricted in doing anything until they have an EUA. And is there a way in your mind to get a little more flexibility about going down in age should we see dramatically a more breakthrough -- we know we hate that word -- infections in let's say a population down to age 50 or down to age 40?

DR. MICHAEL NELSON: Dr. Monto, that's an excellent question. And my thinking on this has evolved. I think the original stating of the question to us was, does the data, or evidence, support the need for those broader populations? And I still am of the thinking that it isn't quite there yet.

I am in favor of expanding options for providers and patients in risk-intolerant individuals who may venture or have the need to seek those additional dosages in that age group under 65, with appropriate education with respect to adverse effects and risks associated with those decisions.

I could definitely echo the concerns of everybody that this is getting ultimately extremely

confusing with respect to what patients are confronted with, with decision making. And there is a need to be clear with respect to full recommendations and options. But the ACIP and CDC and I think in collection with the FDA and other experts around the country can get to that endpoint by including more inclusive language. Thank you.

DR. ARNOLD MONTO: Dr. Marks, do you have any comments about this, about how we can get a little more flexibility so we don't have to meet and discuss every time we want to go down in age group as the Israeli data, for example, about the Pfizer/BioNTech vaccine becomes more obvious in the United States, which I think it will?

DR. PETER MARKS: Thanks, Dr. Monto. And I maybe chalk this up to a novice mistake on my part. I think when we tried to be very flexible for the Committee yesterday and the question, we might have done better to have been more specific and said, based on the -- I think for the Pfizer/BioNTech data, the data we saw from Israel, which, granted, Israel is not

the same as the U.S., but there were characteristics of safety that we like to believe probably carry over, and the waning of protection for that particular vaccine may.

And the question would be -- you know, I think, below the age of 40, I think, the data are not there. The question is from -- it does -- they did present at least what seemed, again, just (inaudible) as data that seemed compelling in the 40 and up age range. So the question is, does the Committee feel like, if we were to make a recommendation in our EUA for 40, then actually that lets CDC decide if they would like to come and use -- they can keep it at 65. They can come down to 50. They can come down to 40.

Now what we would do is, if we did that, we would still keep in the distinction for 18 to 40 then, for the risk group, that would stay the same. We'd tweak the language as suggested by some, but we would bring the general population age down, if the sense of the Committee was that made sense.

DR. ARNOLD MONTO: This is the sense of the

Committee; this is not with a vote in other words.

DR. PETER MARKS: Correct. If the Committee would like to vote, I suppose we could huddle and get that together. And I'd be happy to (inaudible) that sense.

DR. ARNOLD MONTO: No, we don't want to do that one.

DR. PETER MARKS: Yeah, the consensus of the Committee.

DR. ARNOLD MONTO: Because people will start counting who votes no.

DR. PETER MARKS: No, I did hear several Committee members -- I actually heard -- when I went back through my notes from yesterday, there were several Committee members who made very compelling statements about -- their concerns were around the issue of risk/benefit in somebody who is 30 or less and male. And I think those were very reasonable concerns.

I think the idea of a cut point of 40, the incidents of myocarditis really below the age of 40 is not a major concern in males. And, the question would

be then, is the Committee -- there was also the issue of people who were below 65 who might have comorbidities that put them -- maybe they weren't, you know, quite in one of the risk categories but still might benefit. So, I would ask the Committee just to comment on that and their comfort level.

I just want to also thank the Committee because I think the discussion that was just had on boosters was remarkably helpful for us at FDA, but I think also for the public to see a very complicated concept that was presented very well by the presenter and then really discussed elegantly by all the Committee members. So, thank you.

DR. ARNOLD MONTO: And, in terms of the age groups, we know that risk differed within the age group, let's say, 40 or 50 and older, including minority groups and people who are living in disadvantaged settings, which really don't fit into some of the recommendations that we have right now. Dr. Gans.

DR. HAYLEY GANS: Hi, I'm hoping you can hear

me better. I hear from Twitter that I'm not heard very well.

DR. ARNOLD MONTO: Here, we hear you loud and clear.

DR. HAYLEY GANS: All right, perfect. I know you do. Anyway, I really appreciate, Dr. Marks, the opportunity to think about that because, since the September meeting, I think several of us have felt that there should be further consideration to allowing individuals, again, down to the -- I think I was the first one to say 50-whatever, 40 sounds reasonable because of the myocarditis -- the opportunity to be further protected by a booster. So we're seeing more and more evidence of without correlative protection -- and we just have to sort of think about that and we got to leave that -- but without correlative protection we are seeing the correlates that we're using, and that we use a lot in other vaccines as well, waning. And so I do think that's very important, and I appreciate it. And I would like to put forth my thoughts that I think that that's a very important way in which we can help

individuals at this point in the pandemic that we've reached.

DR. ARNOLD MONTO: Dr. Rubin.

DR. ERIC RUBIN: I think I'm very supportive of the way that Dr. Marks formulated what he said just now. In fact, we're worried about risk and benefit. We're not really worried about a flat-out no for one group or another. And if, for example, things were to change on the ground and it was more important for younger people to get it, I'm very in favor of allowing the flexibility that FDA allow the flexibility for at least for ACIP to make a recommendation about that.

So, I think that as new data are coming in -- remember last time around, we saw the Israeli data from age 60 and up, and now we're seeing 40 and up. And we're getting a much better idea of risk. So, I think it's a very good idea to get some leeway.

DR. ARNOLD MONTO: Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah, I guess one question I would ask Dr. Marks is, I think part of the area of confusion, one aspect of the

confusion, is that when we say immunity is waning, what are the implication of that? Because I think there is, at least in the general public and actually quite a bit in the medical and public health community, that there is an assumption that (audio skip).

MR. MICHAEL KAWCZYNSKI: All right, go ahead, you're back connected. Take it away.

DR. MICHAEL KURILLA: Yeah, so I think when we talk about, when we say "waning immunity," I think in many people's mind, particularly the public, but I think in general also with many in healthcare and public health community that an increase in infections is obviously going to lead to an increase in symptomatic infections is going to lead to an increase in severe infections and hospitalizations and deaths.

And what we're seeing actually is not that. There is a divergence, and that is we may be getting -- many people may be suffering breakthrough infections, but the protection from severe disease is still holding up quite well for all of the vaccines. Now, that doesn't mean they'll hold on forever. We still have to

evaluate durability, but I think it's important to ask, when the concern is for waning immunity, what exactly are we trying to target by trying to increase the flexibility and increase the availability of vaccines for the population?

If we're trying to drive to zero COVID, I think that's not going to work. So, I think we just need to be a little bit more careful and deliberate in terms of what impact are we actually trying to create here.

DR. ARNOLD MONTO: Dr. Marks, would you care to comment from the Israeli data about holding up against severe disease because, from what I understand, it's starting to wane against severe disease as well. I know hospitalizations have gone up in the vaccinated.

DR. PETER MARKS: Dr. Monto, that's correct. And actually, there are data that have been -- actually some was submitted to the docket. There are data that are coming from various sources, kind of one's a grass-roots data collection, of breakthrough infections in healthcare providers and others that are younger than

age 60 that have ended up hospitalized or with what would qualify as severe COVID.

Now we have not obviously -- those are not FDA-reviewed data, but, on an anecdotal basis, I think it makes us realize that we're concerned that what was seen in Israel could be seen here. And I think going back to what Dr. Rubin said, I think we want to prevent severe -- we don't want to have a wave of severe COVID-19 before we deploy boosters. I think we want to, when we see waning start, to prevent that from happening. I agree with you though; we're not looking here to stop every last case of COVID. I think Dr. Offit said that more elegantly than I could previously.

So, I think there is a balance here, and, again, going back to what Dr. Rubin said, in this particular case, it's a risk/benefit issue. And I think, if we're not seeing severe COVID-19 in the younger population yet, so benefit/risk there, so we don't go down below age 40 especially because there we know there's a myocarditis risk in males that might be more of an issue.

So, I think the flexibility is helpful. I was at a meeting this morning with WHO, and I think the word of the day was "agility." Agility has been probably one of the most important things to have in this pandemic, and that's what I think we just want to have here.

DR. MICHAEL KURILLA: Yeah, and my only point, Peter, is that I think we need to be clear. When we say "waning immunity" and we need to do something about that, I think we need to be clear what we're really targeting in terms of the clinical impact we expect to have.

DR. PETER MARKS: Point taken. So I think we're starting to see the appearance of cases, yep.

DR. ARNOLD MONTO: Okay, Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Arnold. I want to come back to something that Peter Marks said at the beginning. That there is this -- although we can't prevent every infection with boosters and I think that's really key, we need to sort of get away from this idea that a booster is going to prevent every

single infection.

The idea that we can prevent additional infections in some of those does provide some value in the sense that COVID does have tremendous downstream effects even for those who are not hospitalized. And, so, I think whenever we can prevent significant morbidity in a population, there're advantages to that.

And I think, if we are starting to see this concern in these groups, which many of us have seen bits and pieces of this data and certainly the Israeli date suggest this, I'd really be in the camp that would definitely be moving towards a lower age range for allowing boosters, partially for that reason. And, because we know that hospitalizations and deaths are going to lag, what we're going to see is primary infections first and then those later. And we don't want to be in a situation as we're coming into the winter with additional people coming into the hospital because of changes.

So, I'm very supportive of this. In fact, I think at the last meeting we talked about Pfizer; I was

supportive of going down to a lower age range.

DR. ARNOLD MONTO: Dr. Rubin. I believe you may have the last word. No, Dr. Levy wants to come back again, so you go next, Dr. Rubin.

DR. ERIC RUBIN: You have the last word because I left my hand up. Sorry.

DR. ARNOLD MONTO: Oh, okay. Dr. Levy.

DR. OFER LEVY: This is a dynamic pandemic. We don't know what the winter will bring. What the dynamic of spread will be. What variants may emerge, and also what new research will come forward in terms of the impact of the pandemic on those younger age groups, including potentially long-COVID and how that might play out in young individuals and even children.

So I think we need to keep an open mind. Also keep open mind about the fact that if we can reach herd immunity, then there are direct and indirect benefits of the booster potentially, and the Israeli date spoke to that. It appeared from the Israeli data yesterday to my eye that they may have seen something along the lines of herd immunity as they rolled out their booster

campaign.

So this is a complex topic, and I think we need to follow the data and keep an open mind. And I'm generally supportive of coming down in age on the boosters. And I look forward to those conversations. Thank you.

DR. ARNOLD MONTO: Dr. Perlman.

DR. STANLEY PERLMAN: Yeah, I just wanted to say that, in general, I wasn't a fan of reducing the cutoff to a lower age because I think the severe disease isn't terribly great in that population. But, hearing all of these arguments I would support that now more.

I think the thing I really want to say is I hope we can present this in a way that it's not confusing for the public because it's already con- -- what we do is we follow the science. We listen to what we see, but the people who aren't doing this, they think that the rules are changing all the time. So I just hope we can do this in a way that it doesn't look like we're changing the rules all the time.

DR. ARNOLD MONTO: Thank you, Dr. Perlman. And now finally the last word for Dr. Cohn.

CAPT. AMANDA COHN: Thanks. I will let all of those comments stand as they were excellent comments. But I just want to leave the committee with the reminder that already 60 percent of adults, aged 18 to 64, do fall into one of those two categories. So, you could argue either way on that.

One, we have access and availability to a large portion of that group who have the option of getting vaccinated. But you could also argue that there's a small portion, so 40 percent, of U.S. adults aren't included in that.

And, so, those two bullet points on high-risk conditions and occupational risk are very complicated and already encompass a huge portion of the U.S. population.

DR. ARNOLD MONTO: Dr. Cohn, as somebody who experienced the dropping of ages for influenza vaccine for just the reason of trying to avoid confusion about whether you go into a risk category or not, that's one

of the reasons why I'm a very strong advocate of doing something that's understandable and age based.

Okay, this draws our lengthy meeting, going on for two days, to an end. I think we have been very successful in voting for two products recommending that they get emergency use authorization and made some important points in terms of discussion.

This concludes the meeting. And I would like to hand this over to Dr. Marks. You will have the honor of closing the meeting, please.

MEETING ADJOURNMENT

DR. PETER MARKS: No, no, no. I'll hand it over to Dr. Atreya in a moment. And I promise I'm not going to ask any more questions to the Committee. I just really want to sincerely thank all the members of the Committee because I really feel like every member of the Committee spoke up. And we really got a lot of very good feedback.

We have a lot to digest on our end, but I

greatly appreciate this. And I also really greatly appreciate the dialog that I think has been wonderful in a public venue. So, thank you all so much.

I also need to thank a number of individuals. The staff from FDA worked tirelessly to go through a tremendous amount of information to try to verify as much of it as they possibly could before this meeting and incredibly grateful to that. And also very grateful to our ACom staff, the Advisory Committee staff, who really put on an incredibly technically flawless meeting over the past two days. So, yes, there are always little glitches, but, given that we're all in separate locations, it was quite remarkable. So thank you so much and thank you to all of you.

And now I'll turn it over to Dr. Atreya. Thank you, Dr. Monto, as well. Thank you for a wonderful -- chairing this meeting, thanks. Dr. Atreya?

DR. ATREYA PRABHAKARA: Thank you, Dr. Marks and Dr. Monto, for the wonderful meeting. And we appreciate everything you do. And so, with these

remarks, the meeting is adjourned formally now 3:28 p.m.

[MEETING ADJOURNED]